UNIVERSITÉ DE GENÈVE

Archive ouverte UNIGE
https://archive-ouverte.unige.ch

Livre 2005 Published version Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Clinical drug trials : studying the safety and efficacy of new pharmaceuticals

Junod, Valérie

How to cite

JUNOD, Valérie. Clinical drug trials : studying the safety and efficacy of new pharmaceuticals. Genève : Schulthess, 2005. (Collection genevoise)

This publication URL: https://archive-ouverte.unige.ch/unige:43019

© This document is protected by copyright. Please refer to copyright holder(s) for terms of use.

Valérie Junod

Clinical drug trials

Studying the safety and efficacy of new pharmaceuticals

Faculté de droit de Genève

BRUYLANT BRUXELLES

Schulthess §

Collection Genevoise

Valérie Junod

Clinical drug trials

Faculté de droit de Genève

Valérie Junod

Clinical drug trials

Studying the safety and efficacy of new pharmaceuticals

BRUYLANT
BRUXELLES
2005

Schulthess § 2005
55

Thèse n° 755 de la Faculté de droit de l'Université de Genève

La Faculté de droit autorise l'impression de la présente dissertation sans entendre émettre par là une opinion sur les propositions qui s'y trouvent énoncées.

Information bibliographique: ‹Die Deutsche Bibliothek›.
Die Deutsche Bibliothek a répertorié cette publication dans la Deutsche Nationalbibliografie; les données bibliographiques détaillées peuvent être consultées sur Internet à l'adresse ‹http://dnb.ddb.de›.

Tous droits réservés. Toute traduction, reproduction, représentation ou adaptation intégrale ou partielle de cette publication, par quelque procédé que ce soit (graphique, électronique ou mécanique, y compris photocopie et microfilm), et toutes formes d'enregistrement sont strictement interdites sans l'autorisation expresse et écrite de l'éditeur.

© Schulthess Médias Juridiques SA, Genève · Zurich · Bâle 2005

ISBN 3 7255 5022 0 Schulthess Médias Juridiques SA, Genève · Zurich · Bâle
ISBN 2 8027 2163 1 Bruylant, Bruxelles

www.schulthess.com
www.bruylant.be

To my fantastic parents

"All professions are conspiracies against the laity."

George Bernard Shaw, The Doctor's Dilemma

Acknowledgments

The following persons very kindly provided me with precious information, documents and/or advice on a variety of themes related to pharmaceuticals. Michel Balea (UCSF Medical Center), Henri Bounameaux (ethics committee president at the Geneva's University hospitals); Stefano Dozio (Swiss Competition Commission); Pascale Erbeia (lawyer in Geneva and ethics committee member); Jeremy Lack (legal counsel in Geneva); Cathy Lawi (Medabiotech); Benoît Merkt (lawyer in Geneva); Laurent Miéville (Unitec at the University of Geneva); Alexandre Mauron (bioethicist at the University of Geneva); Thomas Schuler (OFSP); Pierre Studer (OFSP); Thierry Tanquerel (Professor at the University of Geneva Law School).

Many others are not mentioned here, but their assistance has been nonetheless greatly appreciated. I would also like to extend special thanks to the many people at Swissmedic who patiently and expertly answered my numerous questions; I am particularly grateful to Jean-Christophe Méroz (legal department) and to the entire GCP department.

Obviously, the opinions contained in this thesis may not reflect the views of the persons mentioned above. Moreover, all errors – and, alas, some will certainly remain – are my responsibility only.

My deep gratitude goes to:

- Professor Christian Bovet, the best thesis director I could dream of.
- Professors Dominique Manaï, Philippe Ducor (Law School of the University of Geneva), Pierre Dayer (Medical School of the University of Geneva), and Benoît Dubuis (Swiss Federal Institute of Technology, Lausanne). Their insightful observations and advice during the oral defense of this thesis were invaluable.
- The law firm of 'Junod, Guyet, Muhlstein & Lévy', particularly Dr. Alain B. Lévy and the secretaries, for assisting me in my project in so many ways.
- Ms. Alia Rahal for careful proofreading the final draft.
- The Stanford Law School, for its superb facilities and the guidance given by my two advisors, Professors John Barton and Jonathan Greenberg, during the year I spent there.
- The Swiss National Science Foundation ("SNSF"), for generously funding my research and my stay at Stanford.
- Lexis and Google: How is legal research at all possible without these tools?

Last, but certainly not least, I want to thank my incredible family. My parents and Tony Reynard read several drafts and came back with amazingly sharp comments. It is to my father that I owe my taste for law. My mother encouraged me to start writing, and above all, to finish this thesis: Without her, I would still be collecting notes today. Finally, I am indebted to Tony who supported me unwaveringly during this delightful ordeal.

June 30, 2004

Summary of contents

Acronyms XIII

List of Principal Laws and Regulations cited XVII

1. Introduction 1

Part I 9

2. Historical overview of clinical trial regulations 9

3. Definition of clinical trials 36

4. The economic dimension of clinical trials 76

Part II 127

5. The professional participants in a clinical trial 127

6. The types and characteristics of drug clinical trials 174

Part III 257

7. Approval of clinical trials 257

8. Research subjects 318

9. Supervision of clinical trials 468

10. End of clinical trials 502

11. Conclusion 521

Glossary 523

List of court cases cited 527

Short Bibliography 531

Index 533

Table of contents 535

Acronyms

ADR:	Adverse Drug Reaction.
AE:	Adverse Event.
AMA:	American Medical Association.
ANDA:	Abbreviated New Drug Application.
ARR:	Absolute Risk Reduction.
ATF:	(Swiss) from the French: recueil officiel des arrêts du Tribunal fédéral.
BMJ:	British Medical Journals.
C.F.R.:	(U.S.) Code of Federal Regulations.
CAFC:	(U.S.) Court of Appeals for the Federal Circuit.
CAM:	Complementary and Alternative Medicines.
CBER:	(U.S) Center for Biologics Evaluation and Review.
CCNE:	(France): from the French: Comité consultatif national d'éthique.
CDER:	(U.S) Center for Drug Evaluation and Review.
C.F.R.:	(U.S.) Code of Federal Regulations.
CIOMS:	Council for International Organizations of Medical Sciences.
CPMP:	(E.U.) Committee for Proprietary Medicinal Products (presently Committeee for Medicinal Products for Human Use, CHMP)
CRADA:	Cooperative Research and Development Agreement.
CRF:	Case Report Form.
CRO:	Contract Research Organization.
DoD:	(U.S.) Department of Defense.
DSMB:	Data and Safety Monitoring Board.
EBM:	Evidence-Based Medicine.
EGE:	(E.U.) European Group on Ethics in Science and New Technologies.
EMEA:	European Medicines Agency (previously European Agency for the Evaluation of Medicinal Products).
EPAR:	European Public Assessment Report.
ESC:	Embryonic Stem Cells.
FDA:	(U.S.) Food and Drug Administration.
FDCA:	(U.S.) Food, Drug, and Cosmetic Act.
Fed.Reg.:	(U.S.) Federal Register.
FF:	(Switzerland) from the French: Feuille Fédérale.
FOIA:	(U.S.) Freedom of Information Act.
FOPH:	(Swiss) Federal Office for Public Health.
GAO:	(U.S.) General Accounting Office.
GCP:	Good Clinical Practices.
GLP:	Good Laboratory Practices.
GMP:	Good Manufacturing Practices.
HHS:	(U.S.) Department of Health and Human Services.
HUG:	(Switzerland) from the French: Hôpitaux Universitaires de Genève; translation. (Geneva University Hospitals).

IBD:	International Birth Date (of a drug).
ICCPR:	International Covenant on Civil and Political Rights.
ICF:	Informed Consent Form.
ICH:	International Conference on Harmonisation.
IFPMA:	International Federation of Pharmaceutical Manufacturers Associations.
IND:	(U.S.) Investigational New Drug.
IOCM:	Intercantonal Office for the Control of Medicaments.
IRB:	(U.S.) Institutional Review Board (an institutional ethics committee).
JAAC:	(Switzerland) from the French: Jurisprudence des autorités administratives de la Confédération.
JAMA:	Journal of the American Medical Association.
JdT:	(Switzerland) from the French: Journal des Tribunaux.
MAH:	Marketing Authorization Holder.
NBAC:	(U.S.) National Bioethics Advisory Commission.
NCE:	New Chemical Entity.
NCI:	(U.S.) National Cancer Institute.
NDA:	(U.S.) New Drug Application.
NIH:	(U.S.) National Institutes of Health.
NLS:	Nonclinical Laboratory Study.
NNT:	Number Needed to Treat.
OHRP:	(U.S.) Office of Human Research Protections.
OIG:	(U.S.) Office of Inspector General.
OTA:	(U.S.) Office of Technology Assessment.
OTC:	Over-the-counter (medicines).
PhRMA:	Pharmaceutical Researchers and Manufacturers of America.
PHS:	(U.S.) Public Health Service.
PI:	Principal Investigator.
PIL:	(E.U.) Patient Information Leaflet.
PSURs:	Periodic safety update reports.
QoL:	Quality of Life.
R&D:	Research and Development.
RCT:	Randomized Clinical Trial.
REC:	Research Ethics Committee.
RRR:	Relative Risk Reduction.
RS:	(Swiss) from the French: Recueil systématique du droit fédéral.
Rx:	Prescription (drugs).
SAE:	Serious Adverse Event.
SAMS:	Swiss Academy of Medical Sciences.
SSCI:	Swiss Society of Chemical Industries.
SEC:	(U.S.) Securities and Exchange Commission.
SECO:	(Swiss) State Secretariat for Economic Affairs.
SJ:	(Swiss) Semaine Judiciaire.
SMO:	Site Management Organization.
SNSF:	Swiss National Science Foundation.

SOP:	Standard Operating Procedures.
SPC:	(E.U.) Summary of Product Characteristics.
SSCI:	Swiss Society of Chemical Industries.
U.S.C.:	(U.S.) United States Code.
WMA:	World Medical Association.

List of Principal Laws and Regulations cited

Swiss Legal Texts

CC:	In French: "*Code civil suisse*"; December 10, 1907; RS 210.
CO:	In French: "*Code des obligations suisse*"; March 30, 1911; RS 220.
CP:	In French: "*Code pénal suisse*"; December 21, 1937; RS 311.
Cst:	Swiss Constitution; April 18, 1999; entered into force on January 1, 2002; RS 101.
(LATh)	(In French: "*Loi sur les agents thérapeutiques*"; former name of the LPTh when initially proposed by the Federal Council)
LRFP:	In French: "*Loi fédérale sur la responsibilité du fait des produits*"; my translation: Federal Law on product liability; June 18, 1993; entered into force on January 1, 1994; RS 221.112.944.
LPD:	In French: "*Loi fédérale sur la protection des données*"; my translation: Federal Law on data protection; June 19, 1992; entered into force on July 1, 1993; RS 235.1.
LPMA:	In French: "*Loi fédérale sur la procréation médicament assistée*"; my translation: Federal Law on medically assisted procreation; December 18, 1998; entered into force on January 1, 2001; RS 814.90.
LPTh:	In French: "*Loi fédérale sur les produits thérapeutiques*"; my translation: Federal Law on therapeutic products; December 15, 2000; entered into force on January 1, 2002; RS 812.21.
LRCS:	In French: "*Loi fédérale relative à la recherche sur les cellules souches embryonnaires*"; my translation: Federal Law on embryonic stem cell research; December 19, 2003; entered into force on March 1, 2005; RS 810.31.
OAMéd:	In French: "*Ordonnance sur les autorisations dans le domaine des médicaments*"; my translation: Federal Council's Ordinance on authorizations in the sector of pharmaceuticals; October 17, 2001; entered into force on January 1, 2002; RS 812.212.1.
OASMéd:	In French: "*Ordonnance de l'Institut Suisse des produits thérapeutiques sur l'autorisation simplifiée et l'annonce obligatoire des médicaments*"; my translation: Swissmedic's Ordinance on the simplified authorization and the mandatory notification of pharmaceuticals; November 9, 2001; entered into force on January 1, 2002; RS 812.212.23.
OClin:	In French: "*Ordonnance sur les essais cliniques*"; my translation: Federal Council's Ordinance on clinical trials; October 17, 2001; entered into force on January 1, 2002; RS 812.214.2.
OEMéd:	In French: "*Ordonnance de l'Institut Suisse des produits thérapeutiques sur les exigences relatives à l'autorisation de mise sur le marché des médicaments*"; my

translation: Swissmedic's Ordinance on the requirements regarding the marketing authorization for pharmaceutical products; November 9, 2001; entered into force on January 1, 2002; RS 812.212.22.

OLPD: In French: "*Ordonnance relative à la loi fédérale sur la protection des données*"; my translation: Federal Council's Ordinance regarding the LPD; June 14, 1993, entered into force on July 1, 1993; RS 235.11.

OMéd: In French: "*Ordonnance sur les médicaments*"; my translation: Federal Council's Ordinance on pharmaceuticals; October 17, 2001; entered into force on January 1, 2002; RS 812.212.21.

ORCS: In French: "*Ordonnance relative à la recherche sur les cellules souches embryonnaires*"; my translation: Federal Council's Ordinance regarding embryonic stem cell research; February 2, 2005; entered into force on March 1, 2005; RS 810.311.

OUC: In French: "*Ordonnance sur l'utilisation des organismes en milieu confiné*"; my translation: Ordinance on the use of organisms in confined settings; August 25, 1999; entered into force on November 1, 1999; RS 814.912.

Swiss Draft Laws (as of July 2005)

LAGH: In French: "*Loi fédérale sur l'analyse génétique humaine*"; my translation: Federal Law on human genetic analysis; October 8, 2004; no RS number yet.

LTrans: In French: "*Loi fédérale sur le principe de transparency dans l'administration*"; my translation: Federal Law on transparency in the administration; December 17, 2004, no RS number yet.

LTransplant: In French: "*Loi sur la transplantation d'organes, de tissus et de cellules*"; my translation: Federal Law on transplantation; October 8, 2004; no RS number yet; my abbreviation.

U.S. Legal Texts

Title 21 (Food and Drugs) of United States Code (U.S.C.), chapter 9 (Federal Food, Drug, and Cosmetic Act), subchapter 5 (drugs and devices), part A (drugs and devices), particularly § 355(a) and § 355(b).

Title 21 (Food and Drugs) of the Code of Federal Regulations (C.F.R.), particularly part 50 (protection of human subjects), part 54 (financial disclosure by clinical investigators), 56 (institutional review boards), part 312 (investigational new drug application).

Title 45 (Public Welfare) of the Code of Federal Regulations (C.F.R.) part 46 (protection of human subjects) (§ 46.101 to §46.409).

E.U. Legal Texts

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal product for human use, published in the Official Journal ("OJ") L 121, 1.5.2001, p.34; entered into force on May 5, 2001.

Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human use, published in OJ L 311, 28.11.2001, p. 67-128, as modified in particular by Directive 2004/27/EC of 31 March 2004, published in OJ L 136, 30.04.2004, p. 34-57.

Regulation 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, published in OJ L 136, 30.4.2004. p. 1-33.

European Commission, Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 23, 2004.

European Commission, Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module), April 23, 2004.

European Commission, Detailed guidance on the European clinical trials database (EUDRACT Database), April 23, 2004.

European Commission, Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use, April 23, 2004.

European Commission, Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial, April 23, 2004.

1. Introduction

1.1. Scope of the thesis

The objective of this thesis is to present a thorough review of clinical trial regulations. The analysis is limited to clinical trials of drugs, more precisely *therapeutic* drugs.[1] Trials of *diagnostic drugs and vaccines* present certain distinct features and are therefore not discussed in any depth.[2] Clinical trials of medical *devices* (e.g., an artificial hip) and *therapeutic procedures* (e.g., heart surgery)[3] are also beyond the scope of this thesis as they obey partly different rules.[4] Treatments that do not involve a therapeutic product, such as *psychological* (e.g., psychotherapy), *behavioral* (e.g., physical exercise[5]) or *nutritional* (e.g., low-fat diet[6]) studies, are not reviewed.

Programs extending compassionate access to experimental drugs share common characteristics with clinical trials and will be analyzed in subsection 3.4.6.2.

---

1 The words "drug" and "pharmaceutical" are used interchangeably in this thesis. The term "drug" is the one commonly used in the United States. It is also the expression most frequently encountered in the medical literature. I refer – of course – to *licit drugs*, not illegal substances

2 Pharmaceuticals include drugs administered not only to prevent and treat diseases, but also to diagnose them. *See also* NCI (U.S. National Cancer Institute), Data and Safety Monitoring Guidelines, at http://www.nci.nih.gov/clinicaltrials/conducting/dsm-guidelines/page2 (explaining when use of a diagnostic test involves a clinical trial). Many diagnostic products can be approved without extensive testing directly on humans (i.e., administration of the investigational product to human research subjects). Instead, tests may be performed on biological material.

3 On clinical trials of surgical procedures, see for instance Karen Antman et al., *Designing and Funding Clinical Trials of Novel Therapies*, 344 NEW. ENG. J. MED. 762-763 (Mar. 8, 2001), at http://content.nejm.org/cgi/reprint/344/10/762.pdf; Nicholas J. Petrelli, *Clinical Trials Are Mandatory for Improving Surgical Cancer Care*, Editorial, 287 JAMA 377-78 (2002), at http://jama.ama-assn.org/cgi/reprint/287/3/377.pdf; Peter McCulloch et al., *Randomised trials in surgery: problems and possible solutions*, 323 BMJ 1448-51 (June 15, 2002), at http://bmj.bmjjournals.com/cgi/reprint/324/7351/1448.pdf; Henry K. Beecher, *Ethics and Experimental Therapy*, 186 JAMA 858-59 (Nov. 30, 1963) (stressing the need to distinguish between the placebo effect and the true results of surgery).

4 *See* Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J. L. AND MED. 361, at 392 (2002). Noah highlights the paradox in that studies of surgical techniques and other non-drug therapy are relatively unregulated. *See also* ARTHUR AND ELAINE SHAPIRO, THE POWERFUL PLACEBO, FROM ANCIENT PRIEST TO MODERN PHYSICIAN 83 (John Hopkins University Press 1997) [hereinafter THE SHAPIROS].

5 *See, e.g.*, Matti Viljanen et al., *Effectiveness of dynamic muscle training, relaxation training, or ordinary activity for chronic neck pain: randomised controlled trial*, 327 BMJ 475 (Aug. 30, 2003) http://bmj.com/cgi/reprint/327/7413/475.pdf; John M. Jakicic et al., *Effect of Exercise Duration and Intensity on Weight Loss in Overweight, Sedentary Women, A Randomized Trial*, 290 JAMA 1323-1330 (2003), at http://jama.ama-assn.org/cgi/reprint/290/10/1323.pdf.

6 A nutritional study can also be combined with a drug clinical trial. *See, e.g.,* David J. A. Jenkins et al., *Effects of a Dietary Portfolio of Cholesterol-Lowering Foods vs Lovastatin on Serum Lipids and C-Reactive Protein*, 290 JAMA 502-510 (2003), at http://jama.ama-assn.org/cgi/reprint/290/4/502.pdf.

1.2. Focus of the thesis

This thesis strives to approach the topic from a *multidisciplinary* perspective. To fully understand clinical trials, I believe that it is crucial to expand the focus beyond statutes, regulations and case law; it is essential to further consider guidelines as well as medical and economic literature.

1.2.1. A broad regulatory outlook

The Swiss Law on therapeutic products ("LPTh")[7] and the Swiss Ordinance on clinical trials ("OClin")[8] constitute the main subject matter of this thesis.[9] I aim to highlight their weaknesses, inconsistencies, and gaps. I am therefore chiefly interested in *administrative* law, while civil law only plays a peripheral role here.[10]

The thesis looks into both binding and non-binding *regulatory* prescriptions. References to guidelines are indispensable because laws and ordinances contain only few general provisions. Statutory material chiefly contains procedural rules (e.g., a 30 day deadline to issue an opinion), while substantive rules are mostly explained by guidelines (e.g., how an ethics committee should reach its decisions). Furthermore, non-binding guidelines have long been at the basis of Western countries' legislations concerning clinical trials. These were not devised by parliaments, but by medical associa-

---

7 *See* Federal Law on therapeutic products of December 15, 2000; RS 812.21; entered into force on January 1, 2002; in French: "*Loi fédérale sur les médicaments et les dispositifs médicaux (loi sur les produits thérapeutiques)*"; abbreviated (from the French): LPTh; text in English (unofficial translation) at http://www.swissmedic.ch/files/pdf/HMG_English_New_version.pdf; in French at http://www.admin.ch/ch/f/rs/8/812.21.fr.pdf; in German at http://www.admin.ch/ch/d/sr/8/812.21.de.pdf; in Italian at http://www.admin.ch/ch/i/rs/8/812.21.it.pdf.
The LPTh was the subject of debate before the Swiss Parliament from March to December 1999. The transcripts of these discussions are available from http://www.parlament.ch/ab/frameset/d/n/4602/8187/d_n_4602_8187_8363.htm. The Federal Council issued its Message on March 1, 1999; FF 1999 3151; text (in French) at http://www.bag.admin.ch/heilmitt/gesetz/f/botschaft%20hmg_f.pdf. Previously, a draft law (then called law on therapeutic agents or "LAth") had been circulated among interested parties for comments. *See* Department of Home Affairs ("DHA"), Rapport sur les résultats de la procédure de consultation concernant l'avant-projet de loi sur les agents thérapeutiques [Report on the results of the consultation procedure regarding the draft law on therapeutic agents], (Dec. 8, 1997) [hereinafter DHA 1997 Consultation Report]; DHA, Rapport explicatif sur l'avant-projet de loi sur les agents thérapeutiques [Explicative Report on the draft law on therapeutic agents], (Feb. 19, 1997) [hereinafter DHA 1997 Explicative Report]. *See also* Paul Richli, *Instrumente des Gesundheits- und Lebensschutzes im neuen Heilmittelgesetz vor dem Hintergrund der Grundrecht*, 3/2002 PRATIQUE JURIDIQUE ACTUELLE (PJA) 340-44 (2002).

8 *See* Federal Council's Ordinance on clinical trials of therapeutic products of October 17, 2001; RS 812.124.2; entered into force on January 1, 2002; in French: "*Ordonnance sur les essais cliniques de produits thérapeutiques*"; abbreviated (from the French): OClin; text in French at http://www.admin.ch/ch/f/rs/8/812.214.2.fr.pdf; in German at http://www.admin.ch/ch/d/sr/8/812.214.2.de.pdf; in Italian, at http://www.admin.ch/ch/i/rs/8/812.214.2.it.pdf.
The OClin is loosely based on a proposed text prepared by the Federal Office for Public Health ("FOPH") in December 2000; this draft is cited hereinafter as the "2000 draft OClin."

9 When referring to the LPTh and the OClin jointly, I speak of the "2002 Federal Regulation."

10 Issues regarding contract law (e.g., qualification of the legal relationship between the investigator and the subject) and tort law (e.g., liability of the investigator toward the subject) are only briefly addressed (see respectively subsection 8.2. and 8.6.5.).

tions, international organizations, commissions and courts. The consequence is that statutes tend to lag behind the guidelines that these groups regularly produce. For example, the Swiss legislation on clinical trials[11] is a much abridged version of key international guidelines.[12]

One difficulty is that all guidelines are not equally observed. While the pharmaceutical industry consistently abides by guidelines of the International Conference on Harmonization ("ICH"), they pay less attention to others, such as those of the Council for International Organizations of Medical Sciences ("CIOMS"). To indicate that a prescription is not necessarily strictly followed, I use the modal verb "should," instead of "must."[13] For example, the principle according to which pharmaceutical companies are to offer the investigational product to former research subjects who responded positively to the drug is not strictly compulsory;[14] I would therefore write that the company *should* – and not, must – offer follow-up supplies of the investigational product.

1.2.2. Medical literature

Pharmaceutical regulations have not been the preserve of jurists and lawyers. Regulatory departments of pharmaceutical companies are not staffed by jurists, but by people with medical, biological, or chemical backgrounds. For a long time, the regulatory norms that these people had to master were not found in laws or ordinances, but in technical guidances. There was very little case law because law suits deriving from clinical trials were fairly rare.

One consequence of this situation is that comments on these guidances were mostly published in medical journals. This is still partly true today. For example, over the last fifty years, the most comprehensive discussions of issues related to informed consent of research subjects has taken place in medical, and not legal journals. Moreover, medical articles exhibit a practical perspective that legal journals sometimes lack.[15]

Lastly, I think basic knowledge of medical concepts is important to understand how clinical trials are conducted and regulated. However, I would like to draw the readers' attention to the fact that I have neither medical expertise nor a scientific background. This should make this thesis all the more comprehensible to nonscientists.

---

11 I refer here to the Law on therapeutic products (LPTh) together with the Ordinance on clinical trials (OClin).

12 The OClin takes was inspired by the ICH E6 Guideline. *See* International Conference on Harmonization's Harmonized Tripartite E6 Guideline for Good Clinical Practice, (Step 4 of ICH Process), (May 1, 1996), from http://www.ich.org/cache/compo/475-272-1.html#E6 [hereinafter ICH E6].

13 As the FDA says in its own guidelines, "[t]he use of the word *should* … means that something is suggested or recommended, but not required." *See, e.g.,* FDA, Fast Track Drug Development Programs – Designation, Development, and Application Review, Guidance for Industry, at 1 (July 2004), at http://www.fda.gov/cber/gdlns/fsttrk.pdf.

14 This principle is continuing to gain in importance; providing post-trial access may become a strictly compulsory component of trial organization in the future. *See* subsection 8.6.2.3. below

15 For example, medical articles are often based on surveys designed to find out how the informed consent process is understood by clinical researchers and human research subjects.

1.2.3. Economic literature

I find numbers and statistics fascinating. I acknowledge that they can be misleading, but I have nonetheless chosen to use them extensively. Figures shed an instructive light on the topics under review; they flesh out the subject matter. Although one might argue that the issue of, say, clinical trial costs is beyond the scope of a legal thesis, I consider it indispensable to grasp the impact of clinical trials.

1.2.4. Ethics

When hearing the expression "clinical trial," "ethics" immediately comes to mind. However, I have deliberately left *general* ethical issues (e.g., the Dignity of Human Beings) aside. What is ethics or bioethics? How do they differ from religious morality or professional deontology? How can they be delineated in concrete cases? These are all thorny (and possibly unanswerable) questions that I will not discuss here.[16] I will only comment on ethical doctrines to the extent that they are incorporated into guidelines. In any event, existing guidelines are so excruciatingly detailed that, in my view, they obviate the need to apply general ethical principles.

1.3. Laws under analysis

Regulation of clinical trials is analyzed chiefly under *Swiss* law. However, to understand Swiss regulations, it is helpful to refer to those of other countries, in particular the United States.[17] Several reasons justify this broader orientation.

First, the Swiss regulatory system is not as elaborate as the American.[18] To illustrate this, the U.S. Food and Drug Administration ("FDA")[19] regulations on clinical trials span some 40 pages,[20] whereas the Swiss equivalent Ordinance is only 14 pages long.[21]

---

16 For possible approaches, see for example TOM L. BEAUCHAMP & JAMES F. CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS, mainly at chapters 1, 2, 8 and 9 (Oxford Univ. Press, 5th ed., 2001). *See also* DOMINIQUE SPRUMONT, LA PROTECTION DES SUJETS DE RECHERCHE NOTAMMENT DANS LE DOMAINE BIOMÉDICAL, at 53-62 (Ed. Staempfli, Berne, 1993) [hereinafter SPRUMONT]; Dominique Sprumont, *Regard critique sur les rapports entre éthique et droit médical*, 40(3/4) CMS 255-68 (1996); DOMINIQUE MANAÏ, LES DROITS DU PATIENT FACE À LA MÉDECINE CONTEMPORAINE at 29-30 and at 44-45 (Helbing & Lichtenhahn, 1999) [hereinafter MANAÏ (CONTEMPORAINE)]. See also the excellent comments regarding the flaws in some bioethical reasonings, Alexandre Mauron, *Recherche biomédicale, l'éthique sur la brèche*, 2419 MED. ET HYG. (Jan. 8, 2003), at http://www.revmed.ch/article.php3?sid=22762, and Part II, 2420 MED. ET HYG. (Jan. 15, 2003), at http://www.revmed.ch/article.php3?sid=22810; *Bioéthique et sciences humaines: quel dialogue, quelles missions* ! MED. ET HYG., at ! http://www.revmed.ch/article.php3?sid=22443;

17 When a chapter successively describes Swiss and U.S. regulations, the Swiss subsection usually comes first.

18 In this thesis, I refer mostly to regulations applicable to FDA-governed clinical trials. Trials receiving federal funding, for example from the NIH, follow slightly different rules set forth by the Department of Human Health and Services ("HHS"). *See* subsection 2.3.2. below.

19 Home page of the FDA, at http://www.fda.gov.

20 *See* 21 C.F.R. [Code of Federal Regulations] § 312.1 to § 312.145, from http://www.accessdata. fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312. The number of FDA guidelines also far exceeds those of Swissmedic. For 2000 alone, the FDA's Center for Drug Evaluation and

The American drug agency, the FDA, has some 9,000 employees, including 700 who only deal with drug applications;[22] in comparison, the Swiss drug agency, Swissmedic,[23] only has 265 employees.[24] The FDA spent some $187 million in 2000 to review new drug applications ("NDAs");[25] its total budget in 2003 exceeded $1,7 billion,[26] compared with CHF 54.5 million for the entire Swissmedic's operations.[27] According to the FDA's own slogan, "drug review and approval in the United States now represent the *international gold standard*."[28]

Second, the United States is a country with a population of over 280 million people.[29] This is bound to result in more lawsuits. For instance, U.S. courts have issued dozens of decisions pertaining to the conduct of clinical trials in general, and the rights of subjects in particular.[30] In sharp contrast until 2005, there were *no* reported decisions by Swiss courts.[31] The consequence is that many legal questions which are left unanswered in Switzerland have found a legal solution under U.S. law.

Third, information originating from the United States is infinitely *easier to access* than information from Switzerland. For example, accounts of abuses in experimental research are broadly divulged to the American public.[32] The FDA has always acknowledged the value of transparency.[33] In contrast, what happens in Swiss clinical trials tends to stay confidential: there are no lawsuits, no Freedom of Information Act

---

Review ("CDER") issued 40 guidelines. Office of Inspector General ("OIG"), FDA's Review Process for New Drug Applications, A Management Review, at 8, (Mar. 2003) (OEI-01-01-00590), at http://oig.hhs.gov/oei/reports/oei-01-01-00590.pdf [hereinafter OIG (FDA Review)].

21 This Ordinance is the "OClin," see note 8 *supra*.

22 See FDA, Protecting Consumers, Promoting Public Health (Apr. 2000), at http://www.fda.gov/oc/opacom/fda101/fda101text.html; OIG (FDA Review), *supra* note 20, at ii.

23 The full name of Swissmedic is the Swiss Agency for Therapeutic Products.

24 E-mail of Dr Michel Ballif, Swissmedic, (Mar. 28, 2004) (on file with author).

25 *See* OIG (FDA Review), *supra* note 20, at 2. Of these $187 million, $86 were paid by the industry through "user fees." *Id.* Note that all "$" signs refer to U.S. dollars.

26 *See* FDA, Budget Proposal for FY 2003, FDA Talk Paper, (Feb. 4, 2002), at http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01135.html; FDA, Budget Proposal for FY 2004, FDA Talk Paper, (Feb. 3, 2003), at http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01195.html.

27 E-mail of Dr Michel Ballif, *supra* note 24.

28 Letter of the FDA to the Inspector General (Dec. 24, 2002), printed in OIG (FDA Review), *supra* note 20, at 25 (emphasis in the original text).

29 *See* Census Bureau, U.S. Summary 2000, Census 2000 Profile (July 2002), at http://www.census.gov/prod/2002pubs/c2kprof00-us.pdf.

30 Court decisions on the reimbursement of experimental treatments by insurance plans are not taken into account.

31 In its ATF 114 Ia 350, the Swiss Supreme Court had to decide, *in abstracto*, whether a Geneva law requiring informed consent (for ordinary medical interventions and for medical research, though under different terms) was constitutional. The Court did not rule on a concrete case involving clinical trials. In its decision of July 4, 2003 (2A.450/2002), the Court had to rule on the admissibility of an ethic committee. Once again, it was not a decision on a specific clinical trial (*see also infra* note 2135). Finally, in August 2005, the Swiss Supreme Court had decide whether a non-interventional study falls within the definition of a clinical trial and therefore is subject to prior review and clearance by Swissmedic (2A.522/2004).

32 It is also significantly easier to trace back regulation of clinical trials in U.S. history than in Swiss history. There is little historical information available about the IOCM, while the FDA has done excellent work in conserving historical data and making them easily available. *See, e.g.,* FDA, FDA History, at http://www.fda.gov/oc/history/default.htm.

33 See as early as 1973, Peter Barton Hutt, *Philosophy of Regulation under the Federal Food, Drug and Cosmetic Act*, 50 FOOD & DRUG L.J. 101, at 104 (1995), initially published in 28 FOOD DRUG COSM. L.J. 177 (1973).

("FOIA"),[34] and scant investigative journalism.[35] This explains why the section on U.S. scandals is much more detailed than its Swiss counterpart (see subsections 2.2.2. and 2.3.1. below).

Finally, there is a tendency in Switzerland to defer to the opinions of the FDA and, to a similar degree, to those of the European Medicines Agency ("EMEA").[36] It is increasingly perceived as an anomaly that a small country like Switzerland should have a full-fledged regulatory drug system. This is particularly obvious with respect to marketing authorizations.[37] With respect to clinical trials, the question is whether Switzerland could justify regulations that would differ from those of the United States or the European Union. Could it claim that it knows better or that local circumstances warrant different solutions? In my view, the answer is no. Swiss clinical trial regulations should – and will – grow to resemble those of leading industrialized nations – even if this hurts Swiss national pride. Reference to the ICH guidelines (see further subsection 4.3.1. below) illustrates this point: The substantive provisions of the Swiss Ordinance on clinical trials are generally less precise, less clear, and less complete than those of the ICH.[38] A more elegant solution would have been to include in this Ordinance only provisions that add to (e.g., procedural rules), or perhaps contradict, the ICH Guideline.[39]

By and large, Swiss, U.S., and E.U. regulations have a lot in common.[40] When legal provisions are essentially similar, the corresponding reference is simply given in a footnote.[41] However, when Swiss regulations do differ from those of the United States or of

---

[34] In the United States: 5 U.S.C. § 552, at http://www.nih.gov/icd/od/foia/efoia.htm. In December 2004, overcoming some difficulties, the Swiss Parliament succeeded in adopting a Federal Law on the transparency of the administration ("LTrans"), but the law has not yet entered into force.

[35] The same is apparently true for other European countries. See for instance in France, M. Ezratty, *Opening of Symposium*, 4 (special issue) INTERN. J. OF BIOETH. 8 (Mar. 1993).

[36] Home page at http://www.emea.eu.int. This name was changed from "European Agency for the Evaluation of Medicinal Products." See whereas (2) of the Regulation 726/2004 of the European Parliament and of the Council of 31 March 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p.1-33, at http://pharmacos.eudra.org/F2/eudralex/vol-1/REG_2004_726/REG_2004_726_EN.pdf.

[37] Why should Swissmedic duplicate the work that has already been conducted thoroughly in the United States or in the European Union? It makes little sense. Agencies throughout the world are supposed to receive essentially the same files on which they then base their opinions. Hence, the key difference is how they will interpret them. In most cases, all agencies reach the same decision as to whether a marketing authorization should be granted. There are only few instances of disagreement. Do they justify the time and money spent by Swissmedic? This question goes beyond the scope of this thesis and therefore needs not be further explored – although, in my opinion, the answer is no.
See, e.g., interpellation by Swiss Parliamentary member Simonetta Sommaruga of March 22, 2002, and answer of the Swiss Federal Council on June 14, 2002, at http://www.parlament.ch/afs/data/f/gesch/2002/f_gesch_20023168.htm.

[38] The ICH E6 Guideline is made applicable under Article 53.1 LPTh and Article 4.1 OClin.

[39] Ummel and Mandofia made a similar point with respect to the former IOCM regulation and its accompanying Good Clinical Practices; both texts had to be read in conjunction; they overlapped and partly contradicted each other. *See* Marinette Ummel & Marina Mandofia Berney, *Le règlement sur les médicaments au stade d'essai clinique de l'OICM et la protection des sujets de recherche*, 93 SJZ 61 (1997) [hereinafter Ummel & Mandofia]. The same can be said of the OClin and the ICH E6.

[40] To simplify the text, I sometimes refer to the United States, the European Union and Switzerland as *three regions*.

[41] Citation format follows the U.S. "Bluebook." (a uniform system of citation, 17th ed). However, references to Internet (URL) addresses do not strictly follow rule 18.2.1.(b) of the Bluebook. Instead, they are indicated with a simple "at." Moreover, footnotes from cited material are always omitted.

the European Union, the differences are explained in a distinct subsection. Divergences are slightly more frequent *vis-à-vis* U.S. law for two reasons. First, Swiss regulators are particularly careful to maintain compatibility with E.U. law.[42] Second, the FDA tends to act as a pioneer. It usually takes the Swiss agency – Swissmedic[43] – and the European central authority – the EMEA – a few years to emulate the example set by the FDA.[44]

1.4. Plan of the thesis

This thesis is divided in three parts.

Part I goes over *general issues*, starting with an historical overview. It then analyzes the definition of clinical trials and reviews the scope of existing Swiss regulations. It explores economic aspects related to clinical trials. Information in this subsection should contribute to a more accurate understanding of the role and importance of clinical trials.

Part II contains the technical and *scientific standards* governing clinical trials. It describes the role played by all key participants in clinical trials. It presents the various means currently utilized to achieve reliable clinical trial results by minimizing sources of bias.[45] It provides "medical" notions that jurists may not be acquainted with.

Part III focuses chiefly on *legal provisions*. It is the part with the greatest focus on *Swiss* statutory provisions. Part III is further divided into four sections, respectively reviewing the procedures governing trial approvals, the rights of human research subjects (i.e., volunteers in a clinical trial), reporting obligations during a clinical trial, and publication policies after trial completion.

A list of abbreviations and a glossary are provided. Words that are defined in the glossary are indicated in the main text with an asterisk. A short index at the end of the thesis should make it possible to rapidly find particular issues.

You will notice that this text is replete with footnotes, especially in the first two parts of the thesis. To highlight those that contain interesting citations, – as opposed to footnotes only containing supporting data or references to legal norms –, I have put in bold type their footnote reference. I went to great efforts to systematically provide the

---

42 *See, e.g.,* decision of the Swiss appeal commission for pharmaceuticals, JAAC 67.58, at point 2.3.1. (Dec. 23, 2002), at http://www.vpb.admin.ch/franz/doc/67/67.58.html. *See more generally*, Articles 4.2, 9.1, 11.2.a, 14.1, 53.1 LPTh and Article 26.1 OClin referring to international norms. *See also* subsection 4.3.3. below.

43 *See* Swissmedic's home page in English, at http://www.swissmedic.ch/?lang=2.

44 The regulation of orphan* drugs is a good example. To encourage pharmaceutical companies to develop treatments for these rare diseases, the United States offers them special periods of exclusivity (a monopoly right somewhat similar to a patent). The European Union subsequently adopted an analogous system of incentives. *See* Regulation (EC) No 141/2000 of the European parliament and of the Council of 16 December 1999 on orphan medicinal products, in particular at whereas n° (2) and (8), at http://europa.eu.int/eur-lex/pri/en/oj/dat/2000/l_018/l_01820000122en00010005.pdf [hereinafter Regulation 141/2000/EC]. *See also* European Forum for Good Clinical Practice ("EFGCP"), The EFGCP News, at 7 (Spring 2002), at http://www.efgcp.org/webitems/doc/newsletters/2002_Spring.pdf. Switzerland intends to amend the existing OASMéd to facilitate the development of orphan drugs; the changes would take effect in 2005 or 2006.

45 "Bias is any influence that distorts the outcome [of a clinical trial, leading to] erroneous conclusions." *Variability, probability and power*, 4 STATISTICS IN DIVIDED DOSES (May 2002), at http://www.ukmi.nhs.uk/Research/Documents/STATSDIVIDEDNO4.pdf. *See* further subsection 6.3.

URLs for cited documents.[46] URLs are however highly perishable information and I apologize in advance for the inevitable frustration caused by outdated Internet addresses.[47] Given the very large number of references, the bibliography I have included only lists the books and articles most often cited.

Finally, I endeavored to take into account materials published until the end of June 2004.[48] However, important legal changes under Swiss law have been incorporated if they occurred before July 2005.

[46] In addition, some websites require user registration (e.g., Medscape), while others require subscription (e.g., the New England Journal of Medicine).

[47] My website (www.pharmalaw.org) also contains some of the material cited in this thesis (e.g., IOCM documents).

[48] Several Swiss ordinances, including the one on clinical trials, underwent (usually minor technical) changes, which went into force on September 1, 2004. These minor modifications are mentioned *in the footnotes,* usually referring explicitly to the 2004 revision (e.g., under the 2004 OClin revision …).

Part I

2. Historical overview of clinical trial regulations

Drug and clinical trial regulations are an achievement of the second half of the 20th century. While experimentation on animals was well developed already in the mid-1800s,[49] scientific experimentation of drugs on human beings was rare until the beginning of the 20th century.[50] Physicians relied on their own intuition … with the result that most remedies were *at best ineffective*.[51] Scientific experimentation on human beings took off in the 1960s. Concomitantly, reports of experiments started to receive widespread publicity in medical and layman journals.

Nevertheless, until the last quarter of the 20th century, the majority of drugs on the market had not been tested for safety[52] and efficacy, as there was no requirement to do so.[53]. When – exceptionally – drugs had been tested, it was often on unaware human "guinea pigs."[54] Protection of research participants enrolled in clinical studies[55] (i.e.,

---

49 *See, e.g.,* PAUL DE KRUIF, MICROBE HUNTERS (Harvest Book 1926) (an amusing book describing the early achievements of scientific pioneers such as Koch, Pasteur, Roux and Behring).

50 The most famous exception is a controlled experiment on scurvy carried out by physician James Lind in 1747. *See* Colin Currie, *Clinical arithmetic, An Enlightenment legacy still needs defending – against more subtle adversaries*, 327 BMJ 1418-19 (Dec. 20-27, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7429/1418.pdf. *See also* THE SHAPIROS, *supra* note 4, at 125.

51 As the Shapiros argue convincingly, before the era of controlled clinical trials, most existing remedies were little more than placebos – the main exceptions being quinine against malaria starting in the 17th century, aspirin in the 19th century, Paul Ehrlich's salvarsan against syphilis in the early 1900s, insulin replacement therapy in 1921, vitamin treatment for scurvy, sulfonamides in the 1930s, penicillin and streptomycin in the 1950s, digitalis for heart failure in the 1970s. *See* THE SHAPIROS, *supra* note 4, at 20, 32, 75-76. This led to the oft-repeated saying that, until quite recently, at best "the history of medicine was largely the history of the placebo effect." *Id.* at 2. At worse, "the history of medicine is mostly a history of ineffective and often dangerous treatments." Richard Smith, *Do patients need to read research?*, 326 BMJ 1307 (2003), at http://bmj.bmjjournals.com/cgi/content/full/326/7402/1307 [hereinafter Smith (Read Research)]. *See also* John P. Swann, *The Pharmaceutical Sciences in America, 1902-1952*, 41 JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION 829, at 830 (Nov./Dec. 2001).

52 In the United States, safety testing was introduced in 1938 as the upshot of the deaths of several patients, mostly children, who had taken poisonous elixir sulfanilamide. For a review of the 1938 Act, see David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and its Substantive Provisions*, 6 LAW & CONTEMP. PROBS. 2-42 (1939). For more background on the 1938 Act, see FDA, FDA Oral History Program, Interview with William W. Goodrich, Office of the General Counsel, 1939-1971, (1986), Part I, at http://www.fda.gov/oc/history/oralhistories/goodrich/default.htm [hereinafter FDA (Interview Goodrich I)]. *See* also subsection 4.1.1.1.1. below.

53 This legal requirement was first introduced in 1962 in the United States. *See* subsection 4.1.1.2.1. below.

54 *See generally* SUSAN E. LEDERER, SUBJECTED TO SCIENCE (John Hopkins University Press 1995).

55 Here, the words "clinical study," "clinical trial," and "clinical research" are used as synonyms, although literature usually considers clinical trials to be a subset of clinical research. The United States thus distinguishes between three main categories of clinical research: i) patient-oriented research, ii) epidemiologic and behavioral studies, and iii) outcomes and health service research. *See, e.g.,* NIH Director's Panel on Clinical Research Report (Dec. 1997), Executive Summary, at section 2, at http://www.nih.gov/news/crp/97report/execsum.htm [hereinafter NIH 1997 Report]. *See also* NIH, Office of Extramural Research, NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, at section IV.A. (Oct. 2001), at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm [hereinafter NIH (Women Inclusion)].

"subjects") emerged progressively as the consequence of abuses and scandals (see subsection 2.3. below).

Between 1875 and the First World War, people worried about becoming the unwilling object of experimentation.[56] Hospitals were feared, not only because they tended to spread infectious diseases, but also because they were suspected of experimenting with new treatments.[57] The two World Wars shifted the public focus from the protection of vulnerable elements of society exploited in research (e.g., children) to the need for sacrifices for the greater good. At about the same time, the first truly effective treatments (e.g., penicillin) became available.[58] U.S. medical research emerged from the Second World War cast in glory. As a result, the public became thrilled with the potential of scientific and medical progress.[59] For almost twenty years, the protection of research subjects and the regulation of the pharmaceutical industry took the back seat.

2.1. International principles

2.1.1. The Nuremberg Code

Still today, the Nuremberg Code is the text *most often referred to* – though mostly in general terms – in the context of clinical trials. It marks the beginning of a radically different perspective on experimentation. Instead of a purely scientific-medical view point, the Nuremberg Code introduces a legal and ethical perspective.[60] Furthermore, it suggests that this perspective is to prevail over the traditional medical stance. As a result, this Code became the prototype for a succession of many other bioethical norms.[61] Rare are the bioethical statements that do not allude to the Nuremberg Code.

Despite the historical importance of the Nuremberg Code, its *practical* significance was far more limited. For several years following its enactment, it was basically ignored (see below). This paradox deserves an explanation, which is the reason why I have chosen to describe in some details the Nuremberg Code and its consequences, although most readers are probably familiar with this document.

---

56 *See* LEDERER, *supra* note 54.

57 *See* Jochen Vollmann & Rolf Winau, *Informed consent in human experimentation before the Nuremberg code*, 313 BMJ 1445-47 (Dec. 7, 1996), at http://bmj.com/cgi/content/full/313/7070/1445.
This same apprehension is still underscored in an advice issued by the French National Ethics Committee *in 1984*, see CCNE, Avis sur les essais de nouveaux traitements chez l'homme, réflexions et propositions, Avis N°2 [Advice on trials of new treatments on man: thoughts and proposals, Advice N°2], at 6 (Oct. 9, 1984), at http://www.ccne-ethique.fr/francais/pdf/avis002.pdf [hereinafter CCNE N°2].

58 *See supra* note 51.

59 *See* Wendy K. Mariner, *AIDS Research and the Nuremberg Code*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 286, 288 (Oxford University Press 1992). *See also* SPRUMONT, *supra* note 16, at 116.

60 *See generally* Dominique Manaï, *Le contrat de soins entre l'éthique et le droit, in* PACTE, CONVENTION, CONTRAT, MÉLANGES EN L'HONNEUR DU PROF. SCHMIDLIN 301, 303 (Helbing & Lichtenhahn, 1998) [hereinafter Manaï (l'éthique et le droit)].

61 See, for example, the introduction and note 1 to the (U.S.) Belmont Report on Ethical Principles and Guidelines for the Protection of Human Subjects of Research that was adopted by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, (Apr. 18, 1979); the text is available at http://ohsr.od.nih.gov/guidelines/belmont.html [hereinafter Belmont report].

With the end of the Second World War, the Nazi's horrific experiments came to full light. Prisoners in concentration camps had been subjected to experiments that did not even aim at finding or testing possible remedies. While German physicians may have believed that they were engaging in valid scientific projects as part of the war effort,[62] their experiments were mostly torture and genocide under the guise of research.[63] This cruelty had been supported by the German chemical and pharmaceutical industry.[64]

The United States' response was the enactment in 1947 of the Nuremberg Code.[65] The Code is part of the Nuremberg Tribunal's decision in the Doctors' trial (also called the "Medical Case").[66] The Tribunal aimed to bring to justice 26 Nazi doctors and scientists who had tortured and murdered Jews, Slavs, Russians, Gypsies, homosexuals, political dissidents, and prisoners.[67] The trial was led by the U.S. government.[68] The Tribunal's judges and lawyers (for the prosecution) were Americans.[69] The key witnesses

---

62 *See* Jesse A. Goldner, *An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS L.J. 63, at 90 (1993).

63 Nonetheless, Americans and British scientists tried to retrieve the results of Nazi experiments. *See* Paul Weindling, *Human guinea pigs and the ethics of experimentation: the BMJ's correspondent at the Nuremberg medical trial*, 313 BMJ 1467-70 (Dec. 7, 1996), *at* http://bmj.com/cgi/content/full/313/7070/1467.
The dubious position of the United States was further revealed during the Japanese War Crimes trials:

> "The United States had evidence that Japanese physicians had engaged in extensive lethal human experimentation on American prisoners of war in China at Unit 731. These experiments involved freezing, plague, gas gangrene, and other experiments of biological warfare not distinguishable in kind from those performed on concentration camp prisoners by the Nazi doctors. Nonetheless, the United States informed the Japanese physicians of Unit 731 that they would not be prosecuted if they agreed to turn over their records and findings to the United States. At least part of the explanation for this decision seems to be that the United States did not want to reveal the results of the Japanese biological warfare studies to the Russians."

George J. Annas & Michael A. Grodin, *Where Do We Go From Here?*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 307, 310 (Oxford University Press 1992). *See also* PAUL M. MCNEIL, THE ETHICS AND POLITICS OF HUMAN EXPERIMENTATION 23-26 (Cambridge Univ. Press, 1993).

64 For instance, IG Farben, which was later dismantled into Hoechst, BASF and Bayer, wrote to Nazi officers at Auschwitz:

> "In contemplation of experiments with the new soporific drug, we would appreciate your procuring for us a number of women … We received your answer but consider the price of 200 marks a woman excessive. We propose to pay no more than 170 marks a head. If agreeable, we will take possession of the women. We need approximately 150… Received the order of 150 women. Despite their emaciated condition, they were found satisfactory. We shall keep you posted on developments concerning this experiment…. The tests were made. All subjects died. We shall contact you shortly on the subject of a new load."

JOHN BRAITHWAITE, CORPORATE CRIME IN THE PHARMACEUTICAL INDUSTRY 5 (Routledge & Kegan Paul 1984), (citing to JONATHAN GLOVER, CAUSING DEATH AND SAVING LIVES 58 (Penguin 1977)).

65 The text of the Code is available for example from http://bmj.com/cgi/content/full/313/7070/1448.

66 *See, e.g.*, George J. Annas & Michael A. Grodin, *Introduction*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 3, 4 (Oxford University Press 1992); Michael A. Grodin, *Historical Origins of the Nuremberg Code*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 121, at 121 (Oxford University Press 1992) [hereinafter Grodin (Historical Origins)].

67 On the relationship between the charges of genocide and unethical medical experimentation, see Arthur L. Caplan, *The Doctors' Trial and Analogies to the Holocaust in Contemporary Bioethical Debates*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 258, 265 and also 259 (Oxford University Press 1992).

68 The Medical Case was different from the other Nuremberg trials of war criminals, in that these other trials represented a common initiative sponsored by Britain, France, Russia and the United States. *See* Paul Weindling, *supra* note 63. *See also* Jennifer Leaning, *War crimes and medical science*, Editorial, 313 BMJ 1413-1415 (Dec. 7, 1996), *at* http://bmj.com/cgi/content/full/313/7070/1413; Robert F. Drinan, *The Nuremberg Principles in International Law*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 174, 176 (Oxford University Press 1992); George J. Annas, *The Nuremberg Code in U.S. Courts: Ethics versus Expediency*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 201 and 204 (Oxford University Press 1992) [hereinafter Annas (Expediency)].

69 *See, e.g.*, In Re Cincinnati Radiation Litigation, 874 F. Supp. 796, at 820 (S.D. Ohio 1995).

for the accusation were American scientists. The Tribunal applied American procedures.[70]

Although the Nuremberg Tribunal purported to *codify preexisting* ethical principles,[71] there had not been any previous comprehensive (national or international) regulation of clinical trials.[72] At best, one could cite a few isolated national regulatory attempts.[73] The earliest guidelines were adopted by pre-war Prussia at the start of the 20th century.[74] Ironically, the most comprehensive and humane text was a 1931 Nazi Guideline;[75] its ethical principles reached even further than the Nuremberg Code.[76] In the United States, a few courts had taken into consideration the lack of informed consent by the patient to rule on malpractice cases brought against doctors trying experimental treatments.[77]

Paradoxically given the American influence on the entire process, the Nuremberg Medical Trial and the ensuing Code received little press coverage in the United States. Consequently, for the next two decades, researchers saw the Code's relevance as fundamentally limited to Nazi Germany.[78] The Code was also viewed as extremely strict,

---

70 *See, e.g.*, GEORGE J. ANNAS ET AL., INFORMED CONSENT TO HUMAN EXPERIMENTATION: THE SUBJECT'S DILEMMA, at 7 (Ballinger Publishing Company 1977), chapter 1 (Origins of the Law of Informed Consent to Human Experimentation) [hereinafter Annas (Dilemma)].

71 The Tribunal was not entitled to formulate original legal norms. Pursuant to the principle of legality and non-retroactivity, it had to apply *existing* legal principles. *See* Jay Katz, *The Consent Principle of the Nuremberg Code: Its Significance Then and Now*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 227, 236 (Oxford University Press 1992) [hereinafter Katz].

72 *See* Delon Human & Sev S. Fluss, The World Medical Association's Declaration of Helsinki: Historical and Contemporary Perspectives, (July 2001), at 4, at http://www.wma.net/e/ethicsunit/pdf/draft_historical_contemporary_perspectives.pdf [hereinafter Human & Fluss]; Sharon Perley et al., *The Nuremberg Code: An International Overview*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 149, 150 (Oxford University Press 1992); Jay Katz, *supra* note 71, at 228.

73 *See, e.g.*, Grodin (Historical Origins), *supra* note 66, at 124-26 (Oxford University Press 1992); Sharon Perley et al., *supra* note 72, at 150-51 (Oxford University Press 1992).

74 *See* Vollmann & Winau, *supra* note 57. The authors discuss a first 1891 Prussian Directive prohibiting tuberculosis experimentation on unwilling prison inmates. A few years later, a Prussian doctor – Albert Neisser – was accused of having injected syphilis to unwitting patients so as to test his investigational vaccine. Neisser was fined for not having obtained prior consent from his patients. Following the scandal, the Prussian Parliament appointed a commission to investigate unethical conduct by physicians. The Commission issued a report stating basic principles of ethical research. The report was followed in 1900 by a ministerial directive which mandated prior informed consent for experiments taking place in hospitals. However, the directive was not legally binding. *See also* Grodin (Historical Origins), *supra* note 66, at 127-28; Marinette Ummel, La réglementation de l'expérimentation humaine et l'organisation des commissions d'éthique médicale en Suisse, at 3-6, Thèse genevoise médecine, n° 9219 (1991) (on file with the Library of the Medical School at the University of Geneva) [hereinafter Ummel (1990)]; Pierre Dayer, *Limites de la recherche sur l'homme*, 20 CAHIERS DE LA FACULTÉ DE MÉDECINE 57, at 58 (1991) [hereinafter Dayer (Limites)].

75 *See* Vollmann & Winau, *supra* note 57. The Guideline was still in effect during the second World War. *See also* Grodin (Historical Origins), *supra* note 66, at 129-32; Katz, *supra* note 71, at 227.

76 For Grodin, the 1931 Guideline was "visionary in [its] scope and depth." *Supra* note 66, at 131.

77 *See* Annas (Dilemma), *supra* note 70, at 2-3 (in the United States, in addition to three cases from 1767, 1871 and 1895, there has been only "dozen additional cases … prior to World War II, and almost all dealt with them in a substantially similar manner, i.e. treating any departure from standard medical practice as 'experimentation,' and treating experimentation as something improper." *Id.* at 3.).
On the 1960s U.S. malpractice crisis, see OLIVIER GUILLOD, LE CONSENTEMENT ÉCLAIRÉ DU PATIENT, AUTODÉTERMINATION OU PATERNALISME? 33 (Editions Ides et Calendes, 1986) (with reference to informed consent and liability issues).

78 Jay Katz puts it very well: "It was a good code for barbarians but an unnecessary code for ordinary physician-scientists." Katz, *supra* note 71, at 228. *See also* JAMES H. JONES, BAD BLOOD, THE TUSKEGEE SYPHILIS EXPERIMENT 179-80, and 188 (The Free Press 1981) [hereinafter JONES (TUSKEGEE)]; Ruth R. Faden et al., *US Medical Researchers, the Nuremberg Doctors Trial and the Nuremberg Code: A Review of Findings of the*

and thus unpractical.[79] Emblematically, it opens with the compelling principle that "voluntary consent" of research subjects is "absolutely essential."[80] There are no exceptions for incapacitated or underage research participants.[81] This stringent approach is in part imputable to the fact that the Code focuses mainly on *nontherapeutic* research,[82] as none of the Nazi experiments were intended for the benefit of the prisoners-subjects.[83]

Despite the Code, physicians and researchers continued for a long time to believe that they were the ones who ought to decide how to conduct clinical trials.[84] They reckoned that scientific progress for the good of the entire community should take precedence, in particular over the protests of individual patients. In their view, provided that responsible physicians were in charge of research, the state and the public should abstain from meddling in their affairs.[85]

2.1.2. The Helsinki Declaration and other texts

The Nuremberg Code was followed, almost twenty years later,[86] by the Helsinki Declaration.[87] The Declaration was produced by the World Medical Association ("WMA").[88] Despite being more detailed, the Helsinki Declaration was a toned-down adaptation of

---

Advisory Committee on Human Radiation Experiments, 276 JAMA 1667-71 (Nov. 27, 1996), abstract at http://jama.ama-assn.org/cgi/content/abstract/276/20/1667; Leaning, *supra* note 68; Perley et al., *supra* note 72, at 150; SPRUMONT, *supra* note 16, at 24.

79 *See* Annas (Expediency), *supra* note 68, at 204.

80 Article 1 of the Nuremberg Code. See the interesting opposite view on the essential character of consent expressed by H. M. Evans, *Should patients be allowed to veto their participation in clinical research?*, 30 J. MED. ETHICS 198-203 (2004), at http://jme.bmjjournals.com/cgi/content/full/30/2/198.

81 *See, e.g.,* Grodin (Historical Origins), *supra* note 66, at 139; Perley et al., *supra* note 72, at 155; Jeffrey P. Burns, *Research in Children*, 31 CRIT. CARE MED 131-136, at 132 (2003). *See also* subsection 8.4. below.

82 Therapeutic studies aim, at least in part, to benefit the patient, while nontherapeutic studies do not intend to confer any benefit to the volunteer. *See also* subsection 6.1.1.3. below.
For another definition of therapeutic and nontherapeutic research, *see e.g.*, Whitlock v. Duke University, 637 F. Supp. 1463, at 1467 (M.D.N.C. 1986), *aff'd* 829 F.2d 1340 (4th Cir. 1987); Grimes v. Kennedy Krieger Institute, 782 A.2d 807 (Md. 2001).

83 *See* Leaning, *supra* note 68; Leonard H. Glantz, *The Influence of the Nuremberg Code on U.S. Statutes and Regulations*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 183, 185 (Oxford University Press 1992); Mariner, *supra* note 59, at 286.

84 *See, e.g.,* Michelle D. Miller, *The Informed-Consent Policy of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Knowledge is the Best Medicine,* 30 CORNELL INT'L L.J. 203, 204 (1997) [hereinafter M. Miller].

85 *See* JONES (TUSKEGEE), *supra* note 78, at 95-97 (describing the attitude of the medical community in the 1930s).

86 Before the Declaration of Helsinki, in 1954, the World Medical Association had adopted five principles governing medical experimentation. According to its principle 5, "It should be required that each person who submits to experimentation be informed of the nature of, the reason for, and the risk of the proposed experiment." WMA, Principles for those in Research and Experimentation, (1954) at http://www.iit.edu/departments/csep/codes/coe/World_Medical_Association_Principles_for_Those_in_Research_1954.html.

87 On the history of the Declaration of Helsinki, see, for instance, Human & Fluss, *supra* note 72, at 4-6; Perley et al., *supra* note 72, at 157-59; Annas, *supra* note 66, at 204-5; Ummel (1990), *supra* note 74, at 9-10. The text of the 2002 Declaration of Helsinki [hereinafter Helsinki Declaration] is available at http://www.wma.net/e/policy/b3.htm.

88 Already in 1946, the American Medical Association had enacted three short principles. *See* Grodin (Historical Origins), *supra* note 66, at 134.

the Nuremberg Code.[89] It was both made by and aimed at physicians.[90] As such, it was couched in a language that still upheld the traditional superiority of physicians over patients-subjects.[91] At least implicitly, the initial Helsinki Declaration endorsed self-regulation by physicians, in good part to dodge government interference.[92] Hence, in its initial version of 1964,[93] the Declaration imposed consent for therapeutic research only to the extent that it was "consistent with patient psychology."[94] Not until its 1975 revision did it mandate prior approval of clinical trials by ethics committees*.[95]

The year 1966 saw the enactment of the International Covenant on Civil and Political Rights ("ICCPR").[96] Its article 7 prohibits experiments conducted without the "free consent" of the concerned persons. The Covenant is the first multilateral treaty to mention research.[97]

Despite these initial good intentions, it was not until end of the 1960s that the research community began to truly adhere to the chief ethical tenet of informed consent.[98] It certainly did not help that both the Nuremberg Code and the Helsinki Declaration

---

89 "The spirit of the Nuremberg Code was not, and perhaps could not be, taken seriously. Its language was too uncompromising and too inhospitable to the advancement of science that subsequent codes reintroduced by giving physicians-scientists considerable discretion in pursuing their objectives." Katz, *supra* note 71, at 236. *See also Grimes*, 782 A.2d at 850.

90 *See* Mariner, *supra* note 59, at 289.

91 *See* Katz, *supra* note 71, at 231, 234 and 237.

92 *See also* Weindling, *supra* note 63. The same is true for most other guidelines adopted throughout the Western World following the Helsinki Declaration. For Switzerland, see Sprumont's comments regarding the 1970 and 1981 guidelines of the Swiss Academy of Medical Sciences ("SAMS"). SPRUMONT, *supra* note 16, at 185.

93 The initial text of the Declaration is reproduced in the book THE NAZI DOCTORS AND THE NUREMBERG CODE, *supra* note 59, at p.331-33.

94 Under the 1964 Declaration, consent was imperative only for *nontherapeutic* experiments. But, even for these experiments, this key principle was mentioned only toward the end of the Declaration (at section III, point 3a.). *See* Katz, *supra* note 71, at 234; *also* Leaning, *supra* note 68.

Even in the 2000 version, informed consent is only mentioned fairly late in paragraphs 20 and 22. *See also* M. Miller, *supra* note 84, at 217.

95 Ethical committees nowadays are entrusted with the task of reviewing critically clinical trial protocols before the corresponding trials can begin. *See* subsection 7.1.
See paragraph I.1. of the 1975 Helsinki Declaration (revised at Tokyo). *See also* Perley et al., *supra* note 72, at 159.
The United States first introduced this requirement for FDA-regulated clinical trials in 1971. *See, e.g.,* OIG, HHS, FDA Oversight of Clinical Investigators (June 2000), at 11, at http://oig.hhs.gov/oei/reports/oei-05-99-00350.pdf [hereinafter OIG (FDA Oversight)]. According to Sprumont, it was in 1953 that the American NIH first established this obligation for its own trials. *See* SPRUMONT, *supra* note 16, at 95 and 115 (mentioning two different dates).
In Switzerland, as of October 1992, only three cantons had fixed this obligation in their legislation. *Id.* at 219. *See also* Ummel (1990), *supra* note 74, at 22.
Other European countries were also late in implementing this provision of the Helsinki Declaration. For France, see, for instance, CCNE N°2, *supra* note 57, at 5; CCNE, *Recommandations sur les Comités locaux, Rapport,* [Recommendation on local committees, Report] N°13 (Nov. 7, 1988), at http://www.ccne-ethique.fr/francais/pdf/avis013.pdf [hereinafter CCNE N°13].

96 The Covenant entered into force on March 23, 1976; text at http://www.unhchr.ch/html/menu3/b/a_ccpr.htm. For Switzerland, it entered into force in September 1992.

97 *See* Perley et al., *supra* note 72, at 153. See, in Europe, Article 3 of the Convention for the Protection of Human Rights and Fundamental Freedoms, at http://www.echr.coe.int/NR/rdonlyres/D5CC24A7-DC13-4318-B457-5C9014916D7A/0/EnglishAnglais.pdf (prohibiting torture and inhuman or degrading treatments).

98 *See* Faden, *supra* note 78, at 1667-71.

lack binding legal standing.[99] Only few commentators contend that these texts are mandatory as part of public international law or customary law.[100] For most legal authors, they are recommendations that need to be implemented in national legislations to be enforceable.[101] Even the ICCPR is not self-executing.[102]

The last quarter of the 20th century witnessed a multiplication of bioethical initiatives.[103] Famous sets of rules include the CIOMS[104] International Ethical Guidelines for Biomedical Research Involving Human Subjects, first enacted in 1982.[105] The WHO promulgated its own set of Good Clinical Practices in 1995.[106] In 1997, the Council of

---

99 "The rules that they [the Nuremberg Code and the Helsinki Declaration] set out are tenuous, unaccompanied by any real controls, traditional sanctions, or other means of enforcement. Moreover, as a series of general statements, they are ambiguous with respect to both the principles themselves and their practical application." Perley et al., *supra* note 72, at 160. *See also* Annas (Dilemma), *supra* note 70, at 7-9.
Similarly, the Hippocratic Oath, pledged by doctors, is not legally binding. There are different versions of the Hippocratic oath; various examples can be found at http://classics.mit.edu/Hippocrates/hippooath.html, http://www.montchoisi.ch/radiologie/Serment.html, at http://www.indiana.edu/~ancmed/oath.htm.

100 Sprumont holds the view that the Nuremberg Code is mandatory: "il [the Code] constitue en droit international l'expression du jus cogens, à savoir d'un droit impératif auquel les Etats ne peuvent déroger." *See* Dominique Sprumont, *Les principaux modèles de réglementation de la recherche impliquant des êtres humains*, 1 RSDS [Revue Suisse de droit de la santé] 39, at 40-41 (Sept. 2003) [hereinafter Sprumont (RSDS)]. *See also* Perley et al., *supra* note 72, at 152. *See* Annas (Dilemma), *supra* note 70, at 8.

101 There are a few exceptions. For instance, the Court of Appeals of Maryland held that the Code is "part of international common law and may be applied, in both civil and criminal cases, by state, federal and municipal courts in the United States." *Grimes*, 782 A.2d at 835.
A Ohio District Court observed that "[t]he Nuremberg Code is part of the law of humanity. It may be applied in both civil and criminal cases by the federal courts in the United States." *In Re Cincinnati*, 874 F. Supp. at 821. *See also* Annas (Dilemma), *supra* note 70, at 9; paragraph 9 Helsinki Declaration (stating: "No national ethical, legal or regulatory requirements should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.").

102 *See* Abdullahi v. Pfizer, 2002 U.S. Dist. LEXIS 17436 (S.D.N.Y. 2002).

103 "In December 1999, a 20-page, small-print publication identified 62 intergovernmental and nongovernmental international agencies that had produced guidelines on a wide variety of bioethical topics and 29 miscellaneous international texts produced by ad hoc tribunals, congresses, and the like, beginning with the 1947 Nuremberg Code." Bernard M. Dickens, *The Challenge of Equivalent Protection*, *in* ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES, VOLUME II, COMMISSIONED PAPERS AND STAFF ANALYSIS, at A-15, (National Bioethics Advisory Commission, May 2001), at http://www.georgetown.edu/research/nrcbl/nbac/clinical/Vol2.pdf.
On the origin of the bioethics discourse, see for instance Gary S. Belkin & Allan M. Brandt, Bioethics: Using its Historical and Social Context, 39 (3) INT ANESTHESIOL CLIN. 1-11 (Summer 2001). *See also* SPRUMONT, *supra* note 16, at 66-67.
For a criticism of both rigid codes and blind adherence to them, see Henry K. Beecher, *Consent in clinical experimentation: myth and reality*, 195 JAMA 34 (Jan. 3, 1966) [hereinafter Beecher (Myth)]; Henry K. Beecher, *Some guiding principles for clinical investigation*, 95 JAMA 1135 [hereinafter Beecher (Guiding)].

104 "The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949." CIOMS, What is CIOMS?, *at* http://www.cioms.ch/frame_what_is_cioms.htm.

105 The CIOMS Guidelines were revised in 1993 and 2002; they are mainly oriented toward research in developing countries. *See* CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), at http://www.cioms.ch/guidelines_nov_2002_blurb.htm [hereinafter CIOMS 2002 Guidelines].
See also Christian Byk, *Les règles Internationales d'Ethique pour la Recherche Biomédicale impliquant des Sujets Humains*, 4(4) INTERN. J. OF BIOETH. 299-302 (1993) (on the 1993 revision of the CIOMS guidelines); Perley et al., *supra* note 72, at 160-65.

106 *See* WHO, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, TRS850-Annex 3, (1995) at http://www.who.int/medicines/library/par/ggcp/GCPGuidePharmatrials.pdf. *See also* Juhana Idänpään-Heikkilä, *Harmonisation globale, Directives de l'OMS pour de bonnes pratiques cliniques*, 39(2) CMS 223-29 (1995).

Europe adopted the Convention on Human Rights and Biomedicine;[107] it is to be completed by protocols, including one on clinical research.[108] This Convention has been signed by the Swiss Federal Council, but not yet ratified by the Parliament.[109]

2.1.3. Three central ethical principles

All bioethics texts assert, in one way or another, the same key principles: autonomy, beneficence and justice.[110] These principles have specific embodiments in the context of clinical trials.

Autonomy (also referred to as *respect* for the person) implies that the decision to participate in a clinical trial belongs only to the subject; this decision is predicated on the latter's informed assessment of risks and benefits (for further analysis of the requirements of informed consent, see subsection 8.3. below).[111] Vulnerable subjects (see subsections 8.4. and 8.5. below) should benefit from additional protection.[112]

Beneficence obliges physicians and scientists not only to do no harm (to subjects),[113] but also to do good: risks must be minimized and benefits maximized.[114] It implies,

---

107 The full title is Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to the Application of Biology and Medicine. It was signed on April 4, 1997 at Oviedo. It entered into force in the first five signatory countries on December 1, 1999. The text is available at http://conventions.coe.int/treaty/en/treaties/html/164.htm [hereinafter Biomedicine Convention].
Switzerland considers that most of the provisions of the Convention are (will be) self-executing. *See, e.g.,* the Federal Council's Message on the Convention of September 12, 2001, 2002 FF 271, at 273 and 285.

108 Additional protocols under the Biomedicine Convention are in preparation, in particular one on biomedical research (see *infra* note 417). *See also* letter of the Federal Office for Public Health ("FOPH") of Nov. 26, 2001, submitting the protocol to consultation.

109 Switzerland signed the Convention on May 7, 1999, but the Swiss Parliament has not (yet) ratified it. *See* Federal Council's accompanying Message, *supra* note 107, at 278, at http://www.ofj.admin.ch/themen/bioeth/bot-konvention-f.pdf; see also the webpage of the Swiss Federal Department of Foreign Affairs ("DFA") regarding this Convention at http://www.eda.admin.ch/intagr/f/foreign/e_99991841.html. The United States and the European Community (as such) have not signed it.

110 *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 12 (adding, as a distinct norm, the principle of nonmaleficence); Swiss Academy of Medical Sciences (SAMS), Directives pour la recherche expérimentale sur l'être humain, [Directive for experimental research on human beings] (June 5, 1997), at point B, p.5, at http://www.samw.ch/content/Richtlinien/f_Forschungsunters.pdf [hereinafter SAMS 1997 Guidelines]; CIOMS 2002 Guidelines, *supra* note 105, in the introductory section on General Ethical Principles.
Other commonly cited principles include non-exploitation, non-discrimination, non-instrumentalization, and proportionality. *See however* R. Gillon, *Ethics need principles – four can encompass the rest – and respect for autonomy should be "first among equals,"* 29 J. MED. ETHICS 307-312 (2003), at http://jme.bmjjournals.com/cgi/content/full/29/5/307. See also the other articles published in this number of the Journal of Medical Ethics.
See also SPRUMONT, *supra* note 16, at 62-65; European Group on Ethics in Science and New Technologies to the European Commission, Opinion N°17, at 15, at point 2.2, (Feb. 4, 2003), at http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf [hereinafter EGE].

111 *See* SPRUMONT, *supra* note 16, at 59, at 62-64 and at 68.

112 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, in the introductory section on General Ethical Principles.

113 Some ethicists distinguish the principle of nonmaleficence from the principle of beneficence, while others consider that the second principle already includes the first.

114 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, in the introductory section on General Ethical Principles. *See also* MANAÏ (CONTEMPORAINE), *supra* note 16, at 252.

among other things, that an external third party, nowadays typically an ethics committee, has assessed the risks and benefits for all subjects as well as for society and has reached the conclusion that the study is designed so that the benefits outweigh the (duly minimized) risks (see subsection 7.1.2.5. below).[115]

Justice requires notably that benefits and risks of research be fairly distributed across the populations concerned: subjects who participate in the research should not bear an unfair burden or gain inordinate benefits compared to those who do not (for further information, see subsection 8.1.6. below).[116]

These principles occasionally come into conflict. For example, parents may insist that their child be enrolled in a clinical trial in order for him to receive access to a promising new drug. This wish may conflict with physicians' and regulatory authorities' perception that the safety risks are too high to allow children to participate in this clinical trial. Is the principle of autonomy (here the decision of the parents) to prevail over the principle of beneficence (here, the authorities' view that the risks are too high)?

Although sorting out these principles according to their importance is necessary, all classifications are controversial. Nowadays, a majority of people agree that autonomy should take precedence.[117] This acknowledgment of the patient's will is the result of a sustained effort to recognize the patient as the doctor's partner, and not just as a child in need of protection.

2.1.4. Patient empowerment

The regulation of clinical trials has evolved hand in hand with patient autonomy and empowerment.[118] It is associated with a marked decline in physicians' "benevolent paternalism" toward patients.[119] Initially, doctors considered that curing their patients

---

115 Beneficence relates to the overall assessment of risks and benefits. It also posits that the interests of subjects must prevail over the interest of science. The language of the Council of Europe's R(90)3 Recommendation is particularly strong: "[i]n medical research the interests and well-being of the person undergoing medical research must always prevail over the interests of science and society." *See* Principle 2.1. *See also* section 2.3 (p.9) of ICH E6 ("The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society."). The text is available at http://cm.coe.int/ta/rec/1990/90r3.htm. *See also* SPRUMONT, *supra* note 16, at 60 and at 64.

116 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, in the introductory section on General Ethical Principles. *See also* SPRUMONT, *supra* note 16, at 65.

117 *See* SPRUMONT, *supra* note 16, at 60-62. *See also* CCNE, Consentement éclairé et information des personnes qui se prêtent à des actes de soin ou de recherche, Avis N°58, [informed consent and information of people asked to take part in treatment or research activities, Advice N°58] (June 12, 1998), at preamble, at http://www.ccne-ethique.fr/francais/pdf/avis058.pdf [hereinafter CCNE N°58].

118 "Autonomy, or the right to make one's own decisions, is desirable ultimately because it endows the individual with control over his or her own choices and the ability to make those choices consistent with self-interest." William DuBois, *New Drug Research, The Extraterritorial Application of FDA Regulations, and the Need for International Cooperation*, 36 VANDERBILT J. OF TRANSNATIONAL L. 161, at 335 (2003), at http://law.vanderbilt.edu/journal/36-01/DuBois-5.pdf.

119 The Shapiros pointed to many different factors to explain the trend toward patient autonomy. "Other more relevant factors also contributed to the changing face of medicine. These factors included the sense of alienation associated with the Vietnam War, the drawing together of patients on Medicare, Medicaid, and prepaid and managed care, the increased costs of medical care, and mistrust of authority. Other factors included the growing counterculture, the civil rights movement, the women's movement, and concern about

was more important than anything else.[120] To reach this goal, engaging in research was a duty, not just a choice.[121] As for the patient, his own duty was to follow the orders given by his doctor.[122] The patient and the doctor were not partners allied in the pursuit of a common goal: only the doctor was in command and able to take decisions.

It took the AIDS crisis starting in the mid-1980s[123] to eradicate the remnants of the condescending attitudes of the medical community.[124] The AIDS epidemic led patients to band together in order to push their own agenda for medical research in general, and for clinical trials in particular.

> [These patients] empowered themselves in ways never seen before in the health-care arena. Confronted by government apathy and corporate neglect, they refused to remain passive or to be victimized. Instead, they stood on the shoulders of the social revolutions that came before – the civil rights struggle, the peace movement, the women's movement, and the drive for gay rights….[125]

The activism of AIDS patient advocacy groups and support associations significantly altered the face of clinical research. The AIDS movement in turn inspired other patient movements linked with other medical conditions, such as cancer and orphan* diseases.[126] The Internet contributed to this trend by widely disseminating information at practically no cost.[127]

Nowadays, patients and their organizations increasingly demand to be involved at virtually all stages of the drug development process. They insist on giving their input – be it welcome or not – as to which drugs should be developed, how, when, where and

---

the rights of minorities, women, and children, as well as concern about civil liberties." THE SHAPIROS, *supra* note 4, at 210.
On physicians' paternalism, see Jay Katz, *Le consentement éclairé doit-il rester un conte de fées?*, Colloque, Le Consentement Eclairé du Patient, Institut Universitaire Kurt Bösch, Cahier n°4, at 10-12 (Sept. 6, 1993).

120 *See generally* GUILLOD, *supra* note 77, at 27.

121 Even the SAMS 1997 Guidelines state that the "medical science has the *duty* to research constantly" new cures. SAMS 1997 Guideline, *supra* note 110, at point D.1. at 9 [my own translation].
See also, in France, CCNE N°2, *supra* note 57, at 2.

122 *See generally*, CCNE N°58, *supra* note 117, at 6-8 and 10-11.

123 On the history of the AIDS crisis, see LAURIE GARRETT, THE COMING PLAGUE 281-389 (Penguin 1994).

124 See in Switzerland Philippe Esnault, *Regard d'un patient sur l'information médicale*, 39(4) CMS 365-72 particularly at 367-68 (1995).

125 PETER S. ARNO & KARYN L. FEIDEN, AGAINST THE ODDS 2 (HarperCollins 1992).

126 In the United States, an orphan drug is one that targets a disease that affects less than 200,000 people on the U.S. territory. In addition, there must not be a "reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug." *See also* Stoa, Orphan Drugs, Legal Framework,
http://www.europarl.eu.int/stoa/publi/167780/chap3_en.htm.
In the European Union, compare with Article 3 of Regulation 141/2000/EC, *supra* note 44.

127 *See, e.g.*, DANIEL VASELLA & ROBERT SLATER, MAGIC CANCER BULLET, HOW A TINY ORANGE PILL IS REWRITING MEDICAL HISTORY 16-17 (HarperBusiness 2003) ("Today's patients are a demanding a lot. … They have taken to the Internet with a vengeance, and because of the resources available on-line, they are smarter than ever, discovering drugs at a very early stage of development; alerting their physicians to new drugs and therapies. I had every reason to believe that this Internet generation of patients had the potential of making life difficult for a pharmaceutical company that did not live up to their expectations."). *See also id.* at 95 and at 122-123.
See on the negative consequences, BRUNO DONATINI, L'INTOX, QUELQUES VÉRITÉS SUR VOS MÉDICAMENTS, 30 (Ed. M.I.F. 1997).

at what price.[128] Drug development is no longer the exclusive province of pharmaceutical companies, biomedical researchers and governmental agencies.[129]

2.1.5. A fundamental shift from a burden to a benefit

The AIDS protests also highlighted another fundamental change affecting clinical trials. Participating in a trial was no longer viewed as a burden typically falling on the most vulnerable members of society (e.g., poor patients lacking full health insurance coverage); rather, it became a privilege worth fighting for.[130] There were stories of AIDS and cancer patients who called upon their friends in politics to be granted a place into the clinical trial of their choice.

Now rich and educated patients want to participate in clinical trials. Their motivations are simple: the chance to have access to a potentially life-saving drug when all other alternatives have been exhausted. Moreover, patients participating in clinical trials tend to get better care and achieve better medical outcome than do comparable patients treated in ordinary settings.[131] Finally, clinical trials provide treatments for free, a clear advantage in the United States where insurance coverage of prescription drugs is far from universal.[132]

Of course, this change mainly concerns clinical trials of lethal diseases for which no satisfactory therapy is available. Clinical trials of mild conditions and well-treated conditions are not as appealing. Nonetheless, this constitutes a fundamental paradigm shift. Now, regulators must not just worry about socially deprived patients being exploited in clinical research, they also need to make sure that these patients are not deprived of a significant benefit when they are barred access to desirable clinical trials.

This ironical schism also affects pharmaceutical companies. At pain to recruit for some of their clinical trials, they have to refuse patients in others. They are accused of

---

128 Wendy Mariner remarks that the extreme approach of AIDS groups could ultimately eradicate the scientific notion of clinical trials. *Supra* note 59, at 292-7.

129 The government is involved at two junctures: giving out research grants to academic scientists and deciding on the application for drug approval. *See, e.g.*, Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 295 LEGISLATION AND PUBLIC POLICY 295, at 296 (2000) (commenting on FDA's "institutional paternalism" in the wake of the AIDS crisis), at http://www.law.nyu.edu/journals/legislation/articles/vol3num2/greenberg.pdf.

130 *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 203. *See also* Vanessa Merton, *The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (a.k.a. Women) from Biomedical Research*, 19 AM. J. L. AND MED. 369, at 376-77 (1993).

131 "The very nature of protocols, which require standardized and frequent observations to follow outcome, provides the patient with a better assessment of therapeutic result, more safety checks, more attention from the physician and staff, and more access to the medical system. The screening process provides an excellent overall health assessment. The physicians undertaking the research, the consultants, and the laboratories are usually among the best in the community and provide state-of-the-art diagnosis and advice. As a part of the process of encouraging continuation in the study, the attitudes of health providers shift from acting as though they are doing the patient a favor to seeking to please the patient who is doing them a favor. This shift is reflected in waiting time, friendliness, and overall efficiency in using the patient." Merton, *supra* note 130, at 379.

132 *Id.* at 378. "[An] … estimate of the number of people who were uninsured for all of 1998 – the most recent year for which reliable comparative data are available – is 21 million to 31 million, or 9 percent to 13 percent of nonelderly Americans." U.S. Congressional Budget Office ("CBO"), How Many People Lack Health Insurance and For How Long?, at 2 (May 2003), at ftp://ftp.cbo.gov/42xx/doc4210/05-12-Uninsured.pdf.

exploiting underprivileged subjects in developing countries, while being criticized by patient associations in industrialized countries for imposing strict eligibility criteria for other clinical trials. For example, when the pharmaceutical company Glaxo declined to expand its compassionate access programs to AIDS patients, the association Act-up called for a boycott of popular Glaxo products (for which alternatives existed).[133]

One should constantly keep in mind this paradox. For some patients, a clinical trial is a uniquely valuable opportunity – for others, trials are ripe with risks and abuses.

2.2. Historical overview of Swiss regulations on clinical trials

2.2.1. Successive Swiss regulations of clinical trials

2.2.1.1. Cantonal regulations

Before 1995, Swiss clinical trials were regulated – if at all – by each canton separately. Cantonal legislations were scattered, inconsistent and vague.[134] Many cantonal legislators had paid no attention whatsoever to the problems raised by clinical trials; only fourteen cantons regulated research conducted on human beings, while twelve had no provision on the subject.[135] In Geneva, a popular initiative submitted in 1983 led the canton to adopt, in 1987, a law requiring informed consent for all medical interventions and *written* consent for all research and non-standard medical procedures.[136]

2.2.1.2. Prescriptions of the Swiss Academy of Medical Sciences

Subsequent to the first Helsinki Declaration, the Swiss Academy of Medical Sciences ("SAMS") established its own guidelines in December 1970.[137] Because the SAMS is a private entity, its guidelines are not directly mandatory.[138]

---

133 See Act-up page on the boycott at http://www.actupny.org/actions/glaxo-Boycott.html.

134 *See* SPRUMONT, *supra* note 16, at 186-202 and also at 282. Most cantonal legislations were adopted in the late 1980s. *See also* D. Sprumont & M.-L. Béguin, *La nouvelle réglementation des essais cliniques de médicaments*, 83 BULLETIN DES MEDECINS SUISSES 894-906, at 894 (2002), at http://www.saez.ch/pdf/2002/2002-18/2002-18-342.PDF; Marinette Ummel, *Les commissions d'éthique en Suisse, Développements factuels et questions critiques*, 39(1) CAHIERS MÉDICO-SOCIAUX, 81-82 (1995) [hereinafter Ummel (CMS)]. *See also* SAMS 1997 Guideline, at the preamble (also pointing out, several years later, the persistent disarray of existing legislations).

135 *See* SPRUMONT, *supra* note 16, at 186-87, at 207 and at 221.

136 See the former Geneva Law regarding relationships between members of health care professions and patients of December 6, 1987, in particular its Article 6; in French: "*Loi concernant les rapports entre membres des professions de la santé et patients*"; K 1 30 [hereinafter Geneva Regulation K 1 30]; current text in French at http://www.geneve.ch/legislation/rsg/f/s/tab/K1_80.html. *See also* ATF 114 Ia 350, at 353-54, at points A and B.

137 *See* SAMS 1997 Guideline, *supra* note 108. The first version was adopted in December 1970. The Guidelines were then modified in November 1981; the 1981 text is hereinafter referred to as the SAMS 1981 Guidelines. The 1981 Guidelines have been published in: Directives et recommendations d'éthique médicale de l'Académie Suisse des sciences médicales (Schwabe & Co AG, Basel, 1984).
See SPRUMONT, *supra* note 16, at 184-85. On the history of SAMS and its early guidelines, see Ummel (1990), *supra* note 74, at 22-23, respectively at 24-27.

As did the Helsinki Declaration, the early SAMS Directives of 1970 and 1979 stressed the distinction between innovative treatment (where research was combined with medical treatment for the expected benefit of the patient-subject, also called therapeutic studies) and more fundamental clinical research (called purely experimental studies or nontherapeutic studies).[139] Informed consent was absolutely required only for those studies belonging to the second category.[140] For therapeutic studies, consent was to be obtained to the extent feasible given the patient's psychological state.[141] This departure from the rule of informed consent was rectified in 1989.[142]

Prior review of clinical trial protocols*[143] by ethics committees was recommended.[144] It was made "mandatory"[145] by the 1989 SAMS Guidelines on the organization of ethics commissions.[146] The essential contents of these SAMS Guidelines were incorporated in the 2002 federal regulatory system.[147]

2.2.1.3. General federal provisions on informed consent

The most basic rule of informed consent was (and still is) imposed, albeit somewhat indirectly, by the federal Penal Code[148] as well as by general principles of constitutional,[149] civil,[150] tort[151] and contract[152] law.[153] Under these principles, an intervention

---

138 SAMS Guidelines only become binding if the canton incorporates them into its legislation. *See also* SPRUMONT, *supra* note 16, at 183 and 185-86; MANAÏ (CONTEMPORAINE), *supra* note 16, at 36-39; Ummel (1990), *supra* note 74, at 24.

139 Point I. SAMS 1981 Guidelines. On the distinction between therapeutic and nontherapeutic studies, see subsection 6.1.1.3. below.

140 Point IV. SAMS 1981 Guidelines.

141 Point III.1. SAMS 1981 Guidelines.

142 The (former) SAMS Guidelines contained exceptions to the informed consent requirement; they pertained to emergency and epidemiological research. Point 7.4 of the (former) SAMS 1989 Guidelines. See point 7.4 of the (former) Directives pour l'organisation et l'activité des commissions d'éthique médicale chargées de l'examen des projets de recherche expérimentale sur l'homme, (May 11, 1989), now abrogated [hereinafter (former) 1989 Guidelines].

143 A protocol is the written document that describes in details how a clinical trial is to be conducted. *See* subsection 6.2.1. below and the glossary.

144 Point II.7. SAMS 1981 Guidelines.

145 Once again, SAMS Guidelines are neither legally compulsory nor self-executing, unless cantons have decided to incorporate them into their own legislation. *See supra* note 138.

146 *See* SAMS 1989 Guidelines, *supra* note 142.

147 Compare for example point 3 of the (former) SAMS 1989 Guidelines with Articles 30 to 32 OClin, or point 7.8 of the SAMS 1989 Guidelines with Articles 20 to 23 OClin.

148 *See* SPRUMONT, *supra* note 16, at 229. *See, e.g.,* Groupe de travail, Réglementation des essais cliniques, Rapport Final, (Sept. 2000), at 6 [Working Group, Regulations of clinical trials, Final Report] (on file with the author) [hereinafter VanTx Report] (the Attorney General of the Basle Canton initiated a criminal investigation against the VanTx investigator for the criminal offense of bodily harm to human research subjects).
When the State itself conduct experiments on uninformed subjects, the latter can invoke constitutional protections. See in the United States, *In Re Cincinnati*, 874 F. Supp. 796.

149 *See, e.g.,* Jean-Emmanuel Rossel, *L'effet horizontal des droits fondamentaux et son application en droit médical*, *in* ASPECTS DU DROIT MÉDICAL, at 59-74 (Editions Universitaires Fribourg 1987); Michel Rossinelli, *Aspects constitutionnels des droits des patients*, in the same publication, at 53.

150 *See* Article 27 ff of the Swiss Civil Code ("CC"). *See also* SAMS 1997 Guideline, *supra* note 110, at point A.1. *See also* Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 291.

151 *See, e.g.,* ATF 114 Ia 350, at 358-59, at point 6.
See also under U.S. law, Goldner, *supra* note 62, at 70. In the United States, "the judicial development of the legal doctrine of informed consent initially was tied to the legal concept of battery, a non-consensual, inten-

that affects (even slightly) the physical integrity of a person is illegal, unless done with that person's consent.[154] Hence, if a patient is harmed during a medical procedure (including a drug treatment), the doctor is punishable to the extent that she has not sought the patient's consent.[155] The accidental or even inevitable nature of the harm done does not – usually – negate this liability.[156] This rule stands whether the treatment is standard or experimental. Early legislations in Switzerland but also everywhere else tended to treat patients and research subjects essentially in the same manner.[157]

However, criminal, contract and tort law only confers limited protection since they do not specify to which extent the patient or subject's consent has to be informed. Doctors are guilty of a long-standing tradition of not sufficiently explaining the treatments they choose to administer to their patients. They tend to consider that a patient's *general* consent implicitly covers all aspects of the treatment, even though each aspect may not have been individually explained and discussed. In other words, doctors assume that, when a patient willingly consults them for a given medical problem, this patient automatically agree to whatever treatment they recommend.

2.2.1.4. Former intercantonal regulations

In November 1993, the Intercantonal Office for the Control of Medicaments ("IOCM") – the executive body of the intercantonal convention that governed drug approval between 1900 and 2001[158] – enacted its first regulation specifically on clinical trials.[159] This 32-page text entered into force on the 1st of January 1995.[160]

---

tional touching. That theory, in turn, developed out of a basic judicial regard for the principle of individual autonomy, reflecting the belief that an individual has the right to be free from non-consensual interference with his or her person." *Id.* at 74. *See, e.g.,* Scott v. Bradford, 606 P.2d 554, at 557 (Okl. 1979); Canterbury v. Spence, 464 F.2d 772, at 783 (D.C.Cir. 1972).
See also GUILLOD, *supra* note 77, at 65-66; Dennis J. Mazur, *Influence of the law on risk and informed consent*, 327 BMJ 731 (Sept. 27, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7417/731.pdf.

152 Given that the relationship between a doctor and a patient is deemed a contract of mandate, liability of the former toward the latter is governed, under Swiss law, by Article 398 (cum Article 97) of the Swiss Code of Obligations ("CO"). Under this provision, the doctor is liable if he breaches his duties of care and thus causes harm to his patient.

153 *See also generally* SPRUMONT, *supra* note 16, at 221-22; GUILLOD, *supra* note 77, at 37-38.

154 *See, e.g.*, Article 125 of the Swiss Penal Code, available at http://www.admin.ch/ch/f/rs/3/311.0.fr.pdf. *See also* ATF 99 IV 208 = JdT 1974 IV 132; ATF 117 Ib 197, at 200-201 = JdT 1992 I 214, at 216-217; ATF 113 Ib 420 (at point 4) = JdT 1989 I 26 (at point 4). *See also* GUILLOD, *supra* note 77, at 40.
In the United States, see for instance Schloendorff v. The Society of the N.Y. Hospital, 211 N.Y. 125, at 130-13 (N.Y. Ct.App. 1914) ("a surgeon who performs an operation without his patient's consent, commits an assault, for which he is liable in damages.").

155 *See, e.g.,* Dominique Manaï, *Le devoir d'information du médecin en procès*, 2000 SJ 341, at 344 [hereinafter Manaï (procès)].

156 See the Swiss Supreme Court decision at ATF 108 II 59, at 62, at point 3.

157 *See* SPRUMONT, *supra* note 16, at 207-208. *See also* Ummel (1990), *supra* note 74, at 2.
Nowadays, it is commonly accepted that the information given to the research subject must be more extensive than that offered to a patient, receiving standard care. Subjects also benefit from additional safeguards that "standard" patients do not enjoy (e.g., special insurance coverage in case of injuries). *Id.* at 208-209.

158 *See generally* PATRICIA LUTHY, ENREGISTREMENT ET CONTRÔLE DES MÉDICAMENTS SUR LES MARCHÉS DES PRODUITS PHARMACEUTIQUES SUISSE ET EUROPÉEN, 52-54 (Thèse Lausanne, Payot 1993).

159 *See* Règlement sur les médicaments au stade d'essais cliniques, [Regulation on Medicines in Clinical Studies (translation previously proposed by the IOCM on its website)]; November 18, 1993; N°230.1, at http://www.pharmalaw.org/O_reglementessaiclinique.pdf [hereinafter IOCM 1995 Regulation].

The purpose of this regulation (hereinafter the 1995 IOCM Regulation) was to introduce, at the intercantonal level, key safeguards for research participants.[161] For the first time a uniform system was implemented throughout Switzerland.[162] Prior approval by a research ethics committee ("REC"[163]) became a necessary condition for conducting clinical trials. The IOCM also asked to be notified of trials before they started. Clinical trials had to conform to Good Clinical Practices ("GCP"), which were stated in Annex I.[164].

2.2.1.5. Comprehensive federal regulations: the LPTh and the OClin

On January 1, 2002, seven years after the aforementioned IOCM regulation, the intercantonal[165] system gave way to the Federal Law on therapeutic products ("LPTh").[166] The LPTh is accompanied by several Ordinances, including the Ordinance on clinical trials ("OClin").[167]

The regulation project was prepared by a group of experts led by Professor Pierre Dayer. *See* Theodore Weber, *La recherche clinique en Suisse: le point de vue de l'Office intercantonal de contrôle des médicaments*, 39(2) CMS 231 (1995). On the development of the IOCM 1995 Regulation, *see also* Dominique Sprumont, *De l'éthique au droit: la réglementation des recherches sur l'être humain dans l'ordre juridique suisse*, 39(2) CMS 133, at 148-49 (1995) [hereinafter Sprumont (De l'éthique)]; Jean-Christophe Méroz & Dominique Sprumont, *Le Règlement de l'OICM sur les médicaments au stade d'essai clinique, Points de repère pour les investigateurs*, 75 BULLETIN DES MÉDECINS SUISSES 674-75 (Apr. 27, 1994) [hereinafter Méroz & Sprumont]. *See also* SPRUMONT, *supra* note 16, at 278-79 (broadly admitting the jurisdiction of the authorities under the Intercantonal Convention)
See also Article 8ter.2 of the IOCM Regulation on the Execution of the Convention, at http://www.pharmalaw.org/Reglement%20de%20la%20Convention_OICM.pdf. This provision entered into force in October 1994. *See also* Instructions de l'OICM pour la présentation des demandes d'enregistrement de specialités pharmaceutiques contenant de nouveaux principes actifs et destinées à l'usage human, [IOCM Guidance for the Submission of Registration Applications of Pharmaceutical Specialties for Humans with New Active Substances], part IV, (Feb. 14, 1989), at http://www.pharmalaw.org/O_InstructionsOICM.pdf.

160 Article 17 of the (former) IOCM 1995 Regulation.

161 *See* Méroz & Sprumont, *supra* note 159, at 676.

162 *See, e.g.,* Ummel & Mandofia, *supra* note 39, at 57.
This uniformity was supported by the Swiss pharmaceutical industry. *See* Bernard Indermühle, *Point de vue de l'industrie pharmaceutique sur la recherche clinique en Suisse*, 39(2) CMS 241, at 241-42 and 245 (1995).

163 This abbreviation REC is used for example in the United Kingdom. *See* EFGCP, The EFGCP News, at 15 (Winter 2001), at http://www.efgcp.org/webitems/doc/newsletters/2001_Winter.pdf. Another abbreviation in use is "IECs" which stands for "Independent Ethics Committees." *See, e.g.,* EFGCP, European Guidelines for Auditing Independent Ethics Committees, at 3, (2001), at http://www.efgcp.org/webitems/EFGCP_IEC_Audit.pdf [hereinafter EFGCP (Auditing IECs)].

164 These IOCM's GCP were organized in five main chapters, the first one dealing with the protection of research subjects and with the consultation of ethics committee. These GCP were inspired by the European GCP. They also resemble the ICH E6 Guideline on Good Clinical Practice (which was adopted later in May 1996). *See* Weber, *supra* note 159, at 232.
On the reasons underlying the distribution of rules among the 1995 Regulation and its Annex, see Sprumont (De l'éthique), *supra* note 159, at 149.

165 The 2002 Federal Regulation also abrogated the ordinance on clinical trials of immunobiologic products of June 26, 1996 (FO 1996 2342). *See* Article 35 OClin.

166 More specifically, its chapter 4, section 2 (articles 53 to 57) applies to clinical trials.

167 Since 2003, the administration and Swissmedic have been preparing a second and third set of ordinances. The second set of ordinance entered into force on September 1st, 2004. It had limited impact on the conduct of clinical trials and does not directly concern clinical trials. *See also supra* note 48. The third set of ordinance has been submitted for comments. *See* FOPH, Droit d'application des produits thérapeutiques, train

The LPTh and OClin provisions regarding clinical trials are modeled after the former IOCM regulation.[168] The OClin also closely resembles the European Union's 2001/20/EC Directive,[169] which entered into force on May 1, 2001, just a few months before the OClin.[170]

The OClin and the E.U. Directive also share a common source of inspiration: the ICH (International Conference on Harmonization) guideline on Good Clinical Practice (hereinafter "ICH E6").[171] The ICH finalized this detailed guideline in May 1996 with the purpose of unifying clinical research in the three main ICH regions (i.e., the United States, the European Union and Japan) (see subsection 4.3.1. below).[172] Good Clinical Practices ("GCP") are defined as "a set of internationally recognized ethical and scientific quality requirements that must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects."[173] GCP are inherently international standards, even though each country or region may well have its own, slightly different, internal version of GCP. Because of this shared origin, national regulations of clinical trials tend to resemble each other. Comparisons between Swiss, European and U.S. regulations are not only facilitated, but also apposite (see subsection 1.3. above).

---

d'ordonnances II [Executive provisions on therapeutic products: set of ordinance II] (Aug. 18, 2004), at http://www.bag.admin.ch/heilmitt/aktuell/f/index.htm et http://www.bag.admin.ch/heilmitt/gesetz/f/index.htm; Swissmedic, Letter to interested groups (June 16, 2005), at http://www.swissmedic.ch/files/pdf/Begleitbrief_AH_fr_Scan.pdf and the relevant documents from http://www.swissmedic.ch/fr/industrie/overall.asp?lang=3&theme=0.00105.00002&theme_id=518&news_id=4568&page=1.

168 *See* the FOPH's explicative report regarding the draft Ordinance on clinical trials, at 3, (Dec. 2000), at http://www.bag.admin.ch/heilmitt/gesetz/verord/f/vklinver_erl.pdf.

169 The full name of the Directive is Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal product for human use, published in the Official Journal ("OJ") L 121, 1.5.2001, p.34, at http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf [hereinafter Directive 2001/20/EC]. The Directive was initially proposed in 1997; it was then modified in 1999. It was adopted in March 2001 and entered into force on May 5, 2001. Member States had until May 1, 2004 to fully comply with the Directive (Article 22.1 of the aforementioned Directive).
Several commentators have expressed doubts about E.U. readiness for this deadline. *See, e.g.,* Peter O'Donnell, *Squeezing the European Union Into Shape*, APPLIED CLINICAL TRIALS (Nov. 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=77553 [hereinafter O'Donnell (Squeezing)].

170 Article 23 of Directive 2001/20/EC.
The adoption of the European Directive could explain why the December 2000 draft of the OClin is so dissimilar to the actual ordinance. Visibly, the Federal Council and the Federal Administration decided midway that it was more appropriate to follow the European Directive. Some of the OClin's provisions are almost verbatim replica of the European Directive. Compare for example Article 22 OClin with Article 16 of the European Directive 2001/20/EC. Long live euro-compatibility!
Nonetheless, for the time beeing, Swissmedic has decided not to endorse directly this E.U. Directive, believing that it should wait to see exactly how it will be implemented in Member States. *See* Telephone Interview with Yves Chautems, Swissmedic's clinical trial division, (Mar. 25, 2004) [hereinafter Chautems (Mar. 2004)].

171 The ICH E6 Guideline is applicable in Switzerland pursuant to Article 53.1 LPTh and Article 4.1 OClin.

172 On the importance of the ICH GCP, see Sprumont (RSDS), *supra* note 100, at 42.

173 Article 1.2. of the Directive 2001/20/EC. See also the definition of the ICH E6 Guideline, at 1 and 4.

2.2.2. Scandals in Switzerland: the VanTx affair

Scandals have always been a powerful driving force for change. This is also true for Swiss clinical trials. What is commonly known as the "VanTx affair" is a perfect illustration.

In spring 1999, the Swiss authorities realized that the most important Swiss contract research organization ("CRO") had been conducting its clinical trials in gross violation of legal, ethical and scientific rules.[174] The CRO (called successively Clin-Pharma and VanTx)[175] was carrying out 40% of all Swiss phase I* clinical trials[176] submitted to the IOCM.[177] The sponsors which had hired out VanTx were reputable multinational pharmaceutical firms.[178] Yet, the policy of VanTx since 1998 had been to "import" into Switzerland research subjects coming from less developed countries.[179] In exchange for their participation in early phase clinical trials, these subjects were offered money and the promise of a trip through the Alps.[180] As can be expected, the subjects did not fully understand what they were committing to; moreover, the information they received was incomplete and not provided in their own language.[181] The investigator and the research site lacked the necessary authorizations. Clinical trials were not properly conducted;[182] medical follow-up of the subjects was entirely lacking.[183] The ethics committee which had approved the research did not operate properly: It was organized as a private company. Worse, it was chaired by the principal investigator – a gross violation of a basic principle of ethical review.[184]

When the OICM (the Swiss drug agency before Swissmedic) finally caught up with VanTx – after an Estonian newspaper had made the story public –, it appointed a Working Group to assess the situation. In September 2000, this Group, headed by Pierre Dayer and Dominique Sprumont,[185] delivered an illuminating report detailing the failings of the Swiss regulatory system.[186] The report sets forth several recommendations to improve the regulations of clinical trials.[187]

---

174 *See* VanTx Report, *supra* note 148, at 4 and 11.

175 On the relationship between the two contract research organizations, Clin-Pharma and VanTx, *see id.* at 10.

176 Phase I clinical trials correspond to the earliest phase of clinical research. It is during a phase I clinical trial that an investigational drug is first administered to human research subjects. On the various phases of clinical trials, see subsection 6.1. below.

177 Out of 450 clinical trials notified to the IOCM, VanTx/Clin-Pharma was performing 40% of the 150 phase I clinical trials. *See* VanTx Report, *supra* note 148, at 11. VanTx was also conducting many bioequivalence studies in connection with marketing application for generic drugs. *See, e.g.,* Press Release, Swissmedic, Focus: Clinical trials, (Jan. 10, 2003), at http://www.swissmedic.ch/Archiv/Klinische_Studien-F.pdf.

178 *See* VanTx Report, *supra* note 148, at 16.

179 *Id.* at 12. Out of 61 studies that Van-Tx notified to the Swiss authority, at least nine had enrolled foreign subjects. Over 150 foreign subjects were brought to Switzerland. *Id.*

180 *Id.* at 11 and 20.

181 *Id.* at 13.

182 *Id.* at 9.

183 *Id.* at 13-14.

184 *Id.* at 4 and 16-17.

185 See Professor Sprumont's webpage at http://www.unine.ch/droit/profs/profbiog.asp?prof=dsprumont.

186 *See* VanTx Report, *supra* note 148, at 4.

187 At that time, Swiss clinical trials were still governed by the Intercantonal regulation, in particular the (former) 1995 IOCM Regulation.

Unfortunately, the events and the ensuing report did not receive the publicity they deserved.[188] Despite the fact that a criminal investigation was launched against the investigator, the story remained pretty well hushed up. Lamentably, only a summary of the Working Group's report was made publicly available. The full report – 39 pages of a well-conducted exploration into the facts and the law – was kept confidential.[189] Moreover, the Working Group's recommendations to reinforce *controls*, and particularly *inspections*, were only partially implemented. On the positive side, most of the suggested legal amendments made by the Working Group were integrated in the 2002 Federal Regulation; several of its recommendations are further discussed in this thesis.

2.3. Historical overview of U.S. clinical trials regulations

2.3.1. Scandals in the United States

The legal history of clinical trials in the United States consists of a long string of scandals.[190] Contrary to Switzerland, evidence of these scandals has been recorded in medical and lay journals, court cases, congressional records, and books.[191] It is important to relay in some details these appalling events, because they exemplify the state of mind of researchers at the time. Most of these researchers were convinced that they were moral men and praiseworthy researchers acting for the "good" of humanity. It took considerable forces and a long time to change their mindset. Their overconfident attitude is a key element to understand why clinical trial regulations were so long in the offing.

Furthermore, each of these scandals shaped subsequent policies underlying research on human beings. Almost each one gave rise to government investigations, public hearings, and new regulations or guidelines.[192] These scandals are still frequently mentioned in public debates and court decisions.

---

188 See however the various articles by Marie Abbett published in L'Hebdo between May and July 1999.

189 The IOCM refused to supply me with a copy of the report. See letter of Mr. Méroz (legal department of the (then) IOCM) (Aug. 14, 2001) (on file with author). I finally obtained the report (albeit without its annexes) from another source.

190 *See, e.g.,* SPRUMONT, *supra* note 16, at 107.

191 As mentioned below, Switzerland may well have experienced similar scandals, which, contrary to the United States, did not come to light. However, Swiss *governmental* agencies have always been less involved in clinical research than their U.S. counterparts.
See for instance the particularly egregious American case of Barrett v. United States, 660 F. Supp. 1291 (S.D.N.Y. 1987) ("The case arises from the death of Harold Blauer, a mental patient who died in 1953 as a guinea pig in an experiment to test potential chemical warfare agents for the United States Army. Rather than admit its role in Blauer's death, the Government covered up its involvement in the affair …." *Id.* at 1294). *See also* United States v. Stanley, 483 U.S. 669 (1987) (in this case the military secretly administered LSD to one of its soldiers and, when this was finally revealed, claimed immunity); Leonard W. Schroeter, *Human Experimentation, The Hanford Nuclear Site, and Judgment at Nuremberg*, 31 GONZ. L. REV. 147, at 148 (1995/1996).

192 For example, the infamous Tuskegee study led to the enactment of the 1974 National Research Act. *See* Roger L. Jansson, *Researcher Liability for Negligence in Human Subject Research: Informed Consent and Researcher Malpractice Actions*, 78 WASH. L. REV. 229, at 233 and n. 23, (2003).
See also, in relation to the MKULTRA project reported below, U.S. Senate Select Committee on Intelligence, (Aug. 3, 1977), at
http://www.parascope.com/ds/documentslibrary/documents/mkultrahearing/mkultraHearing01.htm; Executive Order No.12333, § 2.10, at http://www.cia.gov/cia/information/eo12333.html.

2.3.1.1. The Tuskegee study

Most shocking for the Americans was the Tuskegee syphilis study.[193] It was run by the U.S. Public Health Service ("PHS"), with the assistance of the Tuskegee Institute and local doctors.[194] Six hundred black and uneducated men in segregated Alabama were enrolled. More than half suffered from syphilis.[195] Inconceivably, these men were never informed of their medical condition; their disease was vaguely referred to as "bad blood."[196] They were led to believe they were receiving treatments for their "bad blood," which was simply not true.[197] They did receive medical examinations,[198] food,[199] and burial insurance[200] in exchange for their participation in the study. However, they were given no or only very partial treatment, since the true but deliberately hidden purpose of the experiment was to observe the natural evolution of *untreated* syphilis, ideally until autopsy.[201] Several men infected their partners, while their children were born with congenital syphilis. The researchers involved went to extraordinary lengths to hide their conditions from the subjects. For instance, men were exempted from serving in the army because, as draftees, they would have received treatment.[202] Amazingly, the experiment spanned forty years (between 1932 and 1972).[203]

At the inception of the study, available drugs against syphilis had several shortcomings:[204] they were costly, they had to be taken over a long period and they could cause serious side effects.[205] The researchers justified their denial of treatment on these

---

193 *See* JONES (TUSKEGEE), *supra* note 78, at 11-14.

194 At the beginning of the experiment, local doctors around Tuskegee were all white practitioners. Towards the end of the study, they were mostly black doctors. However, both groups accepted to collaborate in the study. They agreed not to treat patients identified as research subjects on the list supplied by the PHS. They also referred their moribund patients to the hospital so that an autopsy could be carried out should they die. JONES, *supra* note 78, at 145-46, at 198-99.

195 The study had a control group of patients not infected with syphilis. When a subject in the control group was diagnosed with syphilis, he was often just switched to the "active" syphilis group. *Id.* at 140-41, at 194.

196 *Id.* at 5, 71-73.

197 The subjects did not receive any medical treatment against syphilis. Yet, they believed that the procedures they went through were intended to treat them. *Id.* at 127.

198 Subjects did receive medical attention from the nurse assigned to the study, Nurse Rivers. *Id.* at 6-7, 164-65. They also received aspirin and an iron tonic. *Id.* at 147-48. Most subjects had also received – almost by mistake – a very short course of anti-syphilis therapy at the very beginning of the study. *Id.* at 99, 119, and 173. This attracted most of the concerns of scientists who criticized the study for not being properly aimed at understanding untreated syphilis, but rather *undertreated* syphilis ! *Id.* at 131.

199 *Id.* at 4.

200 The burial stipend was offered to make sure that subjects and their families would accept the autopsy that concluded the follow-up of each subject. *Id.* at 153.

201 Initially, the study was to last only between six month and one year. *Id.* at 95. One of its objectives was to replicate a Norwegian study that had followed untreated syphilis in white patients. *Id.* at 10. The scientific question that fascinated researchers was whether the course of syphilis was the same in white and black patients. *Id.* at 172.

202 *Id.* at 177-78.

203 The Tuskegee study is the "longest nontherapeutic experiment on human beings in medical history." *See* Tuskegee Syphilis Study Legacy Committee, A Request for Redress of the Wrongs of Tuskegee, at http://hsc.virginia.edu/hs-library/historical/apology/report.html.

204 Before the introduction of penicillin, the available drugs were arsphenamine, neoarsphenamine (salvarsan) and bismuth. JONES, *supra* note 78 at 7 and 210.

205 However, in the early 1940s, the duration of treatment could be shortened from one year to one week. *Id.* at 162.

grounds.[206] However, after the Second World War, penicillin became the standard therapy.[207] However, to maintain the study's objectives – a study of untreated syphilis –, the subjects were not given penicillin.[208]

The experiment ended only because a journalist got hold of the story and revealed it to the public in July 1972.[209] Until then, the PHS scientists were certain that the study was perfectly acceptable.[210] Even after the scandal exploded, many physicians continued to defend the experiment as attested by letters to medical journals.[211] A first lawsuit was settled in 1974 with a $10 million payment.[212] In 1997 President Clinton formally apologized.[213]

2.3.1.2. Radiation studies

A study similar to that of Tuskegee was conducted between 1949 and 1960 on miners of the Indian Navajo tribe.[214] It was launched to determine the health risks due to radiation in uranium mines. The U.S. PHS was heading the study and regularly monitored the miners' health parameters. Although the miners knew they were participating in a health study, they were purposely not warned of the "possible potential hazards from radiation in the mines for fear that many miners would quit and others would be difficult to secure because of fear of cancer."[215] In particular, miners were not told of scientific evidence that radiation exposure in the mines caused respiratory tract and lung cancer.[216] Although they were informed of abnormalities detected during their medical check-ups, they were not offered follow-up treatments. In agreement with the mine owners, the PHS did not publicly release its study findings, that is chillingly high cancer and mortality rates among miners.[217]

---

206 *Id.* at 9.

207 *Id.* at 164.

208 *Id.* at 8-9, 178-79, and 211.

209 *Id.* at 1 and 204. *See also* Jean Heller, *Syphillis Victims in U.S. Study Went Untreated for 40 Years*, N.Y. TIMES, July 24, 1972, reprinted in TUSKEGEE'S TRUTHS, RETHINKING THE TUSKEGEE SYPHILLIS STUDY 116 (Ed. Reverby, 2000).

210 JONES, *supra* note 78, at 183 and 193-96.

211 *Id.* at 10.

212 *Id.* at 217. *See also* Schroeter, *supra* note 191, at 156; Larry A. Palmer, *Paying for Suffering: the Problem of Human Experimentation*, 56 MD. L. REV. 604, at 609-10 (1997).

213 President Clinton referred to the Tuskegee study as a "time when our nation failed to live up to its ideals, when our nation broke the trust with our people that is the very foundation of our democracy." Remarks by the President in Apology for Study Done in Tuskegee (May 16, 1997), at http://clinton4.nara.gov/textonly/New/Remarks/Fri/19970516-898.html.

214 *See* Annas, *supra* note 66, at 209-210; Schroeter, *supra* note 191, at 224-35.

215 Begay v. United States, 591 F. Supp. 991, at 995 (D. Ariz. 1984), *aff'd* 768 F.2d 1059 (9th Cir. 1985). *See also* Barnson v. United States, 816 F.2d 549 (10th Cir. 1987).

216 "The PHS and the other federal and state agencies hypothesized that exposure to radiation in the uranium mines may have presented a danger to the miners. After 1959, the statistical data also indicated that the danger was present. The PHS staff, limited in both funds and authority, still did not warn the miners of the increasing evidence of radiation danger in the uranium mines. Even though it may have been suspected by the PHS that some miners would suffer injury from radiation exposure, the goal of the study was to determine the extent of the hazards so that recommendations could be made and standard promulgated." *Begay*, 768 F.2d at 1065-66.

217 *See* Schroeter, *supra* note 191, at 232-33.

The Court seized with the matter observed that the epidemiological study was conducted in accordance with the ethical standards of the time (i.e., prior to the 1960s).[218] It rejected the plaintiffs' claims holding that the government had taken a policy decision in a sensitive area involving national security and was thus immune from liability.[219]

The quest for nuclear weapons which justified hiding the truth to the miners also led the U.S. Military to secretly conduct hundreds of radiation experiments on soldiers, civilians, hospital patients,[220] children and prisoners between 1944 and 1974.[221] Tens of thousands of Americans GIs are believed to have been subjected to experiments, notably to test chemical weapons.[222] Four thousands were enrolled in gas-chamber experiments. More than 210,000 were subjected to radiations.[223] A federal commission of experts appointed in 1994 reached the conclusion that it had been "commonplace during the 1940s and 1950s for physicians to use patients as subjects of research without their awareness or consent."[224]

---

218 *Begay*, 591 F. Supp. at 997-98.

219 For the Court, "all the actions of various governmental agencies … were the result of conscious policy decisions made at high government levels based on considerations of political and national security feasibility factors." They were shielded from review under the discretionary function exception. *Id.* at 1012.

220 In the 1950s and 1960s, the Massachusetts General Hospital conducted "dangerous medical experiments on over 140 terminally ill patients" without their informed consent. *See* Heinrich v. Sweet, 49 F. Supp. 2d 27 (D.C.Mass. 1999), citing to the plaintiffs' complaint.
See also In Re Cincinnati, 874 F. Supp. 796 ("The allegations of the Complaint make out an outrageous tale of government perfidy in dealing with some of its most vulnerable citizens" *Id.* at 800).

221 *See* Advisory Committee on Human Radiation Experiments (ACHRE), Final Report, (1995), at http://tis.eh.doe.gov/ohre/roadmap/achre/chap17_3.html. The Committee observed that "[i]nformation was kept secret out of concern for embarrassment to the government, potential legal liability, and worry that public misunderstanding would jeopardize government programs. In a few instances, people used as experimental subjects and their families were denied the opportunity to pursue redress for possible wrongdoing because of actions taken by the government to keep the truth from them."
See also Jaffee v. United States, 663 F.2d 1226 (3d Cir. 1981) (explaining how soldiers were forced to stay nearby during a nuclear explosion without any protective gear so as to study the health consequences of such exposure. Shockingly, the ex-soldier's lawsuit against both the government and federal officials was dismissed on the ground of military immunity). *See also* the dissent by Judge Gibbons, *id.* at 1247. *See also* Bulloch v. United States, 721 F.2d 713 (10th Cir. 1983) (on alleged government cover-up in the "sheep law suit"); the dissent by Justice Brennan in United States v. Stanley, 483 U.S. 669, at 686 (1987). See also on governmental deceit and cover-up, Schroeter, *supra* note 191, at 203-224. *See also* Annas, *supra* note 66, at 209.

222 According to Schroeter, "far more than 23,000 Americans had been involved in at least 1,400 different projects involving radiation experimentation over a 30-year period following World War II. … what the United States government has admitted by public announcements will, in all likelihood, exceed well over a million involuntary radiated victims, an unknown number of whom died from cancer." *Supra* note 191, at 151-52.
In his dissent, Justice Brennan wrote: "[b]etween 1945 and 1963, an estimated 250,000 military personnel were exposed to large doses of radiation while engaged in maneuvers designed to determine the effectiveness of combat troops in nuclear battlefield conditions. … Soldiers were typically positioned one to three miles from nuclear detonation. They were issued no protective clothing (although Atomic Energy Commission personnel were) and were not warned as to the possible dangers of radiation." Stanley, 483 U.S. at 690.

223 *See* Human Experimentation: An Introduction to the Ethical issues, Research issues Compendium, Physicians Committee for Responsible Medicine, www.pcrm.org/issues/Research_Issues_Compendium/res_comp_1.html.

224 Advisory Committee on Human Radiation Experiments, Executive Summary, (1995), at http://www.pcrm.or/Issues/Research_Issues_Compendium/res_comp_1.html.

2.3.1.3. Mind control experiments

Between 1953 and 1963, the CIA secretly financed experiments intended to control human behavior (the code-named "MKULTRA" program).[225] The program was launched to "counter" research on brainwashing that the United States suspected the Communist Chinese and the Soviet Russian governments of doing. Soon, it went beyond its defensive purpose to take an offensive orientation.[226] It was conducted partly on U.S. soil and partly overseas (including on unwitting non-U.S. citizens).[227] It involved, for example, administering LSD or mescaline to subjects, mostly soldiers or institutionalized patients, without their knowledge.[228] The CIA was looking for drug weapons that would confuse the mind of its enemies and improve that of U.S. soldiers. It sought and obtained the help of academic institutions and pharmaceutical firms.[229] In 1973, the CIA had most of its files concerning MKULTRA intentionally destroyed.[230] An analogous LSD program was organized by the Army with similar disregard for human life and basic human rights.

Perhaps the saddest part is the refusal of the U.S. Supreme Court to make the military accountable for its actions. Instead, the military was "rewarded" with an excessively broad immunity.[231]

---

225 See the documents available from the website at http://www.parascope.com/ds/mkultra0.htm, in particular Appendix A to the report from the 1977 Senate Hearings, at http://www.parascope.com/ds/documentslibrary/documents/mkultrahearing/mkultraHearingAppendixA.htm.

226 *See id.*

227 *Id*. *See also* Orlikow v. United States, 682 F. Supp. 77 (D.C.C. 1988) (Canadian citizens who suffered from psychiatric disorders were covertly administered LSD by their doctor who was secretly working as a contractor for the CIA's MKULTRA project); Kronisch v. United States, 150 F.3d 112 (2d Cir. 1998) (an American painter living in Paris at the time claimed he was drugged with LSD by high-level CIA officers).

228 No subjects had given *valid informed* consent, although some of them had signed a general and vague consent form. *See* Appendix A, *supra* note 224.
See also Central Intelligence Agency et al. v. Sims et al., 471 U.S. 159 (1985).
On the LSD case, see Thornwell v. United States, 471 F. Supp. 344 (D.C.C. 1979) (in which the military used LSD as means of torture on a soldier suspected of treason; the government then tried to conceal its actions); United States v. Stanley, 483 U.S. 669, at 696 (1987) (in which soldier Stanley was one, among some 1,000 other soldiers, who were unwittingly administered LSD). *See also* Schroeter, *supra* note 191, at 252-60.
On the Mescaline case, see the horrific account exposed in the case of *Barrett*, 660 F. Supp. 1291; also Schroeter, *supra* note 191, at 242-52 (commenting the secret governmental experiments with potential warfare agent mescaline which led to the death in 1953 of mental patient Blauer at the prestigious New York State Psychiatric Institute).

229 Some eighty universities and institutions were probably implicated. However, the researchers affiliated to them did not always know that they were in fact helping CIA's warfare-related projects. *See, e.g., Orlikow*, 682 F. Supp. 79; *Central Intelligence Agency*, 471 U.S. at 162 (a Supreme Court decision denying a request under FOIA aiming to get the names of all institutions and researchers that took part in MKULTRA); Select Committee on Intelligence, *supra* note 192.

230 As a result, the remaining available information is only piecemeal. *See, e.g.,* Appendix B to the 1977 Senate Hearing, at http://www.parascope.com/ds/documentslibrary/documents/mkultrahearing/mkultraHearingAppendixB.htm [hereinafter Appendix B]. *See also Kronisch*, 150 F.3d 112.

231 *See* Feres v. United States, 340 U.S. 135 (1950) ("the Government is not liable under the Federal Tort Claims Act for injuries to servicemen where the injuries arise out of or are in the course of activity incident to service.").
The government can also invoke immunity under the "discretionary function exemption" to liability. In the case of Nevin v. United States, the military had released a dangerous strain of bacteria onto San Francisco to conduct a simulated biological warfare attack. *See* 696 F.2d 1229 (9th Cir. 1983).

2.3.1.4. Recent scandals

In his seminal 1996 article, physician Henry Beecher described 22 unethical trials.[232] These trials had put the health or life of the subjects at risk. Moreover, the researchers had not obtained informed consent. Initially, Beecher's article had comprised 50 such trials.[233] The studies were not just taking place in remote minor league facilities, but also in the most prestigious medical centers. As a possible remedy to this widespread "thoughtlessness and carelessness," Beecher recommended that unethical studies be denied publication in journals.[234] Not surprisingly, his advice was not immediately accepted.[235]

Yet, several important statutes and guidelines were adopted subsequent to Beechler's article and the revelation of the aforementioned scandals. Nonetheless, trusting that these bits and pieces of regulations could entirely stop unethical research would be wishful thinking. As late as 1993, the Kennedy Krieger Institute (alongside with the John Hopkins University and in collaboration with both federal and state agencies) launched a study whereby young children were deliberately exposed to lead particles at home. The study's objective was to determine the extent to which *cheap* lead paint abatement methods were effective.[236] The parents were misled into giving consent.[237] Because the families were poor,[238] they were probably swayed by the gifts they received.[239] Referring to the experimental use of these children, the Maryland Court of Appeals made an analogy with "canaries in the mines."[240]

---

232 *See* Henry K. Beecher, *Ethics and Clinical Research*, 74 NEW. ENG. J. MED. 1354-60 (1966), at http://www.who.int/docstore/bulletin/pdf/2001/issue4/vol79.no.4.365-372.pdf (at 367) [hereinafter Beecher (Ethics)]. This article shook researchers and governments out of their contented apathy. At the time, it had more impact than the Nuremberg Code or the Helsinki Declaration. This paper by Beecher has "rightly been deemed the most influential single paper ever written about experimentation involving human subjects." Jon Harkness et al., *Laying ethical foundations for clinical research*, 79(4) Bulletin of the WHO 365-66 (2002), at http://www.who.int/docstore/bulletin/pdf/2001/issue4/vol79.no.4.365-372.pdf. *See also* LEDERER, *supra* note 54, at 139 and 141; SPRUMONT, *supra* note 16, at 23.

233 *See* Vincent Kopp*, Henry Knowles Beecher and the Development of Informed Consent in Anesthesia Research*, 90 ANESTHESIOLOGY 1756-65 (June 1999). Beecher also examined 100 studies that had been published consecutively in 1964 in a prestigious journal and found that 12 seemed unethical. *See* Beecher (Ethics), *supra* note 232.

234 *See* Beecher (Ethics), *supra* note 232; Beecher (Guiding), *supra* note 103, at 158 (evoking the parallel rule in criminal procedures whereby "evidence illegally obtained is never admissible in a court, however valuable the data might be in the pursuit of justice").

235 *See* subsection 10.4.1.4. below.

236 *See Grimes*, 782 A.2d 807.

237 Parents were not told that the chief purpose of the study was to see how much lead would accumulate in their children's blood over the period of observation. *See id.* at 824. Parents were not told to minimize their children's exposure to lead. On the contrary, they were encouraged to stay in their houses for the entire duration of the study.

238 *See id.* at 812.

239 *See id.* at 843.

240 *Id.* at 813. *See also* M. Spriggs, *Canaries in the mines: children, risk, non-therapeutic research, and justice*, 30 J. MED. ETHICS 176-181 (2004), at http://jme.bmjjournals.com/cgi/content/full/30/2/176.

2.3.2. Successive U.S. regulations of clinical trials

As mentioned above (subsection 1.3.), the United States adopted federal regulations of clinical trials long before Switzerland. Today, U.S. federal regulations are split into two sets of regulations.[241] The first one was adopted by the FDA; it applies to clinical trials of drugs and medical devices. The Department of Human Health and Services ("HHS") is the author of the second set of regulations, called the HHS Regulations or "Common Rule."[242] The HHS Regulations are followed by federal research agencies, particularly the National Institutes of Health ("NIH") and by research institutions receiving federal funding.[243] Clinical trials that are neither submitted to the FDA nor funded or otherwise supported by federal institutions may escape federal regulation;[244] they are subject to State legislations only.[245] In this thesis, the emphasis is placed on FDA regulations since they represent a more accurate counterpart to the Swiss OClin.

U.S. efforts to regulate experimentation began in the early 1900s.[246] Several bills were submitted to Congress, only to be defeated by mixed coalitions of interested parties.[247] For instance, doctors banded with the pharmaceutical industry, newspapers and advertisers to oppose any regulations that would constrain the freedom to prescribe or to do business. In 1906, the short Food and Drugs Act was enacted. It only authorized

---

241 The FDA and the HHS regulations may be applicable concurrently, for example when a clinical trial receives funding (directly or indirectly) from the NIH and is to be submitted in support of a drug marketing application. For a list of differences between the two regulations, see FDA, Comparison of FDA and HHS Human Subject Protection Regulations (2000), at http://www.fda.gov/oc/gcp/comparison.html.

242 Because so many U.S. agencies are applying the HHS regulations, these are referred to as the "Common Rule." The Common Rule provides notably for a system of assurance adopted by each recipient institution (e.g., universities) to guarantee compliance with applicable regulations. *See* 45 C.F.R. § 46.103.

243 In addition, many research centers choose to apply the Common Rule even to research projects that do not receive federal funding.

244 This is undeniably a worrisome loophole. Critics have repeatedly asked that this problem be addressed by comprehensive regulations. *See, e.g.,* National Bioethics Advisory Commission ("NBAC"), Ethical and Policy Issues in Research Involving Human Participants, Summary, at 6, (Aug. 2001), at http://www.georgetown.edu/research/nrcbl/nbac/human/oversumm.pdf, [hereinafter NBAC (Issues in Research)].

245 Research projects which fall neither within neither the FDA regulations nor the Common Rule jurisdiction are rare. *See, e.g.,* Harold T. Shapiro & Eric M. Meslin, *Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries*, 345 NEW. ENG. J. MED. 139 (July 12, 2001), at http://content.nejm.org/cgi/reprint/345/2/139.pdf.

246 See SUZANNE PARISIAN, FDA INSIDE AND OUT, at 11-13 (Fast Horse Press, 2001).

247 *See* Russell S. Sobel, *Public Health and the Placebo: The Legacy of the 1906 Pure Food and Drugs Act*, Independent Institute Working Paper No.28, (Apr. 2001), at 5, at http://www.independent.org/pdf/working_papers/28_public_health.pdf. The patent medicine lobby and the media industry (journals lived on medical advertisements) were the most vocal opponents to drug regulations.
"Senator Gallinger introduced in 1900 a proposal for the regulation of human experimentation in the District of Columbia. Senate Bill 3424 required the prior disclosure of an investigator's purpose and procedures in any nontherapeutic experiment on human beings, as well as the written consent of the subjects. The bill explicitly outlawed scientific experimentation on persons considered incapable of giving consent, including newborns and children under the age of twenty, pregnant women or women who had given birth in the previous year, the aged, the insane, the feeble-minded, and people with epilepsy." LEDERER, *supra* note 54, at 71-72.

the FDA to order products to be withdrawn from the market if they were deemed misbranded or adulterated.[248]

In 1962, Congress passed the Kefauver-Harris Amendments to the Food and Drug Cosmetic Act ("FDCA"). These Amendments added the requirement of *informed consent* to clinical investigations of products under the jurisdiction of the FDA.[249] However, the Amendments had excessively broad exceptions for situations where informed consent was found "not feasible" or "contrary to the best interests" of the subjects.[250]

In 1974, the short National Research Act was passed.[251] This Act set up the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[252] In 1979, the Commission published its report, commonly referred to as the "Belmont Report."[253] This Report holds significant importance in the United States,[254] where its role is at least comparable to that of the Helsinki Declaration (on the Helsinki Declaration, see subsection 2.1.2. above).

---

248 *See* PARISIAN, *supra* note 246, at 14. The passage of the 1906 Act was helped by the novel "The Jungle" by Upton Sinclair, which generated public furor at the lack of regulations in the food industry.

249 *See* JONES (TUSKEGEE), *supra* note 78, at 189. *See* Julie A. Grow, *The Legislative History of the 1962 Drug Amendments: A Failure to Forget or A Lesson to Learn From?* Harvard Law School, at 109 at n.536 (May 1, 1997), at http://leda.law.harvard.edu/leda/data/189/jgrow.pdf.
Previously, the American Medical Association started to require that subjects consent to research in 1946. However, its recommendation was not widely followed. *See* LEDERER, *supra* note 54, at 140.
In 1966, the Surgeon-General also issued its own recommendations. *See also* Glantz, *supra* note 83, at 186-87; JONES (TUSKEGEE), *supra* note 78, at 189; Goldner, *supra* note 62, a 95. *See also* SPRUMONT, *supra* note 16, at 117.

250 According to the Amendments (at § 103), experts testing the safety and efficacy of new drugs had "to certify to [the] manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, *except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings*." (emphasis added). As a result, the protection that the Act extended to research subjects was quite limited in practice. *See* Goldner, *supra* note 62, at 94. *See also* SPRUMONT, *supra* note 16, at 113-14.

251 *See* National Research Act, Public Law 93-348, (July 12, 1974) available at http://www.kent.edu/rags/Compliance/IRB-National-Research-Act.cfm. *See also* LEDERER, *supra* note 54, at 142; Palmer, *supra* note 212, at 616-17.

252 *See further* SPRUMONT, *supra* note 16, at 120.

253 Belmont report, *supra* note 61. *See also* ARNO & FEIDEN, *supra* note 125, at 27.
Baram has criticized the Belmont report as being overly permissive. Michael Baram, *Making Clinical Trials Safer for Human Subjects*, 27 AM. J. L. AND MED. 253, at 258 (2001).

254 *See* Burns, *supra* note 81, at 133; Richard A. Rettig, Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense, Rand Report, (Apr. 1999), at chapter 3, access to full text of all chapters from http://www.gulflink.osd.mil/library/randrep/index.html [hereinafter Rand Report]; NBAC (Issues in Research), *supra* note 244, at 2; NBAC, Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, Volume I, Report and Recommendations, at 5, (Apr. 2001), at http://www.georgetown.edu/research/nrcbl/nbac/clinical/Vol1.pdf [hereinafter NBAC (Developing)]; SPRUMONT, *supra* note 16, at 54 and 120.
However, in a 2002 decision, the U.S. Supreme Court of Connecticut agreed with a lower court that the use of the Belmont report as evidence could unduly sway the jury. According to the Court, the Belmont report would invite "the jury to engage in a highly abstract and philosophical level of inquiry into such subjects as respect for the autonomy of persons, the notion of self-determination, the concept of beneficence, and the various theories of justice. It invited the jury to think about using children and criminal prisoners as subjects of medical research. It invited the jury to think about the meaning of the physician's Hippocratic oath, which was neither given in full nor explained in any detail. It invited the jury to compare the hospital's conduct to the infamous Tuskegee study. … We cannot fault the trial court … for determining that submitting this material to the jury would unduly arouse its emotions of prejudice, hostility or sympathy, and would tend to confuse the issues and mislead the jury." Ancheff v. Hartford Hospital, 799 A.2d at 1079 (Conn. 2002).

Even before these statutes entered into force, the NIH and the FDA had adopted their own guidelines. The NIH adopted its first rules in the early 1950s.[255] The FDA enacted its regulations in 1963,[256] which it then revised several times.[257] Starting in 1971, the FDA required clinical studies of investigational[258] products to get approval from *ethics committees*.[259] In 1981, the FDA enacted formal guidelines on clinical trials.[260] In 1996, the Agency authorized and regulated *emergency* clinical research through yet another guideline (see subsection 8.4.2.2. below).[261]

---

255 The first NIH guideline for intra-muros research dates back to 1953. *See* SPRUMONT, *supra* note 16, at 115. *See also In Re Cincinnati*, 874 F. Supp. at 821.

256 *See* 28 Fed. Reg. 179 (Jan. 8, 1963). *See also* SPRUMONT, *supra* note 16, at 113.

257 *See* FDA, Statement on Policy Concerning Consent for Use of Investigational New Drugs on Humans, 31 Fed. Reg. 11,415 (Aug. 1966); 32 Fed. Reg. 8,753 (June 20, 1967).
Even prior to 1966, informed consent was considered as a general obligation, even though the precise shape of the obligation was unclear. *See* Burton v. Brooklyn Doctors Hospital, 452 N.Y.S.2d 875 (N.Y.App. 1982) ("While the law in New York at that time [1953] did not require the detailed imparting of information such as has been statutorily mandated since 1975, either with respect to treatment or the conduct of research, doctors were never free to expose their patients to unwarranted risks without first obtaining their consent." *Id.* at 881). *See also In Re Cincinnati*, 874 F. Supp. at 821 and 826 (mentioning a 1953 Directive by the U.S. Department of Defense). *See also* Glantz, *supra* note 83, at 186. *See also* FDA, FDA Oral History Program, Interview with William W. Goodrich, Office of the General Counsel, 1939-1971, Part III, (1986), at http://www.fda.gov/oc/history/oralhistories/goodrich/part3.html (describing the controversy about the early FDA regulations on clinical investigations).

258 The words "investigational" and "experimental" are often used as synonyms. However, they have a slightly different meaning. The word "investigational" reflects the fact that the drug lacks marketing approval for its considered therapeutic indication. The word "experimental" suggests that little is known about the drug and its indication. A drug that has been used for a long time for its therapeutic indication would no longer be considered experimental, whereas it still remains investigational. However, in this thesis, I sometimes use the two terms synonymously.

259 In the United States, these ethics committees are called Institutional Review Boards ("IRBs"), a term which conveys correctly the fact that their main task is to review research conducted in their institutions. For a definition, see for example 21 Code of Federal Regulations ("C.F.R.") § 50.3(i) or § 56.102(g) (chapter 21, part 50 of the Code of Federal Regulations is available at
http://www.fda.gov/oc/ohrt/irbs/appendixb.html; part 56 at
http://www.fda.gov/oc/ohrt/irbs/appendixc.html); also 45 C.F.R. § 46.102(g) (at
http://www.hhs.gov/ohrp/Humansubjects/guidance/45cfr46.htm#46.102. *See also* FDA, FDA Operations, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators, (1998 update), at http://www.fda.gov/oc/ohrt/irbs/operations.html [hereinafter FDA (Operations)].

260 *See* FDA, HHS, Final Rule, Protection of Human Subjects, Informed Consent, 46 Fed. Reg. 8942 (Jan. 27, 1981) [hereinafter FDA (1981)]

261 *See* FDA, Exception from Informed Consent, Requirements for Emergency Research, Guidance for Institutional Review Boards, Clinical Investigators and Sponsors, Draft Guidance, at 4, (Mar. 30, 2000), at http://www.fda.gov/ora/compliance_ref/bimo/emrfinal.pdf [hereinafter FDA (Emergency Guidance)].

2.4. Historical overview of E.U. regulations

The first European Directive to focus on pharmaceuticals was passed in 1965.[262] It dealt with the general conditions governing national regulatory approvals for pharmaceuticals. The first specific directive to cover clinical trials was adopted in 1975;[263] it set minimal standards, highlighting the importance of double-blinded* controlled trials.[264]

Requirements pertaining to clinical trials did not attract much attention at the European level until a 1987 report by the Committee for Proprietary Medicinal Products "CPMP").[265] Before that time, Member States were mostly free to promulgate their own national requirements. The 1987 CPMP report states basic principles by which clinical researchers should abide. It refers to the Helsinki Declaration. A few years later, the CPMP enacted a guidance on good clinical practices.[266] Although widely followed, it was not compulsory.[267]

In 1992, a European Directive laid down certain technical requirements with respect to the conduct of clinical trials.[268] In 2001, the European Parliament and the Council adopted a comprehensive directive on good clinical practice.[269] Several accompanying guidelines were enacted in 2003.[270]

---

262 *See* (former) Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products, *in* OJ 22, 9.2.1965, p.369, at http://www.ikev.org/docs/eu/365L0065.pdf (this Directive is no longer in force). Contrary to what the name may suggest, European directives are binding in the sense that Member States are legally obliged to adapt their national legislation accordingly.

263 *See* (former) Council Directive 75/318 of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, O.J. L 147 p.1-12 (9.6.1975), at http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31975L0318&model=guichett (this Directive is no longer in force).

264 See part 3, chapter I of the Annex to (former) Directive 75/318. Clinical trial requirements contained in this Annex were further developed by the Commission Directive 91/507/EEC of 19 July 1991, O.J. L 270 p.32-52 (26.9.1991) (no longer in force), at http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31991L0507&model=guichett.

265 *See* SPRUMONT, *supra* note 16, at 159.

266 CPMP Working Party on Efficacy of Medicinal Products, Good Clinical Practice for Trials on Medicinal products in the European Community, Note for Guidance, (III/3976/1988-EN Final). This (former) Guidance came into operation on July 1, 1991.

267 *See* SPRUMONT, *supra* note 16, at 160-61.

268 Directive 91/507/CEE of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products, at http://www.ikev.org/docs/eu/391L0507.htm.

269 Directive 2001/20/EC (note 168 *supra*).

270 *See* European Commission, Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use [E.U. Guidance (Adverse Reaction)]; Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module) [hereinafter E.U. Guidance (SUSARs)]; Detailed guidance on the European clinical trials database (EUDRACT Database) [hereinafter E.U. Guidance (Database)]; Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use [hereinafter E.U. Guidance (Ethics Committee)]; Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial [hereinafter E.U. Guidance (Request)]; all of them of April 23, 2004; and all of them available from http://pharmacos.eudra.org/F2/pharmacos/new.htm.

3. Definition of clinical trials

"Clinical trial" is the current standard – and politically correct – term used to designate experiments on living[271] human beings. Although "clinical trial" sounds better than "experimentation,"[272] patients seem to associate the first expression with a trial-and-error approach; therefore, when dealing with patients, the term "clinical study" was found more suitable.[273]

The term "clinical trial" is opposed to the expression "*preclinical* study," the latter including experiments in the laboratory and on animals (ex vitro and ex vivo). As the word itself indicates, preclinical studies are mostly performed before trials on human beings begin. Some preclinical studies can be conducted in parallel with clinical trials. However, before trials on human subjects can be started, the sponsor must have collected sufficient evidence from animal models to believe in the safety of its experimental compound.

Individuals participating in clinical trials are called human research subjects[274] – which do not sound very auspicious,[275] but is clearly better than "guinea pigs."[276] Research subjects are sometimes classified in two groups: healthy volunteers and patients. Healthy volunteers are human research subjects who do *not* have the disease under study. The word "patient" is used, somewhat misleadingly, to denote that the subject is suffering from the medical condition under investigation.

The precise meaning of "clinical trial" is a delicate question with important ramifications.[277] This section critically analyzes the available definitions. Unavoidably, this section is long and complex. Readers not interested in technical legal issues may want to skip it altogether.

---

271 *See* subsection 3.3. below.

272 The word "experiment" has always had negative connotations. In the past, the word "vivisection" was also used to refer – of course pejoratively – to clinical studies with human subjects. "In the late nineteenth century, … the word vivisection was used to denote any experimental manipulation. … most Americans used *vivisection* and *experimentation* interchangeably. *Human vivisection*, on the other hand, was used to describe only those experiments on human beings undertaken not to benefit an individual subject but to provide medical information. … Use of the term *human vivisection* to refer to nontherapeutic experiments on human beings continued well into the 1930s." LEDERER, *supra* note 54, at xiv-xv, and also at 25, 27-28 and 137.

273 A survey found that calling clinical trials "clinical studies" increased willingness of potential subjects to enroll. *See* HarrisInteractive, Nationwide Survey Reveals Public Support of Clinical Research Studies on the Rise (June 27, 2001), at http://www.harrisinteractive.com/news/printerfriend/index.asp?NewsID=323.

274 For definitions, see section 1.57 (p.8) ICH E6.
In the European Union, see Article 2(i) of Directive 2001/20/EC.
In the United States, see 21 C.F.R. § 50.3(g), § 56.102(e) and § 312.3(b); 45 C.F.R. § 46.102(f).
In Switzerland, see Article 3 OClin, specifying that subjects include both volunteers receiving the tested compound and those receiving the control product (which can be another therapeutic product or a placebo, that is a dummy pill). Under the 2004 OClin revision (entered into force on September 1, 2004), this provision (3 OClin) was moved to Article 5.d OClin; the text of the OClin amendments is available at http://www.bag.admin.ch/heilmitt/aktuell/f/vam_aend.pdf.

275 *See, e.g.,* NBAC (Developing), *supra* note 254, at xv, note 1.

276 According to Lederer, the word "guinea pig" was first put forward by George Bernard Shaw "to make clear the vivisector's equation of human and animal subjects." *Supra* note 54, at xiv.

277 *See* SPRUMONT, *supra* note 16, at 25.

3.1. The three regional definitions

Pursuant to Article 5.a OClin, a clinical trial is "any study on human beings that aims to verify in a systematic manner the security and efficacy as well as other properties of a therapeutic product." [278] This can be broken down into the following conditions:

a) a study;
b) on human beings;
c) that aims to verify;
d) in a systematic manner;
e) the security, efficacy as well as other properties;
f) of a therapeutic product.

These six conditions are analyzed below, but in a different order. Subsection 3.2.1. starts with conditions f) and e). Subsection 3.3. deals with condition b). The longest subsection – 3.4. – concentrates on conditions a), c) and d).

The Swiss definition above compares favorably with the European definition.[279] According to Article 2.a of European Directive 2001/20/EC, a clinical trial is:

> any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of one or more investigational medical product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.

In my opinion, the European definition is excessively concerned with the specific objectives that clinical trials can pursue; it attempts to mention each possible scientific aim of clinical trials.[280] It makes no reference to the use of *systematic* methods (compare with condition d) above).

The United States has many different definitions of clinical trials. The definition set forth by the HHS (Department of Health and Human Services) is perhaps the most helpful of all:

> [r]esearch means a *systematic* investigation, including research development, testing and evaluation, designed to develop or contribute to *generalizable* knowledge.[281]

---

278 This is an unofficial translation from the French: "*On entend par essai clinique: toute étude réalisée sur l'être humain et visant à vérifier de manière systématique la sécurité, l'efficacité ainsi que d'autres propriétés d'un produit thérapeutique.*" The 2004 OClin revision added after "*autres propriétés d'un produit thérapeutique*" the words "*ou la biodisponibilité.*" Compare with the scope of the Directive 2001/20/EC, as delineated in the E.U. Guidance (Request), *supra* note 270.

279 This definition is modeled on the ICH definition at section 1.12 (p.3) of ICH E6.

280 The previous intercantonal system had a definition for "drug clinical trial" very similar to that of the European Directive. However, it had a much broader definition for clinical trials (i.e., "any research on men in the biomedical field"). Moreover, its definition of research matches that of the United States. See the glossary at Annex II of the Good Clinical Practices (GCPs) accompanying the (former) IOCM 1995 Regulation.

281 45 C.F.R. § 46.102(d).
See also this other definition: "clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purpose of this part, an experiment is

This definition is appealing because it incorporates two fundamental criteria: "systematic investigation" and "generalizable knowledge."[282] These criteria were also stressed in the IOCM's definition of research.[283] They have also been espoused by the 1995 Guidelines of the Swiss Academy of Medical Science.[284] However, only the first of these two criteria is present in the OClin definition (see subsection 3.4. below).

3.2. Clinical trials of therapeutic products

Pursuant to its Article 5.a, the OClin only covers clinical trials of *therapeutic products*. When the clinical trial does *not* involve the administration of a therapeutic product, the OClin does not apply.

The following subsection argues that the product-related limitation does not have its place in the *definition* of clinical trials. Subsection 3.2.2. clarifies what is meant by the administration of a therapeutic product. Subsection 3.2.3. focuses on gene therapy.

3.2.1. Is there a rationale for the OClin's product-related limitations

When the LPTh and the OClin were passed, the legislator assumed that a comprehensive federal law on research on human beings would soon be adopted. This law would provide a framework for all research projects (e.g., with or without therapeutic products). To let the expert commission appointed to prepare this law work freely and to avoid having to amend the OClin in a few years time, the legislator limited the OClin's scope of application. It also chose to match the OClin's scope of application with that of the LPTh. As a result, the OClin is chiefly meant to apply to studies that will then be submitted to Swissmedic in order to support a drug's marketing application.[285]

Unfortunately, the legislative project on research has now been in preparation for several years. It has incurred significant delays.[286] Priority was given to another federal

any use of a drug except for the use of a marketed drug in the course of medical practice." 21 C.F.R. § 312.3(b).

[282] These are also the two criteria stressed by Sprumont in his own definition of research. *See* SPRUMONT, *supra* note 16, at 281.

[283] Research is defined as all systematic investigation designed to develop or further generalizable knowledge (in French: "*toute investigation systématique conçue pour développer ou élargir des connaissances généralisables*"). Glossary (under recherche/research) at Annex II to the GCPs accompanying the (former) IOCM 1995 Regulation.

[284] *See* SAMS 1997 Guidelines, *supra* note 110. This Guideline should probably be revised since it does not take into account the fact that the LPTh and the OClin came into force.

[285] This is also true of ICH E6 Guideline which is not automatically applicable to clinical trials that do not involve medicinal products. *See* ICH E6's introduction. Drug clinical studies that are not to be submitted to Swissmedic (for the purpose of securing a marketing authorization) are nonetheless subject to the LPTh and the OClin.

[286] Initially, the consultation procedure was to start in 2002. As of December 2004, it had not yet begun. *See, e.g.,* Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 279 and 313.

law on research involving embryos.[287] In the meantime, a giant loophole has remained.[288] Of course, cantons remain free to regulate – or not to regulate – clinical studies that do not involve therapeutic products or gene therapy. This is evidently not a satisfying situation.

It would have been far more appropriate to define separately clinical trial, on the one hand, and clinical trials of therapeutic products, on the other hand. Presently, Article 5.a OClin merges the first into the second. In good logic, however, clinical trials of drugs are only a *subset* of the broader category of clinical trial. The former IOCM Regulations even distinguished *three* categories: research, clinical trial, and clinical trial of a therapeutic agent.[289] Equaling clinical trial to clinical drug trials is misleading and serves strictly no purpose. I would therefore suggest a change to Article 5 OClin in order to sharply distinguish (at least) these two notions.

A question still remains: Why is the OClin framework not good enough to govern all clinical trials? What could a new law add to the OClin? And how would this law coexist with the OClin? The legislator has not answered these questions and the expert commission (on research on human beings) has yet to issue its reports. This commission will probably ratify most, if not all, the rules set forth by the OClin. Although the OClin is only a general blueprint for clinical trials, it is unlikely that a new law would radically alter the conduct of clinical trials. The reason for this is simple: The OClin already incorporates, or refers to, existing international standards.[290] Only the role of Swissmedic is likely to differ; it may well be that researchers will be dispensed from applying for Swissmedic's clearance when their research protocols do not focus on therapeutic products.

In my opinion, having all experiments on humans governed by one regulation would simplify their supervision.[291] The borderline situations discussed below would

---

287 On December 19, 2003, the Parliament voted the: "*Loi relative à la recherche sur les cellules souches embryonnaires*"; [Federal Law regarding embryonic stem cells]; abbreviated (from the French): LRCS; French text at http://www.admin.ch/ch/f/ff/2003/7481.pdf.
Parliamentary debates, which took place between March and December 2003, can be viewed on-line at http://www.parlament.ch/ab/frameset/d/s/4617/77199/d_s_4617_77199_77252.htm?DisplayTextOid=77253.
See also Federal Council's accompanying Message, at FF 2003 1065, in particular at 1069-70, at http://www.bag.admin.ch/embryonen/bundesgesetz/f/bot_efg.pdf. The LRCS is based on a project prepared by the Federal Administration, which is available at
http://www.bag.admin.ch/embryonen/bundesgesetz/f/efg_entw.pdf. *See also generally* Dominique Sprumont, *La recherche avec les cellules souches: un défi !*, 3 RAPPORT IDS 3 (2003).
The LRCS and its Ordinance entered into force on March 1, 2005, after a referendum against the law was defeated in November 2004.

288 *See* Bertrand Kiefer, *Le débat public sur les recherches avec les cellules souches: un sentiment de déjà vu …*, 3 RAPPORT IDS 37, at 40 (2003) (deploring that the proposal for a law on research on human beings was left aside to rush the draft law on research on embryos, even though the latter has a much smaller impact on the population); Sprumont (RSDS), *supra* note 100, at 40 and 45 (lamenting the delay); Dominique Sprumont, *Loi sur la recherche impliquant des êtres humains: encore un "paquet" paralysant*, LE TEMPS, Apr. 5, 2004, at 14.

289 See the glossary at Annex II of the Good Clinical Practices accompanying the (former) IOCM 1995 Regulation.

290 As already mentioned several times, the principal ICH Guideline on clinical trials (ICH E6) is fully applicable pursuant to Article 4.1. OClin.

291 For example, the canton of Fribourg has chosen to apply good clinical practices to *all* research on human beings, whether or not a therapeutic product is involved. Decree of September 12, 1995, regarding clinical trials on human beings, [In French: "*Arrêté du 12 septembre 1995 concernant les essais cliniques sur l'être humain*"]; 821.20.22; entry into force on January 1, 1996; text at
http://www.fr.ch/v_ofl_bdlf_pdf/en_vigueur/fra/8212022v0002.pdf [hereinafter Fribourg 1995 Decree].

become irrelevant as all studies would be governed by the same set of rules. It would also be preferable for Swissmedic to have authority over all clinical trials, even when no therapeutic product is involved. By overseeing all experimentation on humans, Swissmedic would acquire in-depth expertise of the subject and would be in a position to recognize and monitor positive or worrisome trends in the conduct of trials.

3.2.2. Definition of "therapeutic products"

This subsection describes which products come within the *product scope* of the LPTh. At this stage, it is necessary to note that the *product scope* of the LPTh is poorly formulated. Its Article 2 lists the different categories of products and processes which are regulated by the LPTh. These include pharmaceuticals and medical devices, which are further defined in Article 4.1.a&b LPTh. However, the remainder of the law (as well as the various Ordinances) refers only to pharmaceuticals and medical devices, and not the other products and devices mentioned in Article 2. This leads to interpretation difficulties. For example, one does not know whether provisions of the LPTh or of the OClin regarding pharmaceuticals should also apply to narcotics (Article 2.1.b LPTh) or to therapeutic processes (Article 2.1.c LPTh).

3.2.2.1. Pharmaceuticals

There are two broad categories of therapeutic products: pharmaceuticals (whether for preventive, diagnostic or therapeutic use) and medical devices.[292] Under the LPTh, blood and blood products are held to be pharmaceuticals.[293]

Under the OClin, biologic* drugs (biopharmaceuticals) are regulated exactly as chemical pharmaceuticals.[294] A pharmaceutical can be a prescription-only ("Rx") or an over-the-counter ("OTC") product.[295] Pharmaceuticals encompass products from classic (allopathic) medicine or from complementary/alternative medicine ("CAM").[296] Phar-

---

[292] This is implicit in the full title of the LPTh and in Article 2.1.a LPTh.
Medical devices are defined at Article 4.1.b. LPTh.

[293] *See* Article 4.1.a. *in fine* LPTh.

[294] Biologics, as their name indicates, are products manufactured from living biological material, whether cells, organs or tissues. Marketed biologics include monoclonal antibodies, cytokines, enzymes, growth factors, proteins. In the United States, approval of biologics follows a different procedure. Swiss pharmaceutical law does not distinguish between "classic" pharmaceuticals and biopharmaceuticals.
In the United States, see for instance Karen Weiss, *Biologics Corner: For biologics reviewers, process defines the product*, 9(5) NEWS ALONG THE PIKE (Dec. 3, 2003), at http://www.fda.gov/cder/pike/nov2003.htm#Bio (although some of the views expressed in this article are increasingly challenged by (bio)generic firms).

[295] On the decision to assign a product to the Rx-only category, see, for instance, Robert R. Fenichel, *Which drugs should be available over the counter?*, 329 BMJ 182-83 (July 24, 2004), at http://bmj.bmjjournals.com/cgi/content/full/329/7459/182?ecoll.

[296] *See* the Federal Tribunal Decision of March 28, 2003, (2A.515/2002), at point 3.5, at http://www.polyreg.ch/bgeunpubliziert/Jahr_2002/Entscheide_2A_2002/2A.515__2002.html.
Most randomized double-blind clinical trials of CAM have failed to substantiate the efficacy of such treatments. *See* Wayne B. Jonas et al., *A Critical View of Homeopathy*, 138 Ann. Intern. Med. 393, at 396-97 (2003), at http://www.annals.org/cgi/reprint/138/5/393.pdf. *See however* Klaus Linde et al., *Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials*, 350 LANCET 834-43 (Sept. 20, 1997), and see also the comments at 824 and 825.

maceutical include lightly regulated products, such as a sore throat mint.[297] They include already approved drugs or drugs that have not yet received their marketing authorization (see subsection 6.1. below). The level of risks attendant to the use of the pharmaceutical is indifferent; the absence of any risk (were it conceivable) does not rule out the application of the OClin.[298]

I should however remark that the focus of this thesis is chiefly on clinical trial of *new prescription drugs*. These are also the products most often tested in clinical trials, since "old" drugs, alternative medicines,[299] OTC drugs[300] and line extensions do not go through extensive testing.

3.2.2.2. Transplants

Are *not* considered therapeutic products (under the LPTh) *live* organs, tissues, live cells of human or animal origin used for transplantation purposes (hereinafter "transplants").[301] As of June 2005, organs, tissues and cells used for transplantation were still regulated by the Decree of March 22, 1996, on transplants (hereinafter the 1996 Decree).[302] This Decree is soon to be replaced by a Federal Law on transplantation ("LTransplant").[303] The latter has its own provision (Article 35) on clinical trials.[304] In addition, Articles 53 to 57 LPTh (on clinical trials) are applicable by analogy.[305] However, the OClin itself apparently does not apply.[306]

---

297 However, since these products usually receive their marketing authorization without having to submit evidence of safety or efficacy, they are typically not investigated in clinical trials.

298 In the United States, up until 1981, many voices in the medical community urged to exempt low-risk studies from FDA requirements pertaining to informed consent. *See* FDA (1981), *supra* note 260.

299 *See generally* Franklin G. Miller et al., *Ethical Issues Concerning Research in Complementary and Alternative Medicine*, 291 JAMA 599, at 601, (Feb. 4, 2004), at http://jama.ama-assn.org/cgi/reprint/291/5/599.pdf.

300 *See, e.g.,* Robert G. Pinco, *Implications of FDA's Proposal to Include Foreign Marketing Experience in the Over-the-Counter Drug Review Process*, 53 FOOD & DRUG L. J. 105, at 122 (1998).

301 Compare with the draft LAth at its Articles 4.1.a.&d. and 57 to 60. See also DHA 1997 Explicative Report, *supra* note 7, at 76-78.

302 In French: "*Arrêté fédéral sur le contrôle des transplants*" of March 22, 1996; RS 818.111; at http://www.admin.ch/ch/f/rs/8/818.111.fr.pdf. See also the accompanying Ordinance: in French: "*Ordonnance sur le contrôle des transplants*" of June 26, 1996; RS 818.111.3; at http://www.admin.ch/ch/f/rs/8/818.111.3.fr.pdf.

303 In French: "*Loi fédérale sur la transplantation d'organes, de tissus, et de cellules*"; the text is available at http://www.admin.ch/ch/f/ff/2002/247.pdf. See further the Federal Council's Message of September 12, 2001, FF 2002 19, at http://www.admin.ch/ch/f/ff/2002/19.pdf. *See also* Message of the Federal Council, at FF 1999 3151, at 3268. The Parliament debated the law between December 2003 and October 2004. Eventually, the law was adopted on October 8, 2004. As of June 2005, the necessary ordinance accompanying the law was in preparation.
On the definition of organs, tissues and cells, see Article 3 LTransplant. *See also* the above-mentioned Message, FF 2002 19, at 131-32.

304 Article 37.2 LTransplant applies to clinical trials of transplants of embryonic origin. Article 41.2 LTransplant applies to clinical trials of transplants of animal origin. These two types of clinical trials must be specifically authorized (and not just notified). Compare with Article 35.1 LTransplant. *See also* Federal Council's Message on the LTransplant, FF 2002 19, at 157.

305 *See* Article 35.5 LTransplant. *See* Federal Council's Message on the LTransplant, FF 2002 19, at 157-58. *See also* Article 47.3 LTransplant (for standardized transplants).

306 There are at least two reasons to conclude that the OClin is not applicable. First, Articles 53 to 57 LPTh are only said to apply *by analogy*. Second, the competent authority under the LTransplant and under the

The LTransplant mainly targets *allogeneic* transplants (i.e., the donor and the recipient are different persons). Only Articles 2.3 and 35 LTransplant apply to *autologous** transplants (i.e., the donor and the recipient are the same person).[307]

Organs, tissues and cells coming from *embryos* (including fetuses) fall within the scope of the (future) LTransplant. However, the embryos themselves and the extraction of their stem cells are regulated by the 2005 Federal Law on embryonic stem cell research and, to a lesser extent, by the Federal Law on medically asisted procreation (see subsection 3.2.2.3. below).[308]

Standardized transplants come within the jurisdiction of the (future) LTransplant.[309] However, several provisions of the LPTh are made applicable by analogy, including Article 53 to 57 LPTh on clinical trials.[310] On the other hand, *artificial or "devitalized"* organ, tissue or cell transplants are not transplants, but therapeutic products; they fully fall within the scope of the LPTh and the OClin.[311]

The boundary between biologics (which are regulated as drugs under the LPTh) and standardized transplants is unclear. Many biologics are manufactured using human cells. The distinguishing criterion is likely to be their intended use. The LTransplant is applicable to products *used to replace a missing or damaged* tissue or cell (i.e., a transplantation).[312] When a cell-derived product is used to cure a disease, the LPTh should not apply. Anyhow, further Swissmedic guidance on borderline situations would be welcome.

LPTh/OClin is not the same. Third, in its Article 35.4, the LTransplant sets forth a rule that already exists in the OClin (Article 21). If the latter were applicable, there would have been no reason to repeat this rule.

307 *See* Article 2.3 LTransplant. *See* Federal Council's Message on the LTransplant, FF 2002 19, at 131.

308 *See supra* note 287. In French, "*Loi fédérale sur la procréation médicalement assistée*" of December 18, 1998, which entered into force on January 1, 2001; abbreviated (from the French): LPMA; RS 814.90; text in French at http://www.admin.ch/ch/f/rs/8/814.90.fr.pdf. Article 2.2.d. LTransplant. *See* Federal Council's Message on the LTransplant, FF 2002 19, at 131. See also the Federal Council's Message on the LPMA, at FF 1996 III 197.

309 Standardized transplants are products manufactured from organs, tissues and cells and that can be standardized or whose manufacturing process can be standardized. *See* Articles 2.1 and 3.d. LTransplant. *See also* Federal Council's Message on the LTransplant, FF 2002 19, at 132-33.

310 Article 47 LTransplant, in particular paragraph 3 (applicable only to standardized transplants of human origin). *See also* Federal Council's Message on the LTransplant, FF 2002 19, at 167.

311 *See* Federal Council's Message on the LTransplant, FF 2002 19, at 130.

312 Article 2.1 of the (future) LTransplant. *See also* Federal Council's Message on the LTransplant, FF 2002 19, at 130.
For other applications of stem cell therapy, see TA Swiss (Centre for Technology Assessment), Cells that are causing a political stir, Summary of the TA-Swiss study "Human Stem Cells," at 31, (2003), at http://www.ta-swiss.ch/www-remain/reports_archive/publications/2003/030217_KF_Stammzellen_e.pdf [hereinafter TA Swiss (stir)].

3.2.2.3. Stem cell therapy

High hopes are placed in stem cells.[313] One version of stem cell treatment has "repair" cells being injected to restore a patient's damaged organ or tissue.[314] A now classic intervention in various cancer therapies is to store the patient's own stem cells (here, autologous *hematopoietic* cells) before high-dose chemotherapy.[315] Once the high-dose anti-cancer treatment is over, the patient receives his own stem cells, which will reconstitute the bone marrow destroyed by this chemotherapy.[316] However, the overall benefits of such a therapy are disputed for certain diseases, especially for breast cancer.[317]

Stem cells therapy may also be useful in the treatment of several other diseases.[318] For example, scientists are attempting to administer stem cell-derived cardiomyocytes to repair heart tissue.[319] These cells would then prevent or cure cardiovascular diseases (e.g., heart attacks). Stimulated autologous white blood stem cells are also used to treat renal cancer.[320] In the more distant future, stem cells could even be used to manufacture in vitro organs.[321] This would remove the necessity to call on live or deceased organ donors.

While the use of *adult* stem cells (such as hematopoietic cells) is not particularly contentious, the admissibility of research on *embryonic* stem cells ("ESC")[322] and stem

---

313 *See, e.g.,* SNSF, Position du FNS sur l'utilisation des cellules souches embryonnaires humaines dans la recherche en biomédecine [SNSF's position on the use of human embryonic stem cells in biomedical research], at 1, (Sept. 28, 2001), at http://www.snf.ch/downloads/snf_position_stammzellen_f.pdf.

314 *See* Federal Council's Message on the LTransplant, FF 2002 19, at 34-35; Federal Council's Message on the LRCS, FF 2003 1065, at 1087.

315 The cells are taken from the patient's own bone marrow or from peripheral blood. This is therefore an *autologous* (cell) transplant. For a list of diseases for which stem cell transplants are used, see National Marrow Donor Program, Diseases Treatable by Stem Cell Transplant (2003), at http://www.marrow.org/MEDICAL/diseases_treatable_by_stem_cell_transplants.html.

316 See for example the detailed explanations provided by ECRI (formerly the Emergency Care Research Institute), High-dose chemotherapy with bone marrow transplant for metastatic breast cancer, at 11-15, (Mar. 1996), at http://www.ecri.org/Patient_Information/Patient_Reference_Guide/bc.pdf [hereinafter ECRI (chemotherapy)].

317 *See* Janice Hopkins Tanne, *Stem cell transplants are not helpful in breast cancer, studies say*, 327 BMJ 68 (July 12, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7406/68-b.pdf.

318 See in relation with diabetes, Palle Serup et al., *Islet and stem cell transplantation for treating diabetes*, 322 BMJ 29-32 (Jan. 6, 2001), at http://bmj.bmjjournals.com/cgi/reprint/322/7277/29.pdf. *See also* A. L. Lennard & G. H. Jackson, *Stem cell transplantation*, 321 BMJ 433-37 (Aug. 12, 2000), at http://bmj.bmjjournals.com/cgi/reprint/321/7258/433.pdf.

319 *See, e.g.,* Doris A. Taylor, Cellular cardiomyoplasty with autologous skeletal myoblasts for ischemic heart disease and heart failure, 2 CURR. CONTROL TRIALS CARDIOVASC. MED. (Sept. 10, 2001), at http://www.bioheartinc.com/cvm-2-5-Taylor.pdf.

320 *See, e.g.,* FDA, FDA Expands Access to Experimental Treatment for Advanced Renal Cell Cancer, (Sept. 26, 1995), at http://www.fda.gov/bbs/topics/ANSWERS/ANS00684.html.

321 *See* Federal Council's Message on the LTransplant, FF 2002 19, at 37.

322 Embryonic stem cells (ESC) are extracted from surplus embryos initially produced for the purpose of in-vitro fertilization but then no longer needed. ESC can also be obtained from aborted embryos. However, the LRCS applies only to ESC obtained from surplus embryos (Article 1.1 LRCS).
See TA-Swiss (Centre for Technology Assessment), Ethical and legal questions on stem cell research in Switzerland, (Apr. 15, 2002), at http://www.ta-swiss.ch/www-remain/reports_archive/press_releases/pressemitteilungen2002/PM020415_Menschliche_Stammzellen_en.pdf. *See also* Federal Council's Message accompanying the law on research on embryos, FF 2003 1065, at 1080-81.

cells derived from *clones* ("therapeutic cloning")[323] has generated passionate controversies. Most countries are reticent to allow research that inevitably leads to the destruction of early-stage embryos, including cloned embryos.[324] Similarly, the creation and exploitation of embryos or clones specifically for research purpose is a divisive issue.[325] The debate often centers on the social-religious issue of the point in time when Life is thought to begin (at the time of fecundation, when the fetus is viable, either with or without medical assistance, or at birth?).[326] The concept of "Dignity" is also put forward, the argument being that submitting unconsenting embryos to research is per se degrading.[327]

Switzerland has adopted a strict position to constrain ESC research.[328] A draft law on research on embryos and embryonic stem cells (hereinafter: "LRE") was circulated among interested parties between May and August 2002.[329] In November 2002, the Swiss Home Affair Department issued a report compiling the comments received.[330] It was immediately followed by the Federal Council's Message published in February 2003.[331] The Federal Law on embryonic stem cell research ("LRCS") was adopted by

---

In the United States, see the chapter on ethical issues of the NBAC, ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, VOLUME I, at 45-62, at http://www.georgetown.edu/research/nrcbl/nbac/stemcell.pdf [hereinafter NBAC (Stem cell report)]

323 *See generally* Federal Council's Message on the LTransplant, FF 2002 19, at 37.

324 Of course, the embryos would be destroyed anyway, since this type of research uses surplus (i.e., unnecessary) embryos from in vitro fecondation or cloned embryos that either could develop into a fetus or would not be allowed to do so.
See in Switzerland, TA-Swiss (Centre for Technology Assessment), Recherche sur les cellules souches embryonnaires [Research on embryonic stem cells], PubliFocus, Rapport d'une méthode participative, at http://www.ta-swiss.ch/www-remain/reports_archive/publications/2002/UN_Rapport_entier.pdf. On issues related to the extraction and use of stem cells, see for instance in Switzerland: Central Ethic Commission of the SAMS, Position sur le prélèvement et l'usage des cellules souches pour la recherche scientifique, (Aug. 28, 2001).
For an overview of policies in other countries, see TA Swiss (stir), *supra* note 312, at 29-30 and at 38-39.
In the United States, President Bush linton has excluded *federal funding* for the creation of new embryonic stem cell lines. Only research using existing lines is to receive federal funding. See Remarks by the President on Stem Cell Research (Aug.9,2001), at http://www.whitehouse.gov/news/releases/2001/08/print/20010809-2.html.

325 See more generally Article 19.2.c. of the Swiss Constitution forbidding that "more human ova than are capable of being immediately implanted into the woman" be produced. *See also* Article 36.2.a and 37 of the law on transplantation.

326 See for instance in Switzerland, Groupe de travail "Bioéthique" de la Conférence des évêques suisses, Le statut de l'embryon, Prise de position, (Feb. 27, 2003), at http://www.kath.ch/sbk-ces-cvs/pdf/Der_Status_von_Embryonen_f.pdf. For more in-depth analysis regarding the status of embryos, see two interesting collections of essays: ANTHONY DYSON & JOHN HARRIS (editors), EXPERIMENTS ON EMBRYOS, (Routledge, 1990); JOHN HARRIS & SOREN HOLM, THE FUTURE OF HUMAN REPRODUCTION, (Oxford Univ. Press, 1998).

327 *See* ATF 119 Ia 460, at cons.12, at p.499 = JdT 1995 p.586, at cons.12, at 598.

328 *See* Article 42.2 LPMA, which temporarily authorizes the use for research purposes of research on surplus embryos. These embryos were initially made and stored for procreation purposes. Once the couple has achieved or abandoned this objective, it can authorize research on its now superfluous embryos. Article 42.3 LPMA was voted in October 2003, and entered into force on December 31, 2003. Without this provision, all previously stored surplus embryos would have had to be destroyed.
See also Articles 5-10 of the LRCS as well as the accompanying Federal Council's Message, at FF 2003 1065, at 1067-68.

329 *See* Federal Council's Message on the LRCS, FF 2003 1065, at 1127.

330 *See* Department of Home Affairs, Rapport sur les résultats de la procédure de consultation portant sur le projet de loi relative à la recherche sur les embryons [Report on the results of the comment procedure regarding the draft law concerning research on embryos] (Nov. 2002), at http://www.bag.admin.ch/embryonen/bundesgesetz/f/vern_ber.pdf [hereinafter DHA Embryo Report].

331 Federal Council's on the LRCS, FF 2003 p.1065-1181.

Parliament on December 19, 2003, but was attacked by a popular referendum. [332] The vote took place in November 2004, resulting in a clear majority (over 60%) in favour of the law. The LRCS and its ordinance (the ORCS) entered into force on March 1, 2005.

Under Swiss law, all stem cells are regulated as *transplants*.[333] This includes *hematopoietic* stem cells, even though blood and blood products are regulated by the LPTh as pharmaceuticals.[334] *Embryonic* stem cells used for *transplantation* purposes (on human beings) fall within the scope of the 1996 Decree/LTransplant.[335] Research involving ESC originating from clones is not possible, since Switzerland bans all forms of cloning, including (unwisely, in my view) therapeutic cloning.[336]

The production (or extraction) of ESC is governed by the Federal Law on embryonic stem cell research ("LRCS"), which entered into force on March 1, 2005.[337] While the LPTh and its ordinances are *not* applicable to preclinical and clinical research using ESC, the LRCS refers such research projects to the ethics committees instituted by Article 57 LPTh.[338] The Swiss FOPH is endowed with the authority to oversee ESC research; in particular, it receives advance notification of each project.[339] Prior to this stage, the FOPH must have authorized the production of ESC.[340]

Swissmedic has no jurisdiction over stem cell research, even if stem cells are administered on research subjects in the context of a clinical trial.[341] This is surprising considering that Swissmedic oversees clinical trials involving the use of gene therapy or genetically modified microorganisms. There is a close link between stem cell therapy and gene therapy. Indeed, in many other countries, stem cell therapies follow the same rules as gene therapy (on gene therapy, see subsection 3.2.3. below).[342] Provided that the

---

332 *See supra* note 287.

333 *See* Article 2.2.b. of the future LTransplant.

334 *See* Federal Council's Message on the LTransplant, FF 2002 19, at 131.

335 See Article 1.3 LRCS. *See also* Federal Council's Message accompanying the LRCS, at FF 2003 1065, at 1070 and 1146 (indicating that clinical trial (on human beings) of embryonic stem cell therapies are governed by the LTransplant, and not the LRCS).

336 "All forms of cloning and interference with genetic material of human reproductive cells and embryos is prohibited." Article 119.2.a of the Constitution (English translation proposed by the Swiss administration on its website). *See also* Articles 35.1 and 36.1 LPMA and Article 3.1 LRCS; Federal Council's Message regarding the LRCS, FF 2003 1065, at 1091-92.

337 Article 1.1 LRCS. *See also supra* note 287. Under the LRCS, ESC lines can only be producted if needed for a *specific* research project. Moreover this project must have received the favorable opinion of an ethics committee. Article 7 LRCS. Compare with Federal Council's Message on the LRCS, FF 2003 1065, at 1151-52 (which did not require a specific research project.

338 *See* Article 11 LRCS. *See* Federal Council's Message on the LRCS, FF 2003 1065, at 1138-39 and at 1155-56. See also with respect to research on *embryos*: *id.* at 1150.

339 *See* Article 13.1 LRCS.

340 Both the production of ESC and research on embryos necessitate an authorization delivered by the FOPH. *See* Articles 7, 8, and 10 LRCS. Research on ESC only requires notification. *See* Article 13 LRCS. See also the accompanying Federal Council's Message, FF 2003 1065, at 1143-45, 1149, 1151, 1156.

341 Article 2.1 OClin. *See also* Telephone Interview with Chautems (Mar. 2004), *supra* note 170.

342 In the United States, "[t]he FDA defines somatic-cell therapy as the administration to humans of autologous, allogeneic, or xenogeneic living somatic cells that have been manipulated or processed to change their biologic characteristics. … Gene therapy encompasses interventions that involve deliberate alteration of the genetic material of living cells to diagnose, prevent, or treat disease. The administration of cells that have undergone ex vivo genetic manipulation is considered a combination of somatic-cell therapy and gene therapy." David A. Kessler et al., *Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration*, 329 NEW. ENG. J. MED. 1169 (Oct. 14, 1993). *See also* FDA, Application of Current Statutory

stem cells have undergone some modifications, these other countries regulate them as biopharmaceuticals. This is what the European Union has made clear in 2003.[343] The FDA has claimed full jurisdiction over both stem cell and gene *therapies*.[344] The FDA makes no distinction as to the *origin* of the stem cell (e.g., embryonic, adult or cloned stem cells).

3.2.2.4. Narcotics

It is unclear whether clinical trials of *narcotics* (used here to include any illegal drugs) fall within the scope of the OClin when these products are used as therapeutic products (e.g., marijuana used against AIDS wasting).[345] Although illegal drugs used as therapeutic products are governed by the LPTh,[346] the law does not categorize them as therapeutic products.[347] On the other hand, there are no provisions in the LPTh that deal exclusively with narcotics as such,[348] possibly suggesting that narcotics follow the

---

Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, Notice, 58 Fed. Reg. 53,248, at 53,249, (Oct. 14, 1993), at http://www.fda.gov/cber/genadmin/fr101493.pdf.
In Switzerland, according to the SAMS, the transplant of cells or organs that have been genetically modified is to be qualified as gene therapy, even if the patient's own cells are not genetically modified. *See* SAMS, Medical-ethical guidelines for somatic gene therapy in humans, (June 3, 1998), at http://www.samw.ch/content/Richtlinien/e_SomatischGenth.pdf [hereinafter SAMS (Somatic Gene Therapy)]
In the European Union, see Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells, whereas (4), at http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/1_102/1_10220040407en00480058.pdf; Annex I, Part IV, point 3 of Directive 2003/63/EC.

343 *See* whereas (9) and (10) of the Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community Code relating to medicinal products for human use, at http://pharmacos.eudra.org/F2/eudralex/vol-1/new_v1/direct_comm_2003_63_en.pdf [hereinafter Directive 2003/63/EC]. According to Annex I, Part IV, point 2 of this Directive, "somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means."
See also E.U. Guidance (Request), *supra* note 270, at 25-26 (Annex 1).

344 *See* Robert P. Brady et al., *The Food and Drug Administration's Statutory and Regulatory Authority to Regulate Human Pluripotent Stem Cells*, *in* ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, VOLUME II, COMMISSIONED PAPERS, B-1 to B-16, (NBAC, Jan. 2000), at http://www.georgetown.edu/research/nrcbl/nbac/stemcell2.pdf. Stem cell and gene therapies are most often regulated as *biologics*. *Id.* at B-5 and also at B-10. *See also* FDA, Proposed Approach to Regulation of Cellular and Tissue-Based Products, (Feb. 28, 1997), at http://www.fda.gov/cber/gdlns/celltissue.pdf ("Cells and tissues that were manipulated extensively, combined with non-tissue components, or were to be used for other than their normal functions would be regulated as biologics or devices requiring premarket approval by FDA" *Id.* at 7). *See also* Jodi K. Frederickson, *Umbilical Cord Blood Stem Cells: My Body Makes Them, But Do I Get to Keep Them? Analysis of the FDA Proposed Regulations and the Impact on Individual Constitutional Property Rights*, 14 J. CONTEMP. HEALTH L. & POL'Y 477, at 490-92 (1998).

345 See the very criticial review of Swiss studies on the efficacy of heroin prescription to wean or control drug addiction, External Expert Committee of the WHO, Report, International criticism of Swiss heroin trial, (1999), at http://www.gdpn.org/dpna/resources/criticismheroin.htm.

346 Article 2.1.b LPTh.

347 Article 2 LPTh distinguishes three categories: therapeutic products, narcotics used as therapeutic products, and therapeutic processes when in direct relationship with therapeutic products. Similarly, Article 2 OClin distinguishes between clinical trials of therapeutic products on the one hand, and clinical trials of somatic gene therapy on the other hand.

348 Articles 32.2.b and Article 86.1 LPTh mention narcotics only incidentally.

rules applicable to drugs. There is no reason why clinical trials of narcotics should not fall within the ambit of the OClin.[349]

3.2.3. Gene therapy

Article 5.a OClin (which defines clinical trials) only mentions "therapeutic products." It should have added a reference to *somatic gene therapy*, given that the OClin, pursuant to its Article 2.1, appears to regulate *separately* such a therapy (see subsection 3.2.2. above). Moreover, the LPTh extends its application to therapeutic processes that are in direct relation with a therapeutic product.[350] Gene therapy is explicitly cited as an example.

3.2.3.1. Definition of somatic gene therapy

Neither the LPTh nor the OClin contain a definition of gene therapy.[351] Although a uniform definition is nearly impossible due to constant scientific progress, gene therapy is generally understood as a method to correct defective genes.[352] Defective genes include missing duplicative, overexpressed or otherwise faulty genes.[353] The defective gene can either directly cause a disease (e.g., Huntington disease) or be a factor among others (e.g., cancer[354]).[355] In other cases, genetic material can be added to facilitate treatment by other therapeutic products. This procedure is being explored, for example, to make cancerous cells more sensitive to treatment by anticancer drugs or to make healthy cells

---

349 For an example of a clinical trial with cannabis, see Kristina B. Svendsen et al., *Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial*, 329 BMJ 253 (July 16, 2004), at http://bmj.bmjjournals.com/cgi/reprint/329/7460/253.pdf.

350 Article 2.1.c LPTh.

351 See however the definition of genetic engineering ("*génie génétique*") in the Federal Council's Message on the LTransplant, FF 2002 19, at 201 ("*Méthodes et procédures utilisées pour modifier de façon ciblée le patrimoine génétique et partant certaines propriétés précises d'un organisme.*").

352 In most gene therapy studies, a "normal" gene is inserted into the genome to replace an "abnormal" disease-causing gene." Human Genome Project Information, Gene Therapy, at http://www.ornl.gov/TechResources/Human_Genome/medicine/genetherapy.html. *See also* Joseph M. Rainsbury, *Biotechnology on the RAC – FDA/NIH Regulation of Human Gene Therapy*, 55 FOOD & DRUG L.J. 575 (2000), at http://www.fdli.org/pubs/Journal%20Online/55_4/art5.pdf.
In the European Union, see also the definition set forth at Annex I, Part IV, point 1 of Directive 2003/63/EC ("gene therapy medicinal product shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo.").

353 *See also* Federal Council, Message relatif à la loi fédérale sur l'analyse génétique humaine [Message regarding the federal law on human genetic analysis]; FF 2002 6841, at 6848-50, at http://www.admin.ch/ch/f/ff/2002/6841.pdf. The (future) law is hereinafter abbreviated (from the French): LAGH. The Swiss Parliament debated the law between March and October 2004; the transcripts are available from http://www.parlament.ch/ab/frameset/f/n/4702/101331/f%5Fn%5F4702%5F101331%5F101556.htm. Eventually, the law was adopted on October 8, 2004 (text at http://www.admin.ch/ch/f/ff/2004/5145.pdf). As of June 2005, its necessary accompanying ordinance was still under preparation.

354 *See* Robert M. Frederickson, A Gene Therapy Primer, available from http://www.bio.com/newsfeatures/infocus.jhtml?realmId=&infocusId=in60489&cid=ci54206. *See also* Génie Génétique, Service/Documentation, Pour en savoir plus, Les applications humaines du génie génétique, at http://www.genetic.ch/services/sdes1999.htm.

355 *See, e.g.,* Federal Council's Message on genetic analysis, *supra* note 353, at 6850.

less sensitive to the adverse reactions* caused by existing anticancer treatments.[356] Treatments that accidentally modify the genetic material of cells are not to be qualified as gene therapy.[357]

Somatic gene therapy, by opposition to *germline* therapy, affects genes found on any chromosome, *except for* the sex chromosomes.[358] Genetic changes achieved by somatic therapy are *not* meant to be passed on to the patient's descendants. *A contrario* germline therapy would create inheritable genetic traits.[359] Somatic gene therapy cannot absolutely exclude accidental transfer of modified genetic material to offspring, but this is not its main purpose.[360] For this reason, somatic gene therapy should never have been as controversial as it is today (see subsection below).[361]

The SAMS has laid down a broader and quite complex definition of somatic gene therapy, acknowledging in the process the difficulty of such a task.[362]

3.2.3.2. Opposition to gene therapy

Opposition to gene therapy takes many forms and is based on various grounds. Although I do not share the concerns of the opponents to gene therapy, it is useful to briefly introduce them here.

First, there is a widely-spread fear that some individuals will be tempted to make use of such therapy to genetically "improve" themselves or their children, for example by adding an "extra-intelligence" gene.[363] Such eugenics interventions are fervently disapproved even if they were to affect only the individual who chose them.[364] Some people fear that this would alter the "nature" of mankind, an inadmissible "tinkering"

---

356 *See* National Cancer Institute, Questions and Answers About Gene Therapy (2000), at http://cis.nci.nih.gov/fact/7_18.htm.

357 Excluded from this definition is notably the use of drugs that accidentally or unavoidably "turn off" the expression of genes. SAMS (Somatic Gene Therapy), *supra* note 342, at 2-3.

358 *See, e.g.,* Genetics Home Reference, Help Me Understand Genetics, at chapter 5, at 8, at http://ghr.nlm.nih.gov/dynamicImages/understandGenetics/gene_therapy.pdf.
See generally George Q. Daley, *Cloning and Stem Cells – Handicapping the Political and Scientific Debates*, 349 NEW. ENG. J. MED. 211-212 (July 17, 2003), at http://content.nejm.org/cgi/reprint/349/3/211.pdf (discussing the current bill before U.S. State assemblies and their possible consequences); Nadia Rosenthal, *Prometheus' Vulture and the Stem-Cell Promise*, 349 NEW. ENG. J. MED. 267-274 (July 17, 2003) (discussing the culture of stem cell lines); Konrad Hochedlinger & Rudolf Jaenisch, *Nuclear Transplantation, Embryonic Stem Cells, and the Potential for Cell Therapy*, 349 NEW. ENG. J. MED. 275-286 (July 17, 2003) (discussing the medical problems with reproductive, respectively therapeutic, cloning)]

359 Germline gene therapy is prohibited by the Swiss Constitution. According to its Article 119.2.b., "[n]on-human reproductive and genetic material may neither be introduced into nor combined with human reproductive material."

360 *See also* SAMS (Somatic Gene Therapy), *supra* note 342, at 1-2 and 4; Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 309.

361 *See* Rainsbury, *supra* note 352, at 595-96.

362 *See* SAMS (Somatic Gene Therapy), *supra* note 342, at 1-3.

363 *See* SAMS, Medical-ethical Guidelines for genetic investigations in humans, at 2, (June 3, 1993) at http://www.samw.ch/content/Richtlinien/e_Gen.pdf [hereinafter SAMS (genetic investigations)]. *See generally* Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 309.

364 *See, e.g.,* Christine Willgood, *FDA Regulation: An Answer to the Questions of Human Cloning and Germline Gene Therapy*, 27 AM. J. L. AND MED. 101, at 102 and at 107-110, (2001).

with Nature's or God's will. Others fear that such opportunity would result in a multi-class society, in which some citizens would have the financial means to enhance themselves, while others would be left behind and become second-class citizens (remember the movie Gattaca). Associations representing handicapped persons fear that their members would be (even more) exposed to discrimination if parents are given the option – if not straightforward encouragements – to abort fetuses diagnosed with genetic diseases.[365]

A second concern is that only populations in developed countries are going to benefit from valuable/therapeutic gene therapy, while people in developing countries are left to survive with a sub-minimum food and medical care.[366] Their argument is that money would be better spent on finding vaccines for tropical or infectious diseases, instead of investing in genetic therapy that is only going to benefit a handful of people, at least at the beginning.

A third fear is that not enough is known about gene manipulation: As long as all possible adverse consequences cannot be precisely anticipated, it is too risky to even engage in this avenue of research. Critics of genetic technology invoke the "precautionary principle" and argue that the expected benefits are not sufficiently consequential to offset these unknown and unforeseeable dangers.[367] They would like to see a moratorium on all these techniques, except perhaps the ones with an immediate life-saving potential, until a more precise risk assessment and a more thorough public debate has taken place … in other words a moratorium likely to last forever.

3.2.3.3. Gene therapy and the OClin

In most cases, gene therapy also involves the administration of what the law qualifies as a therapeutic product. A gene, typically encapsulated in the appropriate vector,[368] is injected in the patient's body; the gene aims to correct the genetic deficiency causing the patient's disease. The gene and its vector are both products of biological origin intended to act medically on the human organism. They meet the definition of a pharmaceutical.[369]

The respective scope of the LPTh and the OClin concerning gene therapy differ slightly. The OClin encompasses somatic gene therapy[370], while the LPTh applies to

---

365 *See* SAMS (genetic investigations), *supra* note 363, at 11-12.

366 *Id.* at 3.

367 See generally the results of a French survey according to which 50% of French people think that science has done as much "harm" as it has "done good." *See* French Senate, La Nécessité d'une Relance de la Diffusion de la Culture Scientifique et Technique, at http://www.senat.fr/rap/r02-392/r02-3923.html; Research Directorate-General, European Commission, Europeans, Science and Technology, at 29 (Eurobarometer 55.2) (Dec. 2001), at http://europa.eu.int/comm/public_opinion/archives/eb/ebs_154_en.pdf.

368 "A carrier molecule called a vector must be used to deliver the therapeutic gene to the patient's target cells. Currently, the most common vector is a virus that has been genetically altered to carry normal human DNA. Viruses have evolved a way of encapsulating and delivering their genes to human cells in a pathogenic manner." Human Genome Project Information, *supra* note 407. *See also* Gregory Smutzer, *Delivering the Goods*, 14[19] THE SCIENTIST 28, (Oct. 2, 2000), at http://www.the-scientist.com/yr2000/oct/profile1_001002.html.

369 Article 4.1.a LPTh.

370 Article 2.1 OClin.

gene therapy provided that it is in direct relationship with a therapeutic product.[371] The reason for this divergence is not clear, since the December 2000 draft of the OClin (by the Federal Office for Public Health) only included therapeutic processes in direct relation with therapeutic products.[372]

There may be cases where early research into gene therapy does not involve the administration of a therapeutic genetic product. For example, experimentations with the genetic material of a patient *outside* his body is not "in direct relationship" with a therapeutic product. It is however unclear whether such an experiment constitutes gene *therapy* under Article 2.1 OClin.

3.2.3.4. Ex vivo gene therapy

As for *ex vivo* genetic therapy, it is not entirely clear why it was excluded in the final draft of the OClin.[373] The main difference between *in vivo* and *ex vivo* therapies is not altogether self-evident. According to the Swiss Expert Committee for Biosafety, *in vivo* gene therapy entails transferring the gene "directly inserted in the patient's body by means of vectors" whereas in *ex vivo* gene therapy, "the therapeutic gene is transferred in vitro to cells or tissue before insertion in the patient's body."[374] Furthermore, "[w]hen the genetic manipulation is performed *ex vivo* on cells which are then administered to the patient, this is also a form of somatic cell therapy."[375] The FDA does not distinguish between both types of gene therapy. No convincing rationale has been put forward to justify such a distinction under Swiss law.

3.2.4. The administration of a therapeutic product

If no therapeutic product is administered, the OClin does not apply. This would be the case, for example, of studies that monitor the natural course of influenza in untreated patients or that track the effect of stress on multiple sclerosis.[376] Likewise behavioral studies are outside the scope of the OClin to the extent that no pharmaceutical is administered.

Studies that involve pharmaceuticals but where none is actually *administered* to subjects are also outside the literal scope of the OClin. For example, if prospective patients are questioned in order to evaluate the readability of the drug's notice of use, the OClin should not apply. A similar situation arises if a study is to extract biological ma-

---

371 Article 2.1.c. LPTh.

372 Article 2.1. of the 2000 draft OClin, *supra* note 8.

373 In the FOPH's draft of December 2000, there is no mention of ex vivo genetic therapy.

374 Swiss Expert Committee for Biosafety, Gene Therapy, Legal Basis, at http://www.umwelt-schweiz.ch/buwal/eng/fachgebiete/fg_efbs/rubrik_gentherapie/gen_grundlage/. *See also* Wikipedia Free Encyclopedia, Gene Therpy, at http://en.wikipedia.org/wiki/Gene_therapy.

375 *See* Center for Biologics Evaluation and Research (CBER), FDA, Guidance for Human Somatic Cell Therapy and Gene Therapy, (March 1998), at 3, at http://www.fda.gov/cber/gdlns/somgene.pdf.

376 *See* D. Buljevac et al., *Self reported stressful life events and exacerbations in multiple sclerosis: prospective study*, 327 BMJ 646 (Sept. 20, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7416/646.

terial from subjects to use it to manufacture new drugs.[377] If no drug is administered and is being studied on humans, the OClin does not apply.

What about trials that do not focus on the effects of the drugs, but where one is nonetheless administered? Imagine the situation where researchers investigate the incidence of depression in cancer patients. Although only subjects who are following some form of drug treatments are enrolled in the trial, the latter is not directly exploring these drugs' safety or efficacy profile. Based on the language of Article 5.a OClin, the trial would not be subject to the OClin, unless it is argued that depression is being studied as a side effect of these drugs (and that, therefore, the study is truly exploring drug safety issues).

Such illustrations show that borderline situations are common. As argued in subsection 3.2.1., the more appropriate solution would be to submit all biomedical clinical trials, whether or not they involve a drug study, to essentially the same rules.

3.2.5. Safety, efficacy and other properties

The Swiss OClin at Article 5.a does not list all acceptable objectives, but only mentions safety, efficacy, bioavailability, and "other properties." How drug sponsors prove safety and efficacy is reviewed in subsection 4.1.1. below.

While the first two objectives are clear, the reference to "other properties" is rather vague. Would, for example, a study whose objective is to evaluate the taste of a drug be a clinical trial verifying these "other properties"?

Another question is whether a trial where a drug would be administered only to better understand a physiological phenomenon would fall within the definition of the "objectives" of the OClin. In the case of Ellen Roche – a healthy subject who died in 2001 during a clinical trial at the John Hopkins Medical School – the trial was aimed at understanding the causes of asthma.[378] The researchers believed that certain nerves were involved in the bronchoprotective response. To verify this hypothesis, they aimed to block neurotransmission for these nerves. A drug was administered to healthy volunteers to that effect. The drug lacked FDA approval.[379] Because the trial's objective was not to establish the efficacy or safety of the drug, it would therefore appear that such a trial would have beeen outside the scope of the OClin, had it occured in Switzerland.[380] In the United States, the FDA was unable to provide clear guidance as to whether a clinical trial authorization (i.e., an IND) was mandatory under such circumstances.[381]

---

377 On issues related to biological material, see subsection 8.6.7.2. below.

378 *See* Internal Committee, Report of Internal Investigation into the Death of a Volunteer Research Subject led by Lewis C. Becker, John Hopkins Medical School, (2001), at http://www.hopkinsmedicine.org/press/2001/JULY/report_of_internal_investigation.htm [hereinafter Hopkins Internal Committee Report].

379 The drug had been approved for another therapeutic indication and for a different route of administration. It was withdrawn in 1972 for lack of effectiveness, and not for safety reasons. *Id.*

380 Under Swiss law, other provisions of the LPTh may nonetheless apply to unapproved drugs.

381 Hopkins Internal Report, *supra* note 478.

3.3. A living human subject

Although they do not state this explicitly, the LPTh and the OClin only apply to clinical trials on *living* subjects.[382] Research on *corpses* are beyond the scope of these texts. In most countries, death is defined as brain death.[383] Hence, research on individuals who have just died but still have certain vital body functions ("brain death" as opposed to "cardiac death"[384]) are not governed by these regulations.[385] In practice, this type of research remains rare.[386]

A similar solution has been retained in the United States, where research on corpses or brain dead patients does not fall within the purview of federal regulations.[387] An exception is however made if the investigator starts acquiring data, even very preliminary data, before the death of the patient.[388]

Nonetheless, several groups have urged that rules similar to those applicable to living subjects be also applied to dead subjects. In particular, no research should be undertaken unless allowed by the patient before his death ("premortem consent") or by

---

382 On deciding when death is deemed to have occurred, see for example Olivier Guillod & Jean-François Dumoulin, *Définition de la mort et prélèvement d'organes, aspects constitutionnels*, [Definition of death and organ extraction, constitutional aspects], (Jan. 1999), at http://www.bag.admin.ch/transpla/gesetz/f/gutacht_guillod.pdf. *See also* SAMS, Directives médico-éthiques pour la définition et le diagnostic de la mort en vu d'une transplantation d'organes (1996) (under revision), at http://www.samw.ch/content/Richtlinien/f_Hirntod.pdf.

383 On the notion of brain death, see Shelly Ozark & Michael A. DeVita, *Non-Heartbeating Organ Donation: Ethical Controversies and Medical Considerations*, 39(3) ANESTHESIOLOGY CLINICS 103-118 (Summer 2001). *See also* CCNE, Avis sur l'expérimentation médicale et scientifique sur des sujets en état de mort cérébrale, Avis N°12, [Advice on medical and scientific experimentation on brain dead subjects], (Nov. 7, 1988), at 1, at http://www.ccne-ethique.fr/francais/pdf/avis012.pdf [hereinafter CCNE N°12]. See also in Switzerland Article 9.1 (future) LTransplant.

384 On these two notions, Guillod & Dumoulin, *supra* note 382, at 9-14.

385 For a thorough discussion of the issues associated with research on the newly dead, see Michael A. DeVita et al., *Research involving the newly dead: An institutional response*, 31 CRIT. CARE MED. 385-390 (2003). *See also* American Academy of Pediatrics ("AAP"), Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, 95 Pediatrics 286-294 (Feb. 1995), at http://www.aap.org/policy/00655.html [hereinafter AAP (Guidelines)].

386 A question that has received more attention by practitioners is the use of cadavers to teach important medical techniques to young physicians. *See, e.g.,* Jon Rosenson et al., *Teaching Invasive Procedures to Medical Students,* 291 JAMA 119-120 (Jan. 7, 2004), at http://jama.ama-assn.org/cgi/reprint/291/1/119.pdf; Mark W. Fourre**,** *The Performance of Procedures on the Recently Deceased*, 9 ACAD EMERG MED. 595-598 (June 2002), at http://www.aemj.org/cgi/reprint/9/6/595.pdf?ijkey=b088126a360c858ba4c2cf5d1ec605d729c27319; Council on Ethical and Judicial Affairs of the American Medical Association. *Performing procedures on the newly deceased*, 77 ACAD MED. 1212-1216 (Dec. 2002), at http://www.academicmedicine.org/cgi/reprint/77/12/1212.pdf?ijkey=41609fa62aab868f030f56b2619fa881699c7dda.

387 *See, e.g.*, 45 C.F.R. § 46.102(f) ("human subject means a *living* individual…") (emphasis added).

388 "If permission to obtain tissue from an individual following death is requested from that individual or their surrogate while the individual is still living, and if some pre-death screening or data collection procedure involving the individual is being performed for the purpose of research, then the usual Institutional Review Board rule and jurisdiction apply. The institutional review board is responsible for supervising and regulating all research activities wherein an investigator conducting research obtains data through intervention or interaction with a living individual or obtains identifiable, private information about a living individual." The Committee for the Oversight of Research Involving the Dead, Policy for research involving the dead, 31 CRIT. CARE MED. 391, 391 (2003).

surviving members of his family.[389] The jurisdiction of ethics committees is often extended to encompass such research.

True enough, the ethical dilemma attached to such research warrants widening the scope of the existing regulatory safeguards.[390] Whenever possible, the subject should be asked for his explicit informed consent (obviously when still alive).[391] However, it is doubtful that all other safeguards should be similarly extended (e.g., pre-clearance by a public authority).

3.4. Research as compared to individualized health care

In practice, the issue that most often arises is whether a treatment is given as part of a clinical trial or, on the contrary, belongs to "ordinary" medical practice.[392] This question is significant because the rules governing clinical trials differ markedly from those applying to medical practice.[393] In the first hypothesis, the LPTh and the OClin apply; in the second, they do not. These two texts set forth safeguards that benefit only subjects participating in a clinical trial; patients who receive medical care in ordinary settings do not enjoy these protections.

The distinction between research and medical practice is important in other contexts too. It influences, for example, the standards for doctors' malpractice liability or for health insurance's reimbursement policies.[394] Similarly, doctors must explain much

---

389 Compare with the Swiss Supreme Court decision at ATF 101 II 177 = JdT 1976 I 362. In this case, the Court had to decide whether surviving parents can object to organs being taken from their dead adult son for transplant purposes. In 1969, the hospital had taken their son's heart and successfully transplanted it to a recipient with an urgent need. The family of the dead donor had not been informed and learned of the transplant through the media. The Court expounded on the personality rights of the parents and those of the deceased. This legal analysis of organ transplants should be equally valid for clinical research.

390 *See, e.g.,* AFP, *Cadavres de bébés utilisés pour la recherche nucléaire*, [*Baby cadavers used for nuclear research*], LE TEMPS, (June 7, 2001) at 41; Committee for the Oversight of Research Involving the Dead, *supra* note 388, at 391-93.

391 *See* CCNE N°12, *supra* note 383, at 2.

392 I use the expression "ordinary medical practice" (or "medical care in ordinary setting") for a lack of better terminology. The term "standard care" would incorrectly suggest that the treatment has to be standard or broadly recognized, which is not necessarily true.
See also paragraph 32 Helsinki Declaration (according to which physicians are "free to use unproven or new prophylactic, diagnostic and therapeutic measures" if they offer "hope of saving life, reestablishing health or alleviating suffering" that validated methods do not offer. The physician must first secure the informed consent of his patient.)
On innovative non-standard medical care, see Nancy M. P. King, *The Line Between Clinical Innovation and Human Experimentation*, 32 SETON HALL L. R. 573-582 (2002), at http://law.shu.edu/journals/lawreview/lawrev/events/human_subject_research_symposium/king_article.pdf.

393 "The basic concept behind the definition of *investigational* is the research-practice boundary or the experiment-therapy continuum. … [This continuum] has medical-scientific, regulatory, and informed consent dimensions, which overlap each other without being congruent." *See* Rand Report, *supra* note 254, at chapter 3.

394 In Switzerland, medical insurance companies must reimburse pharmaceuticals that are enumerated in the FOPH's List of Specialties ("LS"). This list contains only drugs which have been authorized by Swissmedic, thus excluding investigational drugs that lack this authorization. There are some very limited exceptions for non-LS drugs.
In the United States, insurance companies have even more discretion in deciding whether or not to reimburse a drug. Usually, experimental treatments will be reimbursed only if the insurance company agrees to it. "Insurers are increasingly attempting to curb their responsibility to pay for extremely costly treatments

more thoroughly the risks related to a treatment administered in the context of a clinical trial, even if the treatment is strictly identical to the one administered under ordinary medical care.[395]

Although drug research and ordinary medical practice may first appear to be two opposite notions (i.e., research being defined as what is not standard care),[396] in practice, this distinction is considerably less obvious.[397] Apart from its Article 5.a, the OClin offers no indication to tell them apart.[398]

This subsection demonstrates that perhaps the most helpful criterion is whether or not the physician's[399] only purpose is to help her patient by giving him the best possible health care based on his own *individualized* medical needs.[400] When, taking into account all circumstances," individualized health care is not *the only* objective of the physician, we leave the realm of "ordinary" health care to enter that of clinical trials.

3.4.1. Systematic methods

According to the OClin definition, clinical trials incorporate *systematic* methods in order to verify the product's characteristics.[401] *A contrario*, a non-systematic study is not a clinical trial. The OClin does not spell out what is meant by "systematic."

Over the course of the last quarter of the 20th century, the medical community has worked out scientific methods to minimize bias* in clinical trials (see subsection 6.3. below). These scientific methods are in all probability what the legislator had in mind when setting forth the "systematic" requirement of the OClin. A systematic study should therefore be conducted according to a plan (i.e., the study protocol; see subsection 6.2.1.) that describes, among other issues, i) what information to collect, when and how, and ii) how to limit bias.

---

that are unlikely to succeed by seeking to apply more scientific definitions and standards of acceptability." Curtis Jantzi, *The Ethical Structure behind Human Experimentation*, 1996, at http://www.goshen.edu/bio/Biol410/Biol410SrSemPapers/Jantzi.html.http://www.goshen.edu/bio/Biol410/Biol410SrSemPapers/Jantzi.html.

395 *See, e.g.,* MANAÏ (CONTEMPORAINE), *supra* note 16, at 248-49.

396 The FDA definition of clinical investigation even hinges on this distinction. *See* 21 C.F.R. § 312.3(b).

397 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at preamble.

398 Pursuant to the Article 5.a OClin definition, a clinical trial is a "study" whose aim is to "verify" a product's characteristic in a "systematic manner" (see subsection 3.1. above).

399 To follow U.S. stylistic convention, I use alternatively the masculine and feminine forms. As my own arbitrary convention, I have used the feminine form for the investigator, the masculine form for the subject, and the neutral form for the sponsor.

400 The American Belmont report contrasts biomedical and behavioral research with the practice of accepted therapy. The second is defined as "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success." Part A Belmont report, *supra* note 61. For more information on the Belmont report: subsection 2.3.2. above. *See also* SPRUMONT, *supra* note 16, at 26-27.
The 1990 Council of Europe's Recommendation R(90)3 (*supra* note 115) defines medical research as "any trial and experimentation carried out on human beings, the purpose of which is to increase medical knowledge."

401 *See* Article 5.a OClin.

However, should a study that *fails* to be systematic be *rewarded* by escaping the requirements of the OClin? Clearly, the answer is no. If that were the case, a researcher could very easily circumvent the existing rules governing clinical trials merely by arguing that the proof that she was just treating her patient (and not conducting research) resides in the fact that she did not use systematic methods.[402]

A U.S. court was confronted with such a situation.[403] Mr. Ancheff complained that he had been subjected to medical research at a hospital, as a consequence of which he had incurred injuries. That research had taken place without his informed consent. The drug he received had been administered at doses higher than those normally prescribed.[404] Perhaps even more telling, all patients enlisted into the hospital program were automatically put on the higher dosage even if their physicians had prescribed less. The hospital was following a protocol and data from each patient receiving the drug was collected and pooled. The hospital's researchers presented their scientific findings to the medical community.

Despite all these circumstances, the Hospital denied that the administration of the drug was part of medical research. It countered that its program had not involved "control groups, randomization or double blinding, which are some hallmarks of research."[405] In addition, the hospital had not planned "to advertise the drug, to secure funding from a drug company, or to report findings to the Federal Drug Administration."[406] The hospital contended that it was chiefly concerned with safety and efficacy outcomes in patients. It asserted that, at the time of the plaintiff's hospitalization, there was enough scientific information available to attest the safety of the drug treatment; hence, the suitability of the drug was not an open scientific question.

The controversy (in this case, an issue of fact submitted to the jury) boiled down to whether use of systematic methods (e.g., control groups, randomization, blind[407]) was a prerequisite to qualify a practice as medical research. Because the appellate court did not have to rule directly on this issue,[408] the legal question remained open.

In my opinion, disregard for systematic methods is not a criterion to be used to demarcate clinical trials from ordinary medical practice. In the aforementioned case, some systematic methods had been employed: for example, the treatment was appar-

---

402 *See also* Annas & Grodin, *supra* note 63, at 308.

403 *See Ancheff*, 799 A.2d 1067. The Connecticut Supreme Court did not have to rule directly on the issue of whether treatment was provided in the context of a clinical trial. Rather, it was submitted questions regarding the admissibility of evidence. In particular, the court had to decide whether the lower court clearly abused its discretion in *refusing* to allow the Belmont Report as evidence (at the plaintiff's request). The Court found that there was no manifest abuse – a conclusion I do not share.

404 *Id.* at 1071.

405 *Id.* at 1072. The expert witness for the hospital stated that "in a research project, control groups [are] used in order to compare 'the new therapy or one therapy to a standard,' represented by the control group; and that the assignment of patients to either the research group or the control group would be accomplished on a random basis." *Id.*

406 *Id.* at 1072.

407 For an explanation of these concepts, see subsection 6.3. below.

408 The Connecticut Supreme Court had to review whether the instructions given to the jury (which aimed to delineate the concept of research and that of standard care) were proper. It found for the defendant, once again a conclusion I would reject. In my view, the explanations provided in these jury instructions should have been viewed as seriously deficient.

ently administered based on a written program or protocol. The quality and the extent of the methods used should not be the decisive criterion.

Rather, it is best to err on the side of excessive caution. As soon as the *primary* purpose of the physician is not to treat patients, one leaves the realm of standard care to enter that of research.[409] In other words, if some features of the treatment serve interests other than those of the patient, the line is crossed.[410] Hence, in the *Ancheff* case above, I would have imposed compliance with clinical trial regulations.

3.4.2. Generalizable information

We saw in subsection 3.1. that, under U.S. law, not only must clinical trials be done in a systematic manner, they must also lead to "generalizable" results.[411] Swiss regulations no longer comprise such a requirement.[412]

To fulfill the U.S. condition of generalizability, the data obtained through a treatment study must not only be of the type: "product A has helped Messrs. X, Y and Z"; this information would be of no direct use to treat Mrs. W. Rather, the treatment must be administered in such a way that the results obtained with a subset of patients can be safely extrapolated to a broader group of patients in a comparable situation.[413]

Because they rarely satisfy this condition, observations reported by physicians about their own patients are not regulated as clinical trials.[414] In contrast, research projects conducted by pharmaceutical companies are purposely designed to fulfill this condition: These companies test their compounds to get a marketing authorization. Logically, their marketing application claims that the data resulting from the trials are generalizable.

The "generality" criterion can be helpful in situations located in-between the two ends of the spectrum. Take the situation of the *Ancheff* case described in the previous

---

409 *See* Part A. Belmont report ("if there is *any element* of research in an activity, that activity should undergo review for the protection of human subjects." (emphasis added)).

410 *See* Rand Report, *supra* note 254, at chapter 3. *See also* part A Belmont report ("For the most part, the term "practice" refers to interventions that are designed *solely* to enhance the well-being of an individual patient or client and that have a reasonable expectation of success." (emphasis added))

411 *See* U.S. Office for Human Research Protection, HHS, Institutional Review Board Guidebook, at chapter 1 (Institutional Administration), all chapters available from http://www.hhs.gov/ohrp/irb/irb_guidebook.htm [hereinafter IRB Guidebook]. *See also* Jantzi, *supra* note 394.

412 Compare Article 5.a. OClin to the definition of research in Annex II of the IOCM 1995 Regulation.

413 *See however* SPRUMONT, *supra* note 16, at 27 (defining 'generalizable' as being subject to confirmation by acceptable scientific observation or deduction). *See also* Sprumont (De l'éthique), *supra* note 159, at 137-38.

414 "[O]bservational studies include, in descending order of persuasiveness, cohort (longitudinal) studies, case-control studies, cross-sectional studies, uncontrolled case series or cohort studies, time-series studies, ecological or cross-population studies, descriptive epidemiology, and case reports." FDA Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements, December 22, 1999, at http://www.cfsan.fda.gov/~dms/ssaguide.html.
See also See IOCM, Complementary Explanations regarding the Regulation on Medicines in Clinical Studies, 5 BULLETIN MENSUEL OICM 170-74, at B.3, at 173 (2000) [hereinafter IOCM former Compassionate Explanations].

subsection. The results of the research/treatment were generalizable to the extent that the research/treatment was done using systematic methods. If patients "treated" were sufficiently numerous and represented a diverse patient population (e.g., both sexes, different age groups), if the drug was administered in a consistent manner (e.g., same dosage, same concomitant medications), if sources of bias were accounted for (e.g., by identifying baseline characteristics of patients treated), then the results were probably generalizable.

This exemplifies that the link between the "generalizable" and the "systematic" criteria. The former is generally the consequence of the latter. The results of a study can hardly be held generalizable if they were not obtained through systematic methods. Similarly, a study that *succeeds* in conforming strictly to all systematic methods tends to generate generalizable results.[415]

As we already observed for the "systematic" criterion, a study can aim at producing "generalizable" results, but fail.[416] Should this failure exonerate the researcher from compliance with the requirements attached to clinical trials? Rewarding the researcher for failing to meet her objectives would be absurd and unpractical. Hence, a researcher should not be allowed to sidestep the clinical trial requirements by alleging that her results were after all not generalizable.

3.4.3. The criterion of intent

The two criteria discussed above (the "systematic" and the "generalizable" criteria) have the advantage of being largely *objective*. A drug agency can determine, habitually in retrospect, to which extent a study was indeed systematic and generalizable. A majority of cases are clear-cut. For example, it makes no doubt that clinical trials sponsored by pharmaceutical companies in order to support future marketing applications use both systematic methods and yield generalizable data. But one might not be able to assess the more difficult cases based only on these two criteria.

A further approach consists in incorporating the *subjective* criterion of intent.[417] The question to be answered is what is the primary objective of the researcher/physician?

---

[415] These results may not be positive (e.g., proof of a difference between the test product and the comparator product). In some situations, the clinical trial may not be able to detect a difference, because there is none. Exceptions to this general causal relation are studies that used systematic methods but did not clearly state their hypotheses. For example, one could imagine a situation where researchers meticulously followed two groups of patients being treated for cancer, but did not make plan to use their observations to confirm or rebut any given hypothesis.

[416] For example, the study was powered to detect a difference between two groups based on the assumption that the rate of adverse events would be 10 per 100 subjects. It noticed too late that the true rate of adverse events is only 1 per 100 subjects. As a result, the study failed to produce generalizable results.

[417] "The distinction between medical research and innovative medical practice *derives from the intent behind the intervention*. In medical practice the sole intention is to benefit the individual patient, not to gain knowledge of general benefit, though such knowledge may emerge from the clinical experience gained." (emphasis added). Explanatory Report [hereinafter COE Explanatory Report] to the Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, (Protocol on Biomedical Research) [hereinafter COE Research Protocol], at 3, (CDBI/INF (2003) 7), (June 30, 2004). The protocol was adopted by the Council of Europe's Committee of Ministers on June 30, 2004. The text of COE Explanatory Report is available at

Did the physician want to get generalizable results and thus at least attempted to use systematic methods? If yes, even if she ultimately failed, her initial intentions should be enough to qualify her project as a clinical trial.[418]

The language of the OClin appears to support this subjective criterion, given that Article 5.a uses the expression "aims to" (in French: "*visant à*"[419]; in Italian: "*con lo scopo*"[420]). In the United States, the FDA takes into consideration whether the "principal intent" is to "develop information about the product's safety and or efficacy."[421] The European Union definition uses the words "intended to" (i.e., intended to discover or verify the properties' of an investigational medicinal product).[422]

Hence, when a physician administers a drug because she wishes to find out more about the drug's characteristics, her practice is akin to an experiment. No longer is the overarching purpose to treat the patient in the best possible way.[423] Gathering information about the drug is just as important, if not more so.[424]

This change of focus may be revealed by the medical procedures that the patient has to undergo. For example, the patient may be asked to give extra blood, to stay longer in the hospital, to go to a different hospital, to eschew certain concomitant medications, to undergo additional tests (e.g., X-ray) which an ordinary patient would not have to. For all these extra procedures, the ordinary patient-doctor relationship is reversed: It is no longer the doctor who is providing a service to her patient, but the subject who is helping the investigator.[425]

However, whenever the patient-subject does not undergo special procedures, the intent of the physician-researcher is difficult to ascertain.[426] Physicians often attempt to excuse their non-compliance with clinical trial regulations by contending that they were only subject to the more flexible requirements governing medical care.[427] For example, in the *Ancheff* case, the doctors argued that they were "using available literature, including prior research and clinical data, for the improvement of patient care and

---

htt'p://conventions.coe.int/Treaty/EN/Reports/HTml/195.htm and the text of the Protocol at http://conventions.coe.int/treaty/en/treaties/html/195.htm.

418 *See* Rand Report, *supra* note 254, at chapter 3.

419 The German version of the OClin is less suggestive of an intent requirement. According to Article 5.a OClin, *"Klinischer Versuch: am Menschen durchgeführte Untersuchung, mit der Sicherheit und Wirksamkeit sowie weitere Eigenschaften eines Heilmittels systematisch überprüft werden."*

420 The entire provision reads *"sperimentazione clinica: ogni studio eseguito sull'essere umano con lo scopo di verificare in modo sistematico la sicurezza e l'efficacia nonché altre proprietà di un agente terapeutico."*

421 *See* FDA, "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators (1998 update), at http://www.fda.gov/oc/ohrt/irbs/offlabel.html [hereinafter FDA (Off-Label)].

422 Article 2(a) of the Directive 2001/20/EC.

423 *See, e.g.,* Sprumont & Béguin, *supra* note 134, at 896; SPRUMONT, *supra* note 16, at 29.

424 *See* Noah, *supra* note 4, at 366 and 388.

425 *See, e.g.,* Hermann Amstad, *Auf der Suche nach Versuchspersonen für klinische Versuche* [*Searching for subjects for clinical trials*], 83(42) BULLETIN DES MÉDECINS SUISSSES 2216 (2002), at http://www.saez.ch/pdf/2002/2002-42/2002-42-1030.PDF [hereinafter Amstad (Suche)].

426 However, in the aforementioned case of Johnson v. Meltzler, the court appeared to agree that "the doctors' predominant intent" is decisive. Johnson v. Meltzler, 134 F.3d 1393, at 1398 (9th Cir. 1998).

427 *See id.* (Doctors asserted that they gave an unapproved compound for the patient's benefit, and not for the research purposes).

safety," and not "validating an untested theory or hypothesis."[428] Reconstructing the true intent after the facts is a task riddled with difficulties. The physician has an obvious interest in stressing the most beneficial objectives. How can the plaintiff prove her wrong? Inevitably, the plaintiff is left to rely on objectives factors, such as the use of systematic methods.

3.4.4. Status of the drug

The fact that the drug administered has not yet been approved by the national drug agency can be viewed as a clue suggesting the existence of a clinical trial. For instance, if a hospital decides to use a completely novel compound to treat its patients, it seems that it should do so within the more regulated framework of a clinical trial. Yet, this clue by itself is no sufficient proof for at least two reasons.

First, physicians have the right to administer, under their own responsibility,[429] drugs that have not been approved (either for the relevant therapeutic indication* or, more rarely, at all).[430] This practice, referred to as "off-label use," does not automatically transform ordinary medical care into a clinical trial,[431] even when the off-label use is not commonly recognized as standard by the profession.[432] Certain off-label uses have emerged as fully accepted treatments, despite the lack of authorization.[433] The physician prescribing off-label may be required to provide more information to her patient to make sure the latter's consent is valid. However, the higher standard for informed consent does not alter the nature of the act. Off-label treatment is normally not labeled as a clinical trial. In particular, the physicians do not have to comply with clinical trial requirements.[434]

---

428 *Ancheff*, 799 A.2d at 1070.

429 *See, e.g.,* James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANN. HEALTH L. 295 (2003) (the physicians' privilege of off-label use is also referred to as the "practice of medicine exemption.").

430 Some unauthorized drugs (or some therapeutic indications) have thus become standard treatments, despite the lack of authorization.

431 *See* FDA (Off-Label), *supra* note 421. ("If the physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner *when the intent is the 'practice of medicine'* does not require the submission of an Investigational New Drug Application." (emphasis in the original text)). *See also* FDA, IND Exemptions for Studies of Lawfully Marketed Drugs or Biological Products for the Treatment of Cancer, Guidance for Industry, (Jan. 2004), at http://www.fda.gov/cber/gdlns/indcancer.pdf (clarifying when the submission to the FDA of an IND (application) is required).

432 *See however* SPRUMONT, *supra* note 16, at 30-31.

433 Daniel B. Klein & Alexander Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? Testing an Argument by Structured Conversations with Experts* (Independent Institute Working Paper No. 47), (Apr. 16, 2003), at http://www.independent.org/pdf/working_papers/47_offlabel.pdf (criticizing the inconsistency of requiring extensive clinical trials for on-label drugs only).
Alexander T. Tabarrok, *Assessing the FDA via the Anomaly of Off-Label Drug Prescribing*, 1 THE INDEPENDENT REVIEW 25, at 26 (Summer 2000), at http://www.independent.org/tii/media/pdf/tir51_tabarrok.pdf [hereinafter Tabarrok]. It is worth mentioning that both authors exhibit a strong, and in my view partly misguided, bias against the FDA.

434 *See, e.g.*, 21 C.F.R. § 312.(d).

Second, there are clinical trials whose express purposes are to learn more about an already marketed drug (and its already authorized therapeutic indications). As we will see in subsection 6.1.4. below, phase IV clinical trials probe more closely the efficacy and safety of *approved* drugs.

3.4.5. Other elements to be taken into account

Other factors may be helpful to decide whether a drug is administered within a clinical trial.

The existence of a *protocol*[435] that calls for the pooling of all data concerning treated patients can be viewed as a factor suggesting clinical trials. This pooling of data acquired through the systematic methods described in the protocol is meant to contribute to generalizable knowledge. Moreover, the existence of a protocol implies that the physician is bound to abide by its contents (see subsection 6.2.1. below).[436] Consequently, she cannot freely depart from the procedures set forth therein, even if these changes would benefit her patient.[437] But once again, it cannot be deduced from the absence of a protocol that the treatment belonged to ordinary medical practice.[438] Rather, this absence may be a warning sign that the investigator flouted the regulations requiring a protocol for all clinical trials.

Data submitted to a drug agency as part of a *marketing application* usually come from projects that qualify as clinical trials. If a pharmaceutical company gathers information from private-practice doctors and submits it to the drug agency, these doctors would be hard-pressed to deny their involvement in a clinical trial. Because drug agencies typically insist on receiving data that derive from systematic and generalizable studies, submission of these reports to the authorities is a reasonable factor on which to decide whether a clinical trial took place. However, the fact that a study was ultimately *not* submitted to a drug agency cannot serve to exclude a clinical trial. For instance, universities which engage in preliminary research endeavors should still comply with Swiss regulations even if their projects are not part of a targeted drug development effort.

Funding by a government or a research agency may be a sign that the project is part of a clinical trial.[439] Usually, doctors and hospitals do not receive grants just to administer treatments to patients. Rather, grants are awarded for projects designed to advance science. Hence, a medical project financed through a grant should generally meet the higher standards applicable to clinical trials. *Publication* of results is also taken as an

---

435 A protocol is defined as "a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial." Section 1.44 of ICH E6; in the European Union: Article 2(h) of Directive 2001/20/EC.

436 The IOCM had remarked that the physician's freedom to prescribe as she sees fit is suspended during a clinical trial. *See* IOCM Compassionate Explanations, *supra* note 471, at 170.

437 Of course, even in a clinical trial, the investigator can deviate from the protocol when necessary to safeguard the health of subjects.

438 *See however* SPRUMONT, *supra* note 16, at 29 and also at 38-39.

439 *See* IRB Guidebook *supra* note 411, at chapter 1, (page 2 out of 11).

indication that these results are indeed generalizable and were obtained in the context of research.

3.4.6. Specific borderline situations

3.4.6.1. Non-interventional studies

The European Directive gives an example of what falls in the intermediate or gray zone. According to the Directive, a "non-interventional trial" is a

> study where the [already-approved] medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing application. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data.[440]

Thus defined, non-interventional trials are synonymous with "observational" studies; the researcher is simply observing the health care that physicians choose to deliver to their patients. The patient is not undergoing any *additional* medical procedure as part of the research.[441] The physician and the patient remain free to decide together on the treatment that is to be provided. Under E.U. law and the specific exemption of the Directive, non-interventional trials are not regulated as clinical trials.[442] This exemption requires however that the medicinal product administrated have a marketing authorization.

Swiss law does not have a similar provision. Hence, it is unclear whether the OClin applies to non-interventional trials. This has become a controversial issue (see also subsection 6.1.4. on phase IV clinical trials).

The pharmaceutical industry claims that observational trials are outside the scope of the OClin. Consequently, it is launching more and more trials of this kind. A pharmaceutical sponsor will hire doctors as investigators and pay them some CHF 150.- (per patient) to observe the evolution of their patients' medical condition (e.g., depression). The sponsoring pharmaceutical company will recommend – explicitly or implicitly – that the doctor use the company's drugs for the "trial." By participating in this essentially commercial study, the doctors make more money than they would in their typical medical practice. In all probability, their semi-commercial semi-scientific interactions with pharmaceutical sponsors influence their choices in prescriptions.[443] To be sure, the

---

440 Article 2(c) of the European Directive 2001/20/EC.

441 See for example the clinical trial on pregnant women infected by HIV sponsored by agencies of the NIH, at http://www.clinicaltrials.gov/ct/show/NCT00028145?order=45.

442 Article 1 of the aforementioned Directive.

443 *See generally* Chris Watkins, *Characteristics of general practitioners who frequently see drug industry representatives: national cross sectional study*, 326 BMJ 1178-1179 (31 May 2003). http://bmj.com/cgi/content/full/326/7400/1178 ("General practitioners who report weekly contact with drug representatives are more likely to express views that will lead to unnecessary prescribing than those who report less frequent contact.")

sponsor is "betting" that the doctor will get into the habit of prescribing its drugs. The sponsor may even try to use the study results in its commercial literature distributed to doctors. Yet, these results may never be eligible for publication in medical journals nor for submission to drug agencies.

Swissmedic holds the position that these trials should fall under the purview of the OClin. These non-interventional studies are not very different from phase IV clinical trials, which do fall within the scope of the OClin (on phase IV trials, see subsection 6.1.4. below). The solution would hinge on whether "systematic" methods are being used. If the gathering of information is conducted in a systematic manner, for example by filling at regular intervals detailed forms about the patient's medical status, then the non-interventional should be held to be a clinical trial as defined by the OClin. In August 2005, the Federal Tribunal ruled that non-interventional studies (as defined by the European Directive) do fall within the Swiss definition of clinical trials and are therefore fully subject to the LPTh and the OClin (decision 2A.522/2004).

3.4.6.2. Expanded access programs

3.4.6.2.1. The international context

Owing chiefly to the AIDS epidemic, drug agencies throughout the world have been confronted with patients demanding access to yet unapproved drugs. Their requests were initially denied, causing a shift in the tactics used by AIDS patients and their organizations. While the movement had initially been dispersed and peaceful, it became much more cohesive and assertive (see also subsection 2.1.4. above).

AIDS activists framed their struggle as one of a right to live pitched against an indifferent administration.[444] They were claiming a right to make their own decisions, a right to choose for themselves the risks they were willing to take and a right to access early promising treatments.[445] In other words, AIDS patients having to choose between a sure death without medical treatment and an improbable survival thanks to a risky drug argued that they were entitled to make this choice for themselves. In the United States, their protests culminated on October 11, 1988, with the siege of the FDA headquarters and the confinement of FDA officers.[446] The FDA protested its innocence and assured it was doing its best to approve as quickly as possible promising medicines against HIV/AIDS. The clash persuaded drug agencies to adopt formal procedures on accelerated access (see subsection below).[447] It also showed the FDA and other drug agen-

---

444 See, in Switzerland, Coordination Genevoise des associations de lutte contre le sida ("COGE"), Ciblé Sida, (Dec. 2002-Jan. 2003), at http://www.groupesida.ch/ciblesida/CIBLESIDA_UN.pdf.

445 In 2003, two organizations initiated action against the FDA claiming that the Agency was unduly restricting patients' access to life-saving, but yet unapproved, treatments. *See* ACRP, *Groups Sue FDA Over Drug Access*, ACRP WIRE, Sept. 2003, http://acrpnet.org/resources/acrpwire/sept_sue.html.

446 *See, e.g.,* Victor F. Zonana, *New Fronts in the AIDS War an Activist Group for the '80S Aims to 'Shame People into Action'*, L.A. TIMES, Apr. 4, 1989, at 1, at http://www.aegis.com/news/lt/1989/LT890403.html.
See generally Larry Thompson, *Experimental Treatments? Unapproved but Not Always Unavailable*, FDA CONSUMER MAGAZINE, (Jan.-Feb. 2000), at http://www.fda.gov/fdac/features/2000/100_exp.html.

447 In the United States, the FDA distinguishes among compassionate use per se (when no protocol is in force), Treatment IND (that accompanies a clinical trial done under a protocol), and the much less frequent parallel track (for anti-cancer and anti-HIV drugs only) (21 C.F.R. § 312.34 and 35). *See* 21 C.F.R. § 312.83. *See also* David A. Kessler, *The Regulation of Investigational Drugs*, 320 NEW. ENG. J. MED. 281, at 284-85 (1989), at http://www.quinacrine.com/archive/kess89a.pdf [hereinafter Kessler (Regulation)]; M. D. Greenberg, *supra*

cies that they had to intensify their efforts to explain to the public and to patients how they operated.

When the sought-after drug is not yet be approved and is only made available in the context of clinical trials, physicians and patients depend on the sponsor-manufacturer's good will to get access. The latter sometimes accepts to supply the drug outside its clinical trials, for example because of pressure exercised by patient advocacy groups. These groups protest the fact that many patients simply cannot enroll in the available clinical trials, because they do not meet the strict eligibility criteria set forth by the sponsor in the protocol. The consequences for these patients can be extremely dire: an unnecessary and avoidable death."

Compassionate access programs set up by sponsors to allow patients to access the investigational compound outside clinical trials pose several problems. I will only mention two here. First, the programs may interfere with the conduct of the formal trial, if patients who could enroll in the trial arrange instead to receive the drug under the compassionate program. If this occurs, the sponsor may never be able to prove the efficacy and safety of its drug, which may either be denied the marketing authorization or be given one based on insufficient scientific data.[448] Second, the sponsor has much less control over compassionate programs and patients receiving the investigational drug are not as carefully monitored as the patients enrolled in the clinical trial. Compassionate programs are generally not under the responsibility of an investigator, but rather under that of the patient's own doctor. The latter often receives less information about the progression of the trial. For example, he may not be told immediately of newly discovered adverse reactions.

Given the problems arising in connection with compassionate access programs, these come under increased regulatory scrutiny. In the United States, the FDA regulates them, though in a "lighter" fashion compared to clinical trials.

3.4.6.2.2. The various forms of compassionate use in the United States

Yielding to pressure from these patient advocacy groups, the FDA has created various opportunities to get early access to yet-unapproved drugs.[449] They are broadly designated under the general label "compassionate use."[450] The principal access mechanisms are briefly described below.[451]

---

note 129, at 315-21 and also at 324-27. *See also* Vivian I. Orlando, *The FDA's Accelerated Approval Process: Does the Pharmaceutical Industry Have Adequate Incentives for Self-Regulation?*, 25 AM. J. L. AND MED. 543 (1999); BARUCH A. BRODY, ETHICAL ISSUES IN DRUG TESTING, APPROVAL, AND PRICING 170 (Oxford Univ. Press, 1995).

448 When a life-threatening disease cannot be properly treated with available therapies, new promising drugs are sometimes approved even though the evidence submitted to prove safety and efficacy is less than complete.

449 These opportunities come in addition to clinical trials themselves. As already mentioned, not all patients can participate in a clinical trial, whether because of entry criteria or for other practical reasons (e.g., no research site near the patient's residence).

450 This term, however, does not appear in the legislation.

451 In addition to these procedures to make unapproved drugs available to patients, other mechanisms provide for an accelerated approval of promising drugs. Drugs approved through an accelerated procedure become available to all patients, since they receive a marketing authorization. Because this authorization is granted on the basis of medical evidence less complete than what is normally required, the sponsor is generally re-

The first category, formally codified in 1987, is *treatment IND*.[452] The FDA has cleared more than 30 drugs for treatment IND.[453] Treatments INDs run parallel to clinical trials and are meant for patients who do not meet current clinical trials' eligibility criteria.[454] For the FDA to "approve" a treatment IND,[455] the investigational drug must offer better therapeutic prospects than available alternatives;[456] it must also treat a serious disease.[457] Treatment INDs are usually granted once the experimental drug has completed phase II.[458] Sponsors must also collect safety information from patients having received the drug under the treatment IND. Treatments IND must be based on a protocol which is reviewed by the FDA.[459] The FDA may stop – i.e., impose a so-called "clinical hold" on – a treatment IND if its regulatory conditions are no longer satisfied.[460]

Patients accepted into a treatment IND must give their consent because of the investigational nature of the drug received.[461] The sponsor must arrange for either an ethics committee approval or an FDA waiver of this requirement.[462] Sponsors can charge for drugs supplied to patients under a treatment IND, provided that they have notified the FDA in advance.

In the early 1990s, the FDA set up its *parallel track* program.[463] While somewhat similar to the Treatment IND, the parallel program is however specific to AIDS.[464] The evidence to be presented to the FDA to get parallel track is less than what is required for approval of Treatment INDs. Hence, parallel track access can be given as early as post-phase I. On the other hand, the organization requirements for a parallel track program resemble that of a clinical trial; for instance, a protocol must be submitted.

---

quired to conduct post-approval clinical trials (see below subsection 6.1.4.1.). Accelerated approval procedures are not analyzed in this thesis, since they are clearly beyond its scope.

452 *See* 21 C.F.R. § 312.34. *See also* FDA, Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, Drugs and Biologics, Expanded Access of Investigational Drugs, at http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html [hereinafter FDA (Expanded access)]; Brody, *supra* note 447, at 171 and at 173.

453 *See* FDA, Treatment Investigational New Drugs (IND) Allowed to Proceed, at http://www.fda.gov/oashi/patrep/treatind.html. For an illustration of the analysis conducted by the FDA prior to its approval of a treatment IND, see FDA, FDA Authorizes Treatment IND for Advanced Pancreatic Cancer, (Feb. 17, 1995), at http://www.fda.gov/bbs/topics/ANSWERS/ANS00644.html.

454 *See* 21 C.F.R. § 312.34(b)(iii).

455 More accurately, the approval amounts to a clearance mechanism. The treatment IND request goes into effect within 30 days of its submission if the FDA does not object. *See* 21 C.F.R. §312.35(a).

456 There must be "no comparable or satisfactory alternative drug … in the intended patient population." *See* 21 C.F.R. § 312.34(b)(ii).

457 The drug must be "intended to treat [or diagnose] a serious or immediately life-threatening disease." *See* 21 C.F.R. § 312.34(b)(ii). For a definition, see 21 C.F.R. § 312.34(b)(3)(ii).

458 *See* 21 C.F.R. § 312.34(a).

459 *See* 21 C.F.R. § 312.35(a)(1).

460 *See* 21 C.F.R. § 312.34(d).

461 *See* 21 C.F.R. § 312.34(c).

462 *Id.*

463 The parallel track regulations were first proposed in May 1990. *See* BRODY, *supra* note 447, at 177.

464 For cancer patients, an expanded access program is available, under the label "Group C" treatment IND. It is organized in cooperation with the (U.S.) National Cancer Institute. *See* FDA (Expanded access), *supra* note 451.

When an investigational drug is to be made available to individually identified patients, the FDA grants a *single-patient IND*. This special IND has to be requested for each patient receiving the drug. Such a request is habitually made by the physician, once he has secured the active cooperation of the manufacturer.

3.4.6.2.3. The various forms of compassionate use in Switzerland

Programs for facilitated access to yet-unapproved drugs are also frequently designated under the generic term of compassionate use. They take several different forms.

First, patients are recognized the right to import medicines (whether authorized abroad or not) for their own personal use without control at the customs.[465] The imported drug must be for personal consumption and the quantity imported must remain small (often limited to a 3-month use).

Second, as we saw before (subsection 3.4.4.), physicians have the right to prescribe and administer drugs "off-label," that is for therapeutic indications which have not been approved in their country.[466]

Third, physicians also have the right to import drugs which have not been authorized in their country.[467] In Switzerland, they must request an authorization from Swissmedic.[468] Since September 2004, this system has been made more flexible by authorizing pharmacists (acting upon requests made by physicians) to freely import small quantities of unapproved drugs.[469] This change relieved the pressure on Swiss-

---

[465] *See* M.D. Greenberg, *supra* note 129, at 316.
In Switzerland, these imported drugs must not contain genetically modified organisms; Article 36.1 of the Federal Council's Ordinance on authorizations in the sector of pharmaceuticals of October 17, 2001; RS 812.212.1; in French: "*Ordonnance sur les autorisations dans le domaine des médicaments*"; abbreviated (from the French): OAMéd, text in French at http://www.admin.ch/ch/f/rs/8/812.212.1.fr.pdf. *See also* Swissmedic, Autorisations spéciales pour les médicaments non autorisés, Swissmedic Journal 1/2002, at 6, at http://www.swissmedic.ch/files/pdf/01_2002.pdf.
In the United States, see FDA, Coverage of Personal Importations, Guidance (Personal Importation Policy), Regulation Procedures Manual, chapter 9, at http://www.fda.gov/ora/compliance_ref/rpm_new2/ch9pers.html.

[466] "Off-label" prescribing is not limited to unapproved therapeutic indications; it may also refer to prescription of a drug at a dosage or in a manner not advised by the approved notice of use. Such conduct does not give rise to a clinical trial if the central motivation is to treat a patient therapeutically, as opposed to research purposes. The FDA has issued a guidance for cancer treatment, since the distinction is particularly unclear in this area. *See* Lester M. Crawford, *IND Submission Exemptions*, 287 JAMA 2936 (June 12, 2002), at http://jama.ama-assn.org/cgi/reprint/287/22/2936-a.pdf ("The proposal emphasizes that exemption from the IND requirement depends primarily on whether the investigation significantly increases risk associated with use of the product. … because in oncology modifications of labeled dosing recommendations are common, oncology studies deviating from the approved labeling can be exempted, provided such changes are supported by the literature and generally known clinical experience…. [These studies should not be] intended to support FDA approval of a new indication, significant change in labeling, or advertising of the product ….").

[467] Physicians who exercise their profession on both sides of the border between Switzerland and a neighboring country have a right to import small quantities of medicines for their patients; Article 11 OAMéd.

[468] Article 36.2 OAMéd.
See also decision of the Swiss federal appeal commission for therapeutic products, JAAC 67.93, at point 5.2. (Jan. 28, 2003), at http://www.vpb.admin.ch/franz/doc/67/67.93.html.

[469] *See* the new Article 36.3 OAMéd, which entered into force on September 1, 2004. *See* also the FOPH explicative report of June 5, 2003, at page 38, http://www.bag.admin.ch/heilmitt/gesetz/f/erl_hmvp_f.pdf.

medic, which had been overwhelmed by the number of physicians' requests under this system.[470]

Article 9.4 LPTh is a general clause granting Swissmedic the authority to allow distribution of non-authorized treatment to patients. Three conditions must be met. First, patients must suffer from a life-threatening disease. Second, the drug must show notable efficacy as determined by Swissmedic. Third, there must not be other equivalent pharmaceutical for these patients.[471] Swissmedic retains the mandate to appreciate if, at this early stage, the anticipated benefits exceed the risks, both known and unknown. It can enjoin the sponsor, the physician or the patients to take additional precautions or to consent to special obligations. The provision does not specify who is supposed to apply for this authorization. In theory at least, it could be anyone. In practice, the request is more likely to come from the sponsor or the patient's physician. However, the latter would presumably prefer to use the simplified procedure set forth by Article 36 OAMéd. New ordinances – submitted for consulation in June 2005 – would clarify the requirements of Article 9.4. LPTh.

In addition, according to Article 5 of the Ordinance on pharmaceuticals,[472] promising drugs against serious diseases can receive their marketing authorization following an accelerated procedure. Swissmedic has not yet passed guidelines to explain how it plans to apply both provisions. By contrast, in the United States, the various circumstances that warrant accelerated access are the subject of detailed provisions.

3.4.6.2.4. Do compassionate access programs come under the OClin?

Under the previous intercantonal system, the IOCM had detailed its position on the compassionate access programs.[473] It distinguished four situations where non-approved drugs were administered to patients outside clinical trials: parallel trial programs,[474] compassionate use,[475] extended access,[476] isolated use.[477] There was, however, some irritating overlap between the IOCM's four categories, particularly between the first two. While parallel trial programs were governed by requirements analogous to those

---

470 In 2002, Swissmedic had to issue some 4500 authorizations for the importation of unapproved drugs, about three times as much as was previously issued by all cantons. *See* Press Release, Swissmedic, Swissmedic: premier bilan après 15 mois [Swissmedic: first assessment after 15 months], (Apr. 14, 2003), at http://www.swissmedic.ch/Archiv/Fazit-f.pdf.

471 *See* Decision of the Swiss Federal Tribunal of September 6, 2004 (2A.469/2003), at http://wwwsrv.bger.ch/cgi-bin/AZA/JumpCGI?id=06.09.2004_2A.469/2003 ("*Die Erteilung einer Bewilligung ist danach nicht nur dann ausgeschlossen, wenn bereits identische Präparate zugelassen sind, sondern auch dann, wenn der gleiche therapeutische Erfolg mit anderen Arzneimitteln erreicht werden kann. Ob diese Präparate umständlicher oder teurer sind, müsse ausser Betracht fallen.*").

472 Federal Council's Ordinance on pharmaceuticals of October 17, 2001; RS 812.212.21; in French: "*Ordonnance sur les médicaments*"; abbreviated (from the French): OMéd; text in French at http://www.admin.ch/ch/f/rs/8/812.212.21.fr.pdf.

473 *See* IOCM former Compassionate Explanations, *supra* note 414, at 170-74.

474 *Id.* at B.2.1, at 171.

475 *Id.* at B.2.2, at 172.

476 *Id.* at B.2.3, at 172.

477 *Id.* at B.2.4, at 172.

applicable to "normal" clinical trials (in particular, approval by an ethics committee), compassionate use only required compliance with cantonal procedures.[478]

In April 2004, Swissmedic subscribed to these four categories of compassionate access. It laid down in four "commentary" the conditions that govern them[479] Although this is not explicitly confirmed in Swissmedic's commentaries, it appears that the OClin is *not* applicable to either of these categories.[480] The following table summarizes the requirements set down by Swissmedic.

Conditions	Compassionate Use	Parallel trial	Extended access	Beyond compassionate use
Conditions pertaining to the drug				
Drug to be used not (yet) registered	☑	☑	☑ (request for authorization has been submitted)	☑
Drug is approved abroad or Sufficient clinical trial data	☑	☑	☑	☑ Drug approved abroad
Major therapeutic benefit expected	☑	☑	☑	☒
No satisfactory alternative available	☑	☑ less stringent		☑
Ongoing clinical trials in Switzerland	n.a.	☑	n.a. (Swiss trials completed)	n.a.
Conditions pertaining to the patient				
Severe, life-threatening debilating disease	☑	☑	☑	☒
Therapy of last resort or emergency	☑	☑ less stringent	☑ less stringent	☑ less stringent
Use for a single patient	☑ any patient	☑ patients not enrolled as subjects	☑ Only former Research subjects	☑
Written consent of the patient	☑	☑	☑	☑

478 *Id.* at 171-72.

479 Swissmedic's commentaries are available at
http://www.swissmedic.ch/files/pdf/Commentary_special_authorization_compassionate_use.pdf;
http://www.swissmedic.ch/files/pdf/Commentary_special_authorization_parallel_trial.pdf;
http://www.swissmedic.ch/files/pdf/Commentary_special_authorization_extended_access.pdf;
http://www.swissmedic.ch/files/pdf/Commentary_special_authorization_exceptional_cases.pdf.

480 *Id.* Article 3 OClin (defining human research subjects) has sometimes been interpreted to mean that this Ordinance applies to patients taking part in some of these programs. However, Article 3 OClin (whose text is to be moved to Article 5.d OClin in September 2004) is not specific enough to encompass all compassionate programs. *See also supra* note 331.
This classification problem does not only arise under Swiss law. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary) and Guideline 13 (commentary) (answering that compassionate access programs are not "properly regarded as research").
In the United States, compassionate programs are not regulated as clinical trials.

Approval procedure				
Approval of the ethics committee	☒	☑ (with help of sponsor)	☑ (with help of sponsor)	☒
Request made by	Physician	Investigator	Investigator or physician	Physician
Authorization granted to physician	☑	☑	☑	☑
Physician has insurance coverage	☑	☑	☑	☑
Duty to report adverse events	☑	☑	☑	☑
Reporting obligation by physician at the end	☑	☑	☑	☑

In September 2004, changes in the Ordinance on the authorizations in the area of drugs ("OAMéd"[481]) transferred Swissmedic's authority to authorize physicians' *imports* of small quantites of unapproved drugs back to the cantons (see subsection 3.4.6.2.3. above). As a result, Swissmedic retains only limited authority in the area of compassionate access; it continues to issue authorizations if the drug imported (in its specific therapeutic indication) has not been approved by a country with a regulatory system comparable to that of Switzerland.[482] Probably early in 2005. Moreover, extended access and parallel trial programs have been merged in the two remaining categories (i.e., compassionate use and beyond compassionate use) since very few authorizations had ever been issued in these two situations. The four commentaries were replaced by two others in April 2005, but the changes occured too late to be analyzed here.

3.4.6.3. Retrospective studies

Another borderline classification relates to retrospective studies. If only data obtained and pooled during a *previous* clinical trial is used for research, is this considered to be a clinical trial (as per the OClin)? The situation can be the following. An *initial* clinical trial was conducted according to the rule of the OClin; a drug was administered to subjects by an investigator to assess its safety and efficacy. Then, a second researcher wants to work with these existing data (the retrospective study[483]). Is that second researcher launching a second clinical trial?

---

[481] On its website, Swissmedic proposes an unofficial translation of the previous version of this ordinance; its title is Ordinance on establishment licences (ELO); http://www.swissmedic.ch/files/pdf/Arzneimittelbewilligungsverordnung-E.pdf. However, this text does not incorporate the 2004 changes.

[482] See the new Article 36 OAMéd, which entered into force on September 1, 2004. See Telephone Interview with Dr. Chautems (Swissmedic, GCP division), of December 7, 2004.

[483] *Retrospective* studies do not involve the planned administration of any product or other test (e.g., survey) to research subjects. In retrospective studies, research subjects have no role (or no longer have any role). The opposite of a retrospective study is a *prospective* study. Drug clinical trials are typically planned as prospective studies.
See for an example of such a retrospective study: Frederick K. Goodwin et al., *Suicide Risk in Bipolar Disorder During Treatment With Lithium and Divalproex*, 290 JAMA 1467-1473, at http://jama.ama-assn.org/cgi/reprint/290/11/1467.pdf.

According to Swissmedic, the answer is negative. If no therapeutic product is administered to patients/subjects, the OClin is simply not applicable.[484] In the United States, clinical trial regulations are inapplicable only to the extent that the data made available to the (second) researcher is entirely anonymous.[485] In the European Union, the 2001/20/EC Directive is not applicable to retrospective studies.

A similar situation arises if our "second" researcher is surveying patients who have already been administered a drug (either in the context of ordinary medical care or in a past clinical trial). In this hypothesis contrary to the previous one, there is a direct (physical) interaction between the researcher and living persons. However, the second researcher does not herself administer any drug, she only questions patients about their previous medical experience. Hence, the answer should also be negative (i.e., the OClin is inapplicable), provided that the decision to prescribe the drug was taken beforehand and is completely independent from the subsequent decision to survey these patients.

Even though the OClin is not applicable in these two hypotheses, the question remains whether subjects should have to consent to the new research. The consent duly given for the initial research normally does *not* cover the new research project. Ethical principles therefore requires that the second researcher seek the consent of subjects/patients.[486]

Of course, if the retrospective study only uses data *made anonymous*, consent becomes difficult or simply impossible. Moreover, the second research then presents only negligible risks to subjects. These subjects may nonetheless feel betrayed if they learn that the information they agreed to provide for a given objective (i.e., the first clinical trial) was then "recycled" without their knowledge and, *a fortiori*, without their consent. An appropriate remedy is to anticipate the problem by having the initial consent form* encompass subsequent research projects (see subsection 8.3.2.7. below).

---

484 Article 5.a. OClin. *See also* Telephone Interview with Gabriel Vital-Durand, Swissmedic's clinical trial division, (Aug. 14, 2003).

485 For trials submitted to HHS regulations, see 45 C.F.R. § 46.101.b.4. with the additional condition that the documents reviewed must be "publicly available" or that subjects must remain unidentifiable. Studies making use of non-anonymous data may nonetheless be eligible for a waiver of informed consent. On the minimum requirements for truly anonymous data, see for example the explanations of the UCSD's guidelines; Standard Operating Policies and Procedures of the University of California at San Diego, at 51-52 (Jan. 21, 2004), at http://irb.ucsd.edu/SOPP_2004-01-21.pdf [hereinafter UCSD-SOPP].
See also IRB Guidebook *supra* note 411, at chapter 1; NIH (Women Inclusion), *supra* note 55, at 13-15; NBAC (Issues in Research), *supra* note 244, at 14-15.
Moreover, FDA regulations do not apply to trials that do not involve the administration of a product regulated by the FDA.

486 Although the OClin does not apply, general legal and ethical principles do require that subjects give their consent.

3.4.6.4. Research on biological material

An important subset of retrospective research studies biological specimens, such as cells, fluids, tissues, or organs (hereinafter biological material).[487] A significant amount of research is done using such material and thousands of specimens have been collected over the years.[488] Patients are usually not aware that their biological material is being routinely stored and used for research.

Research performed on already stored biological material does not fall within the OClin.[489] To the extent that "entire human beings" are not, or no longer, directly involved, the OClin does not apply. Conversely, if the study calls for the collection of biological material from living subjects, this may qualify as a clinical trial provided that the other conditions are met.[490]

This paradoxical situation is not satisfactory. It epitomizes the exceedingly narrow scope of the OClin, especially in its requirement that a therapeutic product be at the center of the study (see also subsection 3.2.1. above). Clearly, the problems arising in connection with retrospective research will be addressed by a future law, at least to the extent that *identified or identifiable patient's material* is used.[491] The Council of Europe has prepared a draft instrument which aims to submit all studies on biological material to the review of a national competent body.[492] Under this proposal, even research using entirely anonymous data would have to be submitted so as to confirm the truly anonymous character of the data set.[493] The competent body would have to decide

---

487 Following the U.S. Office of Technology Assessment ("OTA") definition, biological material includes "all human parts, replenishing and nonreplenishing, living and nonliving, healthy and diseased." OTA, New Developments in Biotechnology: Ownership of Human Tissues and Cells – Special Report, at 24 and also at 3 (OTA-BA-337) (1987) [hereinafter OTA (Ownership)].

488 Only "[in] the United Kingdom, pathology laboratories in the NHS examine and subsequently store over 3 million tissue specimens each year." Peter Furness, *Consent to using human tissue, Implied consent should suffice*, 327 BMJ 759 (Oct. 4, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7418/759.pdf. *See also* D. Gareth Jones et al., *Stored human tissue: an ethical perspective on the date of anonymous, archival material*, 29 J. MED. ETHICS 343-44 (2003), at http://jme.bmjjournals.com/cgi/reprint/29/6/343.pdf.

489 In other words, the OClin would not apply to the review of a cancer tissues library, even if these tissues are linked to their individual donors. There may be legal issues as to whether the researcher is entitled access to this library, but this is another question.

490 If, for example, cancer subjects are asked to provide cells in the context of a cancer research, the OClin could apply provided, notably, that a therapeutic product is being administered and studied. *See also* COE Explanatory Report, *supra* note 417, at paragraph 19, page 6.

491 Such regulation would probably be included in the project of law on research on human beings. *See* subsection 3.2.1. above.
On the difficulty of distinguishing between identifiable and non-identifiable data, see Janlori Goldman & Angela Choy, *Privacy and Confidentiality in Health Research*, *in* RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE, VOLUME II, COMMISSIONED PAPERS, at C-13, (National Bioethics Advisory Commission ("NBAC"), Jan. 2000), at http://www.georgetown.edu/research/nrcbl/nbac/human/overvol2.pdf [the entire volume is hereinafter referred to as "2001 NBAC Biological Report Volume II"].

492 The national body may be an ethics committee.
See Article 10 of the Council of Europe's proposal for an instrument on the use of archived biological materials in biomedical research, (CDBI/INF (2002) 5), (Oct. 17, 2002), at http://www.coe.int/T/E/Legal_affairs/Legal_co-operation/Bioethics/Activities/Biomedical_research/CDBI-INF(2002)5E.pdf [hereinafter draft COE Biological Instrument]. *See also id.* at 6, para.19.

493 Article 10.iii) draft COE Biological Instrument and also Article 2 for the definitions of unlinked anonymized data (text at http://www.coe.int/T/E/Legal%5FAffairs/Legal%5Fco%2Doperation/Bioethics/Activities/Biomedical%5Fresearch/CDBI-INF(2002)5E.pdf). According to the accompanying report, "an individual shall not be regarded as "identifiable" if identification requires an unreasonable amount of time or manpower." Council of

whether the risks related to the research, in particular for the private life of the subjects, exceed its benefits, in which case the study would be rejected.[494] This draft instrument would also require that subjects give their consent whenever possible and that they be informed of the study results.[495]

The Council of Europe's proposal is not without shortcomings. Scientists have criticized this regulatory approach and similar ones as being exceedingly stringent.[496] Much of scientific research may come to a standstill if researchers have to hunt for former patients' consent, or even worse the consent of their offsprings when the donor has died. Moreover, systematically imposing a review procedure creates vexing delays. It is doubtful that the risks incurred by donors justify such "red tape." Having patients systematically sign prospective consent forms whenever they enter a hospital or another medical center would not solve all problems. Indeed, advocates of informed consent insist that the authorization be specific;[497] they also insist on the right to withdraw it at any time.

Under the future Swiss law on human genetic analysis, an individual must normally consent to any re-use of genetic material obtained through an initially approved genetic analysis.[498] The draft law contains one exception: If the individual has been informed of possible re-use for research purposes, the opt-in system (i.e., explicit consent) is replaced by an opt-out system, provided that the genetic sample has been rendered fully anonymous.[499] In other words, research on anonymized genetic samples is permissible if the individual has been duly informed in advance of this possibility and has not explicitly rejected it.

3.4.6.5. Clinical trials versus non-medical activities

Sometimes, what is unclear is not the distinction between "ordinary" medical practice and research, but that between research and *high-risk activities* (e.g., a NASA space voyage).[500]

Europe, Draft Explanatory report to the proposal for an instrument on the use of archived human biological materials in biomedical research, at 5 (CDBI/INF (2002) 6), (Oct. 14, 2002), at http://www.coe.int/T/E/Legal_affairs/Legal_co-operation/Bioethics/Activities/Biomedical_research/CDBI-INF(2002)6E.pdf [hereinafter draft COE Biological Report]. *See also id.* at 6, para.22.

494 Article 6 draft COE Biological Instrument, see also its Articles 5 and 7.

495 Articles 14 to 17 draft COE Biological Instrument.

496 *See* Furness, *supra* note 488, at 759-60. *See also* Julie R. Ingelfinger & Jeffrey M. Drazen, *Registry Research and Medical Privacy*, 350 NEW ENG. J. MED. 1452-53 (Apr. 1, 2004), at

http://content.nejm.org/cgi/content/short/350/14/1452?query=TOC (criticizing the restrictions imposed by the U.S. 1996 Health Insurance Portability and Accountability Act ("HIPAA") on the recording of medical information for research purposes).

497 Compare with the Federal Council's message regarding the Federal Law on human genetic analysis (LAGH), FF 2003 I 6841, at 6902 (indicating that information provided to the individual can be of a *general* nature).

498 Article 20.1 (future) LAGH. See also the accompanying message of the Federal Council, FF 2003 I 6841, at 6901-02.

499 Article 20.2 (future) LAGH and the Federal Council's message, FF 2003 I 6841, at 6901-02 (indication that this exception shall then be replaced by a general provision of the future law on research on human beings).

500 See also the case of Whitlock v. Duke University, 829 F.2d 1340 (4th Cir. 1987) (which involved deep diving in a controlled environment).

For example, a U.S. Court had to decide whether a Nepal trek constituted a clinical trial.[501] The subjects were testing new breathing techniques that should have improved their climbing performances. However, one subject-hiker suffered an adverse reaction from high altitude sickness (cerebral edema). Although in this instance no drug was administered, it could easily have been the case. The Court went over the criteria mentioned above and decided that the trek leader should have complied with the obligations applicable to investigators in clinical trials.

Another interesting intersection between medical treatment and other non-regulated activities involves the practice of *religion*. American courts have had to rule on the proper qualifications of products that are used by religious groups (allegedly in the context of their religious practices), but which can also be qualified as therapeutic products either because they do have physiological effects or because they claim to cure diseases.[502]

A third intersection could be between research and *television games*. Some TV programs have participants go through elaborate tests to assess their physical or mental resistance. For example, one program tested how long participant could stay awake. One can easily imagine that the day a participant is injured during one such "game," he will sue the producer, complaining that he was not properly asked for his informed consent.

3.5. The scope of the OClin

We have already seen that the OClin's scope is limited to clinical trials of certain products and therapies (subsection 3.2.1. above). This subsection introduces two additional limitations to the reach of the OClin: To be regulated by the OClin, a clinical drug trial must have begun after a certain date and must take place within a certain geographical zone.

3.5.1. Temporal scope of the OClin

A trial must have started *after the 1st of January 2002* to be governed by the OClin.[503] If the trial began earlier, it remains entirely governed by the former intercantonal system.[504] Although this rule does not simplify the oversight of clinical trials, it appears to pose little problems to Swissmedic.[505] The fact that the OClin closely resembles the 1995 IOCM Regulation reduces the odds that two clinical trials will be treated differently.

---

501 *See Vodopest*, 128 Wn.2d 840.

502 *See* The Founding Church of Scientology of Washington v. United States, 409 F.2d 1146 (D.C. Cir. 1969); United States v. An Article or Device ..., 333 F. Supp.357 (D.D.C. 1971); The Church of Scientology of California v. Richardson, 437 F.2d 214 (9th Cir. 1971).

503 Article 36.2 OClin.

504 Apparently, Swissmedic would have have to apply the intercantonal regulation on pharmaceuticals at the stage of clinical trials to these studies.

505 Telephone Interview with Vital-Durand, *supra* note 484.

However, there are differences. For example, the IOCM Regulation requires that all trials be monitored, while the OClin does not mention monitoring at all (on monitoring, see subsection 5.4. below).

The OClin seems to follow a slightly different rule with regards to the organization of ethics committees. Cantons had until January 2004 to report their ethics committees to Swissmedic.[506] The word "seem" is used because it is not clear whether Article 36.1 OClin allows a transitory period of one year for *all provisions governing ethics committees*. For instance, do existing ethics committees have one year to readjust their composition so that it meets the requirements of Article 30 OClin? The answer is probably yes.

3.5.2. Geographical scope of the OClin

The OClin does not outline its geographic scope. The choice could be between applicability to any trials submitted to Swissmedic to gain regulatory approval[507] and applicability to all trials taking place in Switzerland. The second hypothesis makes more sense as it avoids likely conflicts of laws with other countries. Therefore, the OClin is applicable only if the *research site* (i.e., the medical facilities) is in Switzerland.[508]

The place of *domicile or residence* of the research subjects, of the sponsor (i.e., the entity launching the clinical trial) or of the investigator (i.e., the individual carrying out the clinical trial) is of no consequence. Thus, if a clinical trial were to take place in a hospital in France, but enroll only Swiss patients, it would *not* be governed by the OClin, even if the sponsor were a Swiss pharmaceutical company and the investigator a Swiss national with her domicile in Geneva.[509] The place of *manufacture* of the investigational drug is also irrelevant in that respect. Swiss clinical trials that use imported drug products are equally subject to the OClin. The importation of an investigational product in Switzerland does not require Swissmedic's authorization.[510]

Source of funding is also indifferent. Thus, clinical trials funded by a Swiss pharmaceutical company or by a Swiss governmental agency, but taking place in research facilities located outside Switzerland, are not subject to the OClin. In contrast, U.S. publicly-funded clinical research has to follow certain U.S. rules.[511]

However, the trend is to recognize that Swiss law should also apply when only a *small part* of the clinical trial process occurs in Switzerland. This is particularly true when part or all of the *recruitment effort* takes place in Switzerland. The recruitment stage is considered part of the clinical trial itself (see further subsection 8.1. below). Thus, if

---

506 Article 36.1 OClin.

507 *See also* Article 16.1.b) of the former 1995 IOCM Regulation (requiring that foreign clinical trials abide by GCP).

508 Article 36.2 OClin.

509 An equivalent rule applies in the United States. *See, e.g.*, DuBois, *supra* note 118, at 200.

510 Article 18 LPTh is not applicable. *See* Telephone Interview with Chautems (Mar. 2004), *supra* note 170. Although importation in Switzerland of an investigational product for clinical trial purposes does not require an authorization, the country of origin may require one for exports. See for example in the United States 21 C.F.R. § 312.110(b).

511 *See* 45 C.F.R. § 46.101.a. However, if non-U.S. regulations confer equivalent protection, the latter can be made solely applicable. *See* 45 C.F.R. § 46.101.h.

advertisements are circulated in Switzerland to recruit Swiss residents and convince them to enroll in a clinical trial abroad, this could be enough to trigger the application of Swiss law. There is still a lot of uncertainty surrounding such a situation.[512] Moreover, when the research site is outside Switzerland, it is difficult to identify which Swiss ethics committee should have jurisdiction over the study. Foreign investigators may be ignorant of Swiss regulations. Finally, Swissmedic has not strongly asserted its own jurisdiction; it has probably more than enough work with Swiss-based trials.

3.5.3. Preemption of cantonal regulations

It is unclear whether cantons have retained jurisdiction to enact requirements that go *beyond* those imposed by the OClin.[513] While the European 2001/20/EC Directive explicitly allows Member States to enact more comprehensive provisions[514] and the U.S. federal regulations similarly confirm that State law is not preempted,[515] both the LPTh and the OClin remain silent on this issue.[516] Nonetheless, it appears that cantons have retained only very limited regulatory powers in connection with clinical trials.[517] The influence that cantons can still wield results from the appointment and supervision of ethics committees[518] and the "licensing" process for investigators and research sites.[519]

According to certain commentators, cantons can also legislate on the rights of subjects.[520] This assertion is far from self-evident. In my opinion, a cantonal legislation pertaining to subjects' rights cannot impose a significant additional burden on the sponsor or on the investigator; for example, a cantonal law requiring that subjects be offered one-year supply of the investigational compound following completion of the trial would encroach upon federal jurisdiction.

---

512 The situation is more likely to happen in the reverse with foreign patients living near the border (in Italy, Germany or France) being recruited to participate in a study taking place in Switzerland. In the VanTx affair, subjects from more distant countries (e.g., Poland, Estonia) were enrolled and brought to Switzerland to participate in phase I clinical trials. *See* VanTx Report, *supra* note 148, at 12. The Working Group appointed by the IOCM concluded that these foreign countries could – and probably should – have regulated the recruitment of their own citizens. *Id.* at 9-10 and 32.

513 For the situation prior to the enactment of both the OClin and the IOCM's regulations, see SPRUMONT, *supra* note 16, at 205-206.

514 Article 3.1 of Directive 2001/20/EC.

515 In the United States, see 21 C.F.R. § 50.25(c), § 56.103(c); 45 C.F.R. § 46.101.f. and § 46.116(e). *See* FDA (1981), *supra* note 250, at comment 49.

516 See generally on the issue of preemption in relation with the LPTh, the unpublished decision of the Swiss Supreme Court, docket case 2P.38/2001 (Aug. 30, 2002), at point. 2.2-2.3., at http://www.polyreg.ch/bgeunpubliziert/Jahr_2001/Entscheide_2P_2001/2P.38__2001.html.

517 E-mail from Jean-Christophe Méroz, legal department, Swissmedic, (Sept. 16, 2003) (on file with author) (confirming that cantons have retained only the powers delineated in the law).
See however the Geneva State Council's Regulation on clinical trials of therapeutic products, K 4 05.18 of December 11, 2002, entered into force on December 19, 2002, at http://www.geneve.ch/legislation/rsg/f/rsg_k4_05p18.html [hereinafter Geneva Regulation K 4 05.18]. Article 4 of this Regulation imposes for example as a new requirement that phase I clinical trials (i.e., early testing) be conducted in a medical institution.

518 *See* Article 57.4 LPTh and Article 29.1 and 29.3 OClin.

519 *See* Article 8 OClin.

520 *See* Sprumont & Béguin, *supra* note 134, at 895.

Of course, cantons are still free to regulate clinical research that does not come under the jurisdiction of the OClin (e.g., clinical trials that do not involve therapeutic products).[521] But cantons can no longer require that OClin governed trials be submitted again for another cantonal authorizations.[522] Except in the areas mentioned above, they cannot impose stricter requirements than those explicitly laid down by the OClin.[523] Of course, their legislation cannot disagree with the OClin.

[521] When Switzerland will adopt a comprehensive law on research on human beings, cantons will lose much of their remaining jurisdiction.

[522] *See* VanTx Report, *supra* note 148, at 29. *See a contrario* Swiss Department of Home Affairs, Rapport de consultation concernant les ordonnances sur les produits thérapeutiques [Consultation report on the ordinances on therapeutic products], at 46 (Oct. 17, 2001), at http://www.bag.admin.ch/heilmitt/aktuell/f/vern_ber.pdf [hereinafter DHA (Ordinance Comments)].

[523] Telephone Interview with Méroz, Swissmedic (Aug. 19, 2003).

4. The economic dimension of clinical trials

This section introduces many different topics of an economic nature. Subsection 4.1. explains why clinical trials are launched. Section 4.2. discusses the costs of clinical development. Section 4.3. describes harmonization efforts undertaken to unify clinical trial regulations. Section 4.4. asks whether Switzerland is an attractive location for clinical trials. Section 4.5. reviews the issues that arise when clinical trials are conducted in developing countries.

4.1. The objectives of clinical trials

Clinical trials serve many different purposes. This subsection looks at nine important objectives of clinical trials. Subsection 4.1.10. explores the additional motivations of the pharmaceutical sponsor having to decide whether to launch a trial.

4.1.1. Obtaining marketing approval

The primary objective of clinical drug trials is to gather information on an experimental pharmaceutical product.[524] Pharmaceutical firms need this information to convince drug agencies to grant marketing approval/authorization.[525] Without this authorization, a drug cannot be sold.[526] On the other hand, drug agencies cannot force companies to perform clinical trials for compounds not intended for marketing.[527]

Because full data from past clinical trials are not publicly available and because of rules on data exclusivity, a firm cannot usually rely on data generated by another party (see further subsection 9,1,2, below).[528] It must launch its own clinical trials even if part or

---

524 *See* Article 5 of Swissmedic's Ordinance on requirements regarding the marketing authorization for pharmaceutical products [Ordonnance de l'Institut Suisse des produits thérapeutiques sur les exigences relatives à l'autorisation de mise sur le marché des médicaments], November 9, 2001, RS 812.212.22, abbreviated (from the French): OEMéd; text in French at http://www.admin.ch/ch/f/rs/8/812.212.22.fr.pdf.

525 The U.S. terminology refers to "marketing approval," while the European Union uses the term "marketing authorization." The expressions "registration" or "licensing" (of pharmaceuticals) are still encountered but are no longer used in regulatory texts. Here, I use all these expressions synonymously.
To see how data from clinical trials is assessed by drug agencies, see for example the clinical review report established by the FDA for the drug Iressa, at
http://www.fda.gov/cder/foi/nda/2003/21-399_IRESSA_Medr_P1.pdf.

526 *See* the Federal Tribunal Decision of March 28, 2003, (2A.515/2002), at point 3.5.

527 If a sponsor has submitted a marketing application, then the drug agency may make approval conditional on the conduct of further phase IV clinical trials (see also subsection 6.1.4.1. below). In addition, the U.S. FDA holds itself to be entitled to request studies after approval, for example to "evaluate widespread off-label use." FDA, CDER, Procedures for Tracking and Reviewing Phase 4 commitments, Manual of Policies and Procedures, at 2 (MAPP 6010.2) (Oct. 1, 1996), at http://www.fda.gov/cder/mapp/6010-2.pdf.

528 In Switzerland, see Article 12 LPTh and Article 17 OMéd.
There are exceptions to this rule. For example, the FDA also approves paper NDAs (literature-based applications), 505(b)(2) applications (NDAs relying on other applications) and generic drug applications ("ANDAs")*. The majority of new drug approvals are still based on the review of *sponsor-generated* clinical trial data.

all of the necessary information (e.g., safety) has already been gathered by another.[529] To be able to use another sponsor's clinical data in its own submission, the firm must get the sponsor's authorization[530] – which it is unlikely to obtain, even against a reasonable price. Alternatively, it may refer to the data once the statutorily defined period of time has elapsed.

Before the start of clinical trials, in vitro testing and animal experiments[531] must have already given the sponsor[532] a good idea of the compound's effects. In particular, these tests must have revealed how toxic the drug can be.[533] Furthermore, these tests should suggest a degree of efficacy against certain diseases or biological targets (e.g., the compound has been shown to bind to cancer cells). However, until the drug is tested on humans, the drug's expected usefulness only derives from inferences acquired with simplified models. A drug may cure a dog and yet be without any effect on human beings.[534] Clinical trials are therefore necessary to offer the best available guarantee that a drug is truly safe and effective for its approved uses. This assurance is essential if the drug is to be approved and prescribed to a large number of patients.[535]

4.1.1.1. Proving the drug's safety

4.1.1.1.1. Historical background

Before it was made subject of mandatory premarketing assessments, safety slowly emerged from sustained use by doctors on patients. Each physician would have to determine what worked and what did not. In this sense, every patient was a guinea pig. Eventually, the physician would get a general idea of possible adverse reactions. However, even that picture could be mottled, because patients report only the most serious and most frequent cases of toxicity. Moreover, the patient and the physician together needed first to identify a given reaction, and then to attribute it correctly to a given

---

529 *See however See* FDA, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, Guidance, at 18-19 (May 1998), at http://www.fda.gov/cder/guidance/1397fnl.pdf [hereinafter FDA (Effectiveness)].

530 In Switzerland, Article 17.1a and 2.a OMéd.

531 Paragraph 11 Helsinki Declaration states that medical research must be based "where appropriate, [on] animal experimentation." *See also* paragraph 12. *See also* Article 3 of the Nuremberg Code.
On the *preclinical* requirements that must be filled before testing can take place on human research subjects, see ICH, Safety Pharmacology Studies for Human Pharmaceuticals, Guideline S7A, Step 4, (Nov. 8, 2000), from http://www.ich.org/cache/compo/502-272-1.html#S7A [hereinafter ICH S7A]; ICH, Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, Guideline M3, Step 4, (Nov. 9, 2000), at http://www.ich.org/MediaServer.jser?@_ID=506&@_MODE=GLB.
In the European Union, see EMEA, CPMP, Position Paper on Non-clinical Safety Studies to Support Clinical Trials with a Single Microdose, CPMP/SWP/2599/02, (Jan. 23, 2003), at http://www.emea.eu.int/pdfs/human/swp/259902en.pdf.

532 I use the word "sponsor" to refer to the entity launching the trial. In commercial clinical trials, the sponsor is generally a pharmaceutical company holding the intellectual property rights to the compound and manufacturing it.

533 *See* section 2.1 of ICH Harmonised Tripartite Guideline on General Considerations for Clinical Trials E8, (step 4 of ICH process, July 17, 1997), at http://www.ich.org/MediaServer.jser?@_ID=484&@_MODE=GLB [hereinafter ICH E8] and section 5.12.1 (p.24) of ICH E6.

534 The contrary may also be true, which is more disturbing because such a compound is abandoned before it is "given a chance" on human beings.

535 *See, e.g.*, paragraph 4 Helsinki Declaration.

drug. In many cases, the patient could "miss" the adverse event* or not know what caused it. For example, the patient may have felt sleepy after taking a drug and attribute it to a short night, and not to the drug.

After many battles, the obligation to test the safety of drugs was first explicitly introduced in the United States in 1938.[536] However, until the 1960s and the introduction of the efficacy requirement (see subsection 4.1.1.2. below), this obligation did not entail extensive testing on human research subjects; it sufficed to test safety on a few people. Safety tests were done mostly on animals, and then again, they were not very reliable.

Although the Food, Drug and Cosmetic Act of 1938 only mentioned safety, and not efficacy, safety has always been viewed as a *relative* concept, to be balanced against the drug's positive effects. Significant health risks can be tolerated in a drug that is extremely effective (e.g., an anti-infective agent), while a drug with few therapeutic benefits must be considerably safer. Drugs that are entirely ineffective but present no inherent dangers are nonetheless viewed as unsafe if their existence leads patients to forestall another effective treatment.

4.1.1.1.2. Safety tests

Because clinical trials attach importance to all adverse effects, whether minor or major, whether frequent or rare, they are able to ascertain a long list of such effects (see further subsection 9.1.2. below). Of course, the list can never be exhaustive and may even include effects wrongly attributed to the drug. This is to be expected given that a large clinical trial enrolls "only" a few thousand subjects. Hence an adverse reaction that occurs only in 1 out of 5'000 patients will probably not be detected.[537] Likewise, clinical trials may not suffice to exclude or validate a causal link between an adverse effect and the intake of a drug. As a result, the adverse effect may end up listed in the label of use, even though causality is not guaranteed.

---

536 *See* Federal Food, Drug, and Cosmetic Act of 1938 ("FDCA"), Pub. L. No.75-717, 52 Stat. 1040 (codified as amended 21 U.S.C. §§301 et seq.).
Between 1905 and 1930, U.S. drugs were reviewed by a private organization, the American Medical Association, and more precisely its Council on Pharmacy and Chemistry. *See* HARRY M. MARKS, THE PROGRESS OF EXPERIMENT, SCIENCE AND THERAPEUTIC REFORM IN THE UNITED STATES, 1900-1990, at 22-41 (Cambridge History of Medicine, 1997).

537 *See* DEUTSCHE BANK, PHARMACEUTICALS FOR BEGINNERS, 35 (Mar. 12, 2003).

4.1.1.2. Proving efficacy

Clinical trials must demonstrate that a drug is effective.[538] Although commentators often use these two terms interchangeably,[539] efficacy and effectiveness are slightly different concepts.[540] According to one set of definitions, a drug is *efficacious* when it has the *desired* effects, which is generally to cure the patient; a drug is *effective* when it has its *intended* effects, which can be less than a cure.[541] According to another definition, a drug is said to be efficacious in reference to results obtained in controlled settings such as those of a clinical trial; its effectiveness is determined based on results obtained from ordinary medical practice.[542] Yet, another definition set forth by the FDA distinguishes the two terms in the following manner: "the term efficacy refers to the findings in an adequate and well-controlled clinical trial … and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data."[543] Regardless of the definition retained, these two terms have a very close meaning. There are therefore used synonymously in this thesis.

4.1.1.2.1. Historical background of the efficacy requirement

This efficacy/effectiveness requirement was first introduced in the United States. Before 1962, drugs could be withdrawn from the market only if the FDA could *prove* that the drugs were indeed ineffective and, thus in the language of the statute, misbranded.[544] An analogous process was followed in other countries.[545]

---

538 *See* 21 C. F.R. § 314.126(a) on adequate and well-controlled studies ("Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs.").

539 For example, the English translation of the LPTh (proposed on Swissmedic's website; *see supra* note 7) uses "effective" for the French "*efficace*," but uses sometimes "efficacy" sometimes "effectiveness" for the French "*efficacité*."
See Grow, *supra* note 249, at 82-83. *See* FDA (Effectiveness), *supra* note 529, at 18-19. In the European Union, the term "efficacy" is more often encountered than the term "effectiveness" but both are in use. *See* Medicinal Products for Human Use: Guidelines, Volume 3C of EudraLex, at http://pharmacos.eudra.org/F2/eudralex/vol-3/home.htm#3c.

540 A synonym of efficacy is efficaciousness; it is however rarely used.
For biologics, the term "potency" is generally used (instead of effectiveness). *See* FDA (Effectiveness), *supra* note 529, at 4.

541 *See* Grow, *supra* note 249, at 82; Jennifer Kulynych, *Will FDA Relinquish the "Gold Standard" for New Drug Approval? Redefining "Substantial Evidence" in the FDA Modernization Act of 1997?*, 54 FOOD & DRUG L.J. 127, at 133 (1999), at http://www.fdli.org/pubs/Journal%20Online/54_1/art12.pdf.

542 *See, e.g.,* Office of Technology Assessment ("OTA"), *The Effectiveness of Drug Abuse Treatment: Implications for Controlling AIDS/HIV Infection* (Sept. 1990), at 119, at http://www.wws.princeton.edu/cgi-bin/byteserv.prl/~ota/disk2/1990/9041/9041.PDF; NBAC (Developing), *supra* note 254, at 28.

543 FDA (Effectiveness), *supra* note 529, at 1 n.2. *See also* Sarah M. R. Cravens, *The Usage and Meaning of "Clinical Significance" in Drug-Related Litigation*, 59 WASH. & LEE L. REV. 553, at 565-68 (Spring 2002).

544 *See, e.g.*, Grow, *supra* note 249, at 21.

545 See in Switzerland, W. Wilbrandt, *Wandlungen in der Beurteilung von Arzneimitteln*, *in* 75 ANS DE CONTRÔLE INTERCANTONAL DES MÉDICAMENTS [75 YEARS OF INTERCANTONAL CONTROL OF DRUGS] 129, at 130 (1975); P. Geiser, *Arzt und Arzneimittelsicherheit*, *in* 75 ANS DE CONTRÔLE INTERCANTONAL DES MÉDICAMENTS [75 YEARS OF INTERCANTONAL CONTROL OF DRUGS] 121, at 122 (1975).

The result was that many, if not most, drugs were simply worthless.[546] A scientific review of U.S. drugs performed between 1966 and 1969[547] (the DESI study) showed that a "substantial numbers of drugs were being marketed [in the U.S.] for which efficacy could not be shown. The panels evaluated some 16,500 claims made on behalf of 4,000 drugs and found that seventy percent of the claims were not supported by substantial evidence of effectiveness. Only 434 drugs were found effective for all their clinical uses."[548] More than a thousand drugs were withdrawn from the market for lack of efficacy.[549]

In 1962, the U.S. Food, Drug and Cosmetic Act ("FDCA") was amended following bills presented by Senator Estes Kefauver and Representative Oren Harris. Initially, the main purpose of the bills that later became the *Kefauver-Harris Amendments* was to protect "the public against unreasonably high-priced drugs" and to reduce – what was already at the time considered to be – excessive profits achieved by pharmaceutical companies.[550] Protecting patients from ineffective drugs was initially only a secondary concern. Moreover, legislators viewed ineffective drugs not so much as a health risk, but as economic treachery: Misled patients were thought to be swindled.[551] Additionally, "[p]roof of efficacy in a new drug application again was offered as a tactic to lower consumer costs, through assuring doctors that they could prescribe an available generic drug without fear that it might be less effective than its brand name counterpart."[552]

The introduction of the efficacy requirement in 1962 was far from self-evident. It was opposed by various groups, including the American Medical Association ("AMA").[553] For the AMA, the assessment of a drug's efficacy should have remained the exclusive province of doctors.[554] The trade group of pharmaceutical companies (called at the time the Pharmaceutical Manufacturers Association or "PMA") supported only limited changes in the way drugs were approved.[555] They wanted to get rid of the "patent medicine" industry (i.e., secret remedies peddled by shady characters) without hurting their own business.[556]

---

546 Even though most drugs were either worthless or harmful, they enjoyed tremendous popular success. Towards the end of the 19th century, "no fewer than 2,060 million – mainly digestive – pills were taken annually in the UK, or one a week for every man, women, and child." T. A. B. Corley, The British Pharmaceutical Industry Since 1851, at 3, (Centre for International Business History, University of Reading, 1999-2000), at http://www.rdg.ac.uk/Econ/Econ/workingpapers/emdp404.pdf.

547 *See, e.g.*, FDA, CDER, A Brief History of the Center for Drug Evaluation and Research, http://www.fda.gov/cder/about/history/Histext.htm and also FDA Oral History Program, Interview with J. Richard Crout, at http://www.fda.gov/oc/history/oralhistories/crout/default.htm#desi.

548 *See, e.g.*, Warner-Lambert v. Heckler, 787 F.2d 147, at 149 (3d Cir. 1986); Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609 (1973), at http://laws.lp.findlaw.com/getcase/US/412/609.html.

549 *See* David J. Horowitz, *FDA proposes incentives to remove illegal Rx drugs*, 9 (5) NEWS ALONG THE PIKE (Dec. 3, 2003), at http://www.fda.gov/cder/pike/nov2003.htm.

550 *See* Grow, *supra* note 249, at 9.

551 *Id.* at 11, 38 and 51.

552 *Id.* at 10.

553 *Id.* at 16.

554 *Id.* at 17 and 75-77.

555 *Id.* at 35-36 and 71-73.

556 While the first patent medicines of the early 19th century were indeed protected by a patent, subsequent patent medicines were kept secret. *See* Elizabeth L. Davoli, Patent Medicines: Ethnic or Socioeconomic Indicators? at 3 (paper presented in 1998), at http://www.uark.edu/campus-resources/archinfo/SHACdavoli.pdf.

The Kefauver-Harris Amendments were ultimately successful owing to the jolt delivered, halfway through the bills' course before Congress, by the *thalidomide catastrophe*.[557] Remarkably enough, the pre-1962 FDCA had been sufficient in blocking thalidomide, since the drug's safety profile had caused enough concern that the FDA refused to consider the marketing application which had been submitted; as for the drug's effectiveness, it had never really been at issue.[558] Yet, the thalidomide outcry shifted the perpectives of Congressmen and assured the adoption of the Amendments.[559]

All Western countries then followed the trail brazen by the United States.[560] In Switzerland, the Intercantonal Office for the Control of Medicaments (IOCM) adopted a directive in 1963 whereby sponsors of new drugs had to provide detailed written evidence of its efficacy and safety.[561]

Consequently, drug agencies now require proof of both safety and efficacy before granting a drug its marketing authorization. Clinical trial results are the key component of the dossier that must be submitted to drug agencies in order to receive the authorization. More precisely, the sponsor-applicant must provide adequate evidence of safety and efficacy for each of the drug's therapeutic indication (i.e., labeled conditions of use).[562] Conversely, if the sponsor cannot present such evidence, its drug will not be approved.[563]

---

557 *See* Grow, *supra* note 249, at 2-4, and also 65-67, 74-75, 88-89, 91-92.

558 *Id.* at 51 and 110.
Somewhat paradoxically, thalidomide received FDA approval based on new safety and efficacy data in 1998. Celgene now sells thalidomide against leprosy and multiple myeloma. It is also being tested and used against cancers as well as AIDS, which would significantly expand its market. Hence, the drug has become very expensive and much sought-after. *See* FDA, Thalidomide Information, at http://www.fda.gov/cder/news/thalinfo/default.htm; posting of Stein Lyftingsmo on e-drug, (Aug. 9, 2003), at http://www.essentialdrugs.org/edrug/archive/200308/msg00022.php; *See* Judy Foreman, *Thalidomide, once pariah drug, finds new life in cancer therapy*, BOSTON GLOBE, Nov. 11, 1999, at http://www.boston.com/globe/search/stories/health/health_sense/111899.htm. See also the FDA's information page for Celgene's Thalidomid, at http://www.fda.gov/cder/news/thalinfo/default.htm.

559 "[I]n the wake of the public outcry about thalidomide, all of these objectives [i.e., to reduce drug costs and false advertising] were practically ignored and the bill's provisions recharacterized as a way to keep drugs like thalidomide out of the U.S. market." *See* Grow, *supra* note 249, at 89.

560 *See, e.g.,* SPRUMONT, *supra* note 16, at 156. In France, see for instance, J. Dangoumau, *La situation de l'expérimentation biomédicale en France au début des années 80*, 4 (special issue) INTERN. J. OF BIOETH. 13-15 (Mar. 1993).

561 *See* P. Fischer, *Développement, tâches et organization de l'Office intercantonal de contrôle des médicaments*, [*Development, tasks and organization of the Intercantonal Office for the control of medicaments*], *in* 75 ANS DE CONTRÔLE INTERCANTONAL DES MÉDICAMENTS [75 YEARS OF INTERCANTONAL CONTROL OF DRUGS] 51, at 59-60 (1975).
See also section 3 of the 1977 IOCM Guidelines on the application file required for marketing approval. In French: "*Directives de l'OICM concernant la documentation requise pour l'enregistrement de médicaments destinés à l'usage humain du 16 décembre 1977*"; 221.11; text at http://www.pharmalaw.org/O_Directives%20enregistrement%20(25.4.01).pdf.

562 *See, e.g.,* decision of the Swiss appeal commission for pharmaceuticals, JAAC 67.31, at point 8.a, (Sept. 13, 2002), at http://www.vpb.admin.ch/franz/doc/67/67.31.html; decision of the Swiss appeal commission for pharmaceuticals, JAAC 67.58, *supra* note 42, at point 2.2.

563 *See, e.g.*, Edison Pharmaceutical Co. v. Food and Drug Administration, 600 F.2d 831 (D.C. Cir. 1979) ("Substantial evidence [of efficacy] is 'evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.' Uncontrolled studies or partially controlled studies alone are insufficient proof of a drug's efficacy. Isolated case reports, random experience, and reports lacking details which permit scientific evaluation will not be considered." *Id.* at 837). *See also Warner-Lambert*, 787 F.2d at 151.

Despite the familiar distinction between safety and efficacy, the two are in fact interconnected. Even before the efficacy requirement was introduced, many considered that the FDA had the authority to ban an ineffective drug under the *safety* requirement (see subsection 4.1.1.1.1. above).[564] Since there is hardly any perfectly safe drug, the agency always has to weigh the safety risk against a backdrop of effectiveness.

4.1.1.2.2. The role of therapeutic indications

As alluded before, marketing authorizations are granted for a specific use; they only extend to the *specific* therapeutic indication that the sponsor applied for and that was supported by adequate clinical evidence. Hence, an already approved drug has to go at least through efficacy clinical trials if its sponsor wants approval for another therapeutic indication. The sponsor cannot actively market (i.e., advertise) an unapproved therapeutic indication, even if the drug itself is already approved and even if physicians can prescribe it off-label for this indication.

Hence, the sponsor must only prove the efficacy of its drug for the requested therapeutic indication (i.e., the drug's intended use).[565] The sponsor decides the indications it wishes to seek. It often does so in a step-by-step manner: applying for one indication after the other. "Staged" development is simpler for several reasons. First, once a drug has obtained its first approval, the safety requirements (and sometimes also the effectiveness requirements[566]) regarding the subsequent uses are significantly lower. Second, the sponsor can design its clinical trials for the new use, using knowledge generated by the clinical trials conducted for the previously approved use as well as by physicians' off-label use. Third, the drug will have already acquired some "name recognition" so that selling the new use to doctors will be easier.

Staged development is also made mandatory by drug agencies' high standards as to proof of safety and efficacy. The FDA observes:

> As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus for example, on a more specific disease stage or clinically distinct population. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use.[567]

What exactly is encompassed by a therapeutic indication is often unclear. Therapeutic indications may target different patient populations (e.g., male and female sexual dysfunction). Different stages of a given disease may correspond to different therapeutic indications (e.g., early and refractory cancer). Usually, when there are clearly distinguishable medical conditions, the drug's therapeutic indications will be similarly dissociated (e.g., depression and schizophrenia).

---

564 *See, e.g.,* Kulynych, *supra* note 541, at 135.

565 There may be possible exceptions when it is obvious that the drug will be used beyond its requested therapeutic indication. *See supra* note 580.

566 *See* FDA (Effectiveness), *supra* note 529, at 6 and 7-12.

567 *See id.* at 2.

As just explained, a drug is approved if it is proven effective for a specific therapeutic indication. In addition, this proof relates to a specific *form* of the drug, and not simply to its active ingredient. Hence, the proof must have been reached for a given product form. This product form includes a given strength* or dosage (e.g., 100mg), dosage form*[568] (e.g., tablet, syrup, injection), dosage regimen (e.g., one tablet a day). Any change to the product form may trigger the obligation for the sponsor to bring forward additional proof of safety and effectiveness Although the level of scientific evidence required is typically lower than for an entirely new drug,[569] the sponsor will nonetheless have to obtain the drug agency's prior approval.

4.1.1.2.3. Required standard of substantiation

The U.S. legislation specifies the necessary level of proof that the sponsor must provide: Effectiveness must be established by "substantial evidence," which is in turn defined as

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.[570]

The FDA has interpreted this statutory provision as requiring at least two well-controlled randomized[571] large scale (phase III) clinical trials.[572] Having two instead of just one proof of effectiveness is a guarantee against intentional or innocent mistakes made in the context of one trial and its resulting misleading conclusions.[573] In other words, it must be possible to replicate the findings of the first trial in a second one ("the replication requirement").[574]

Similarly, the FDA requests that trials be conducted in more than one research site/institution.[575] These two required studies are normally organized as multicentric

---

568 In Europe, the word "galenic form" is also sometimes used. In the United States, the expressions "route of administration" or "delivery system" are used.

569 *See* FDA (Effectiveness), *supra* note 529, at 7-12.

570 Section 505(d) of the FDCA, *supra* note 536. Swiss law does not state what exactly is required to demonstrate effectiveness as per Article 10.1.a LPTh.

571 What is held to be a well-controlled trial is explained in details in subsection 6.3. below.

572 This requirement is referred to as "independent substantiation" or "replication." Each of the two required trials must be convincing on its own. *See* FDA (Effectiveness), *supra* note 529, at 3-5. This interpretation is based on the use of the plural in the above-cited provision (i.e., "investigation*s*, including clinical investigation*s*" (emphasis added)).
However, for drugs against serious diseases (e.g., cancer, AIDS), this requirement is often relaxed, and sponsors submit (at best) a single large randomized phase III trial. *See* American Society of Clinical Oncology ("ASCO")/FDA Lung Cancer Endpoints Workshop, at 10, (Apr. 15, 2003), at http://www.fda.gov/cder/drug/cancer_endpoints/lungFinalSummary.doc [hereinafter ASCO/FDA].

573 *See* FDA (Effectiveness), *supra* note 529, at 4-5.

574 *See, e.g.*, Kulynych, *supra* note 541, at 129-30.

575 *See* FDA (Effectiveness), *supra* note 529, at 5 ("Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet).").

clinical trials.[576] Preferably, the subjects should be evenly distributed among the research centers.[577] The two large studies need not be identical, they can be based on different protocols.[578] Having two different designs is another guarantee against mistakes and source of bias related to the trial design. The results from the different centers should be consistent: If one center yields positive proof of effectiveness, while another one does not, this signals a problem: One of the center must be doing something "wrong."[579]

Exceptions to the rules just described are admitted, particularly when the drug has a life-saving potential.[580] Ethical concerns operates to impose reliance on a single convincing trial[581] if the drug was clearly proved effective in one clinical trial; in such a case, withholding it from the subjects belonging to the control group in a *second* clinical trial would be viewed as unacceptable. Similarly, patients should benefit from the new drug as soon as possible.

Conversely, when submitted studies have recognized flaws, while still acceptable, the sponsor may need to present more than two trials as a way to remedy these deficiencies.[582] Similarly, when past studies have yielded *negative* results,[583] the sponsor may have to compensate these by showing *positive* results in more than two trials.[584]

Finally, the sponsor may reduce risks by planning for more than one clinical trial. Instead of putting all its eggs in one basket, the sponsor spreads its risks across several research sites and different protocols.[585]

Drug agencies have considerable leeway in deciding the appropriate level of substantiation. In the United States, the sponsor and the FDA can discuss and "negotiate" beforehand the acceptable threshold of evidence (see subsection 6.2.1.3.). In Switzerland, Swissmedic rarely accommodates such prior discussions.

---

576 *See* ICH, Guideline E9 on Statistical Principles for Clinical Trials, at section 3.2, p.12-13, (Feb. 5, 1998) (step 4 of ICH process), at http://www.ich.org/MediaServer.jser?@_ID=485&@_MODE=GLB [hereinafter ICH E9]; Kulynych, *supra* note 541, at 142-43.

577 *See generally* FDA (Effectiveness), *supra* note 529, at 13. *See also* Kathleen Squires et al., *Tenofovir Disoproxil Fumarate in Nucleoside-Resistant HIV-1 Infection, A Randomized Trial*, 139 ANN. INTERN. MED. 313-320, at 316 (Sept. 2, 2003) at http://www.annals.org/cgi/reprint/139/5_Part_1/313.pdf ("Enrollment was relatively balanced among all sites: Each enrolled 5% or fewer of the patients in the study with one exception, which enrolled 7%. All baseline characteristics of the two treatment groups were well matched.").

578 *See id.* at 5.

579 *See generally* FDA (Effectiveness), *supra* note 529, at 13.

580 *See id.* at 3-4.

581 *See id.* at 12-13.

582 *See id.* at 6.

583 A negative study is one that concludes that the treatment's effects did not reach the desired level of significance. For a negative result to be taken into consideration, it must be based on an adequately powered clinical trial, that is a trial with a sufficient sample size. See further subsection 6.3.10.1. below. *See* David Moher et al., *Statistical Power, Sample Size, and Their Reporting in Randomized Controlled Trials*, 272 JAMA 122-24 (1994), at http://www.ama-assn.org/public/peer/7_13_94/pv3037x.htm [hereinafter Moher (Sample)].

584 *See* FDA (Effectiveness), *supra* note 529, at 6.

585 *See id.* at 6.

4.1.1.3. Proving bioequivalence

In many countries including Switzerland, generic drugs (i.e., copies of brand-name pharmaceuticals) can obtain their marketing authorization following a simplified procedure.[586] Instead of bringing full proof of safety and efficacy, the sponsor just has to demonstrate that its generic product is bioequivalent* to the brand-name.[587] Bioequivalence is proved if the two drugs contain the same active ingredient at the same strength and in the same dosage form and if both are absorbed in the same way.

Bioequivalence studies may also be necessary when a manufacturer modifies, in some relatively minor aspects, the formulation* of its drug (e.g., use of a different inactive ingredient (excipient*)).[588] The manufacturer must then prove that the modified drug still produces exactly the same effects as its previous version.[589] The proof is normally brought by a bioequivalence study. Such a study compares how the two drug versions are absorbed and detected in blood levels of human research subjects (i.e., a pharmacokinetic assessment).[590]

Bioequivalence studies are somewhat similar to early clinical trials focused on safety (see subsection 4.1.1.1. on phase I above). They involve a small number of subjects, usually healthy volunteers.[591] The protocol generally calls for a "cross-over" design whereby one group of subjects receive first one or more dose of the first product, followed (after a washout period) by one or more dose of the second product. The other group receives the same treatment but in an inverted order. Assignment to the study groups should be randomized.[592]

Data from bioequivalence studies should verify that the two products are absorbed and excreted in the same ways (e.g., same speed). If this is the case – provided a tolerance margin (up to 20%) that depends on the therapeutic index/range of the drug – the two products are deemed bioequivalent.[593] Hence, the sponsor may apply, if all other conditions are met, for a marketing authorization according to the simplified procedure. In most other aspects, bioequivalence studies are similar to other clinical trials.

---

586 Article 14.1.a LPTh.

587 Article 6 of the Swissmedic's Ordinance on the simplified authorization et the mandatory notification of pharmaceuticals of November 9, 2001; RS 812.212.23; in French: "*Ordonnance de l'Institut Suisse des produits thérapeutiques sur l'autorisation simplifiée et l'annonce obligatoire des médicaments*"; abbreviated (from the French): OASMéd; text in French at http://www.admin.ch/ch/f/rs/8/812.212.23.fr.pdf.

588 If the modification is really minor and there are no safety concerns, in vitro tests (e.g., laboratory or animal studies) may replace bioequivalence studies on human subjects.

589 *See, e.g.,* McGill Centre for Translational Research in Cancer, A Study To Compare the Bioequivalence Of Two Formulations of 20 MG Nolvadex Tablets Taken Once Daily, at http://www.mctr.org/en/rp/studies/nolvadex.htm.

590 "Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the side of action and thus in an essentially similar effect, pharmacokinetic data instead of therapeutic results may be used to establish equivalence …" EMEA, Investigation of Bioavailability and Bioequivalence, Note for Guidance (June 1992), at 233, at http://pharmacos.eudra.org/F2/eudralex/vol-3/pdfs-en/3cc15aen.pdf.

591 Twelve volunteers is the minimum, according to the EMEA. *See id.* at 235.

592 *See id.* at 235.

593 See CDER, FDA, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, (Mar. 2003) at http://www.fda.gov/cder/guidance/5356fnl.pdf.

4.1.1.4. The marketing authorization process and its alternatives

Given the costs of the current drug approval process in industrialized countries (see below subsection 4.2.1.), many critics – customarily from the ranks of pro-business groups – have called for radical reforms. They mainly attack the "effectiveness" requirement and the way it has to be substantiated (i.e., through two large randomized well-controlled clinical trials). They wish to place the emphasis on post-marketing studies rather than premarketing trials. They suggest that greater weight be given to the assessment of individual physicians. They stress that the patients should be allowed to decide for themselves, with the assistance of their doctors, whether or not they want to use a drug about which only limited information is available. Brody has set forth a detailed proposal for an alternative regulatory scheme.[594] According to his proposal, the role of drug agencies should be limited to that of a clearing-house for information originating from various sources. Agencies should tolerate on the market any drug provided there is enough information that *at least some reasonable persons* would want to use it. Similarly, a drug should not be withdrawn as long a some reasonable people want to use it.[595]

Needless to say, I disagree with such a proposal. In my mind, reliable information would never come to light under this scheme. Pharmaceutical companies would have no incentive to develop the necessary efficacy data. Quite rationally, they would prefer to "trust" physicians' case reports of patients. Moreover, there would be no way to control the veracity of their advertisements. Neither patients nor physicians would be able to sort out the available information. Physicians are already unable to keep track of all evidence-based drug reviews published in medical journals; too often, they believe what drug representatives tell them. Patients would be seriously misled since few, if any physicians, would ever admit that their medical decisions are based on flimsy evidence, or even worse, on promotional material provided by drug companies.

4.1.2. Contributing to basic knowledge

Clinical trials can also be launched simply to contribute to general knowledge about a given disease or treatment: Their resulting data are not meant to be submitted to a drug agency, but to make science progress. Forty years ago, most clinical trials had only such lofty scientific goals in perspective, largely because they were sponsored by public bodies. Nowadays, these non-commercial trials, especially when they are large and involve pharmaceuticals, are fewer.[596] The cost of clinical trials is so high that only few research centers (e.g., prestigious medical schools) can afford them without funding from an external sponsor, typically a pharmaceutical company.

---

[594] *See* BRODY, *supra* note 447, at 197-201.

[595] *See id.* at 201.

[596] *See however* FDA, Original INDs Received, Calendar Years 1986-2003), (updated on Dec. 31, 2003), at http://www.fda.gov/cder/rdmt/Cyindrec.htm, (indicating that there were almost 1700 *non-commercial* INDs for some 400 commercial INDs in 2003).

The unfortunate corollary is that many important medical questions are left unanswered.[597] This problem is exemplified by old treatments which were placed on the market without appropriate premarketing testing. Commercial sponsors do not have the incentive to test these treatments, because they have no reason to create competition against their own patented products. Why would the company take the risk of loosing money by scientifically proving that an old, cheap and unpatented drug is better than their new proprietary drug?

4.1.3. Assisting physicians

Another objective of clinical trials is to assist doctors in deciding whether and how to administer a drug to their patients.[598] Clinical data are incorporated in the drug's label to which doctors can refer.[599] The more detailed the label, the easier the work of the physician. For instance, the physician will learn whether the drug was tested on a subject population whose characteristics match that of her patient. She will also get an idea of how effective the drug might be for her patient.

Prescription decisions based primarily on clinical trial data are now known as *evidence-based medicine* ("EBM"); this notion is opposed to prescription based on the physicians' personal experience and intuition.[600] To achieve the goal of EBM, clinical data are often summarized in clinical guidelines; these guidelines encapsulate all available and reliable knowledge regarding treatment of a given condition[601] and describe the best treatment regime.[602] These guidelines sometimes have significant impact and can rapidly change the way patients are treated throughout the (Western) world.[603] They often have multiple secondary purposes, such as reducing costs borne by medical insurance systems or circumscribing the liability of physicians in malpractice cases.[604]

---

597 *See* Sean R. Tunis et al., *Practical Clinical Trials, Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, at 1625 and at 1629 (Sept. 24, 2003), at http://jama.ama-assn.org/cgi/reprint/290/12/1624.

598 *See, e.g.,* Grow, *supra* note 249, at 115.

599 See for example the Swiss professional information leaflet (for physicians) for Zoloft: from http://www.kompendium.ch/Result.aspx?lang=fr; compare with the much more detailed labeling approved by the FDA, at http://www.fda.gov/cder/foi/label/2002/19839s39lbl.pdf.

600 *See, e.g.,* Smith (Read Research), *supra* note 51, at 1307.

601 *See generally* Richard N. Shiffman et al., *Standardized Reporting of Clinical Practice Guidelines: A Proposal from the Conference on Guideline Standardization*, 139 ANN. INTERN. MED. 493-500 (Sept.16, 2003), at http://www.annals.org/cgi/reprint/139/6/493.pdf. *See also* PhRMA, Pharmaceutical Industry Profile 2003, at 5 (2003), from http://www.phrma.org/publications/publications/profile02/index.cfm [hereinafter PhRMA (Industry Profile 2003)].

602 *See, e.g.,* Steven H. Woolf et al., *Potential benefits, limitations, and harms of clinical guidelines*, 318 BMJ 527-530 (Feb. 20, 1999), at http://bmj.bmjjournals.com/cgi/content/full/318/7182/527. *See also* Hervé Guillain, *Les recommendations pour la pratique clinique: l'expérience d'une agence gouvernementale américaine*, 37(4) CMS 355-65 (1993).

603 *See, e.g.,* Frank Davidoff et al., *Sponsorship, Authorship and Accountability*, 345 NEW. ENG. J. MED. 825 (Sept. 13, 2001), at http://content.nejm.org/cgi/reprint/345/11/825.pdf. *See also* Randall S. Stafford et al., *Impact of Clinical Trial Results on National Trends in α–Blocker Prescribing, 1996-2002*, 291 JAMA 54-62 (Jan. 7, 2004), at http://jama.ama-assn.org/cgi/reprint/291/1/54.pdf.

604 *See* Oliver Guillod, *Préface*, *in* LES RECOMMENDATIONS DE PRATIQUE CLINIQUE [CLINICAL GUIDELINES], at 3-4, Institut de droit de la santé [Health Law Institute], Cahier N°7 (Nov. 1999).

4.1.4. Advertising the drug

4.1.4.1. Before marketing approval

Only after the drug and its therapeutic indications have been approved can the sponsor use the clinical trial results for marketing campaigns. The rule is that the sponsor should limit its advertising to the officially *approved* indications.[605]

It follows from this rule that sponsors will design their clinical trials keeping in mind the therapeutic indications that will be profitable from a marketing standpoint. This link between the clinical trial design, the approved therapeutic indication(s) and the post-approval advertising message is very important. Marketing departments of pharmaceutical firms get involved early on. The sponsor must have an accurate idea of the label it will apply for as early as possible.[606] Given the label's importance,[607] sponsors engage in crucial negotiations with drug agencies to convince them to accept their propositions.[608]

While gaining approval for a broad range of indications has obvious competitive benefits, seemingly less significant indications may nonetheless be valuable. For example, Schering-Plough was marketing Clarinex as the only drug approved against *indoors* allergies.[609] This should not be taken to mean that other allergy drugs – including Schering's own Claritin[610] – are not effective indoors … they are. The difference is that Schering-Plough designed its clinical trial so the results would support this specific indication and corresponding marketing claim.

Most countries limit drug advertising to therapeutic indications that have been approved by the drug agency.[611] Such a rule is relatively easy to apply to straightforward advertisement campaigns. However, companies are not entirely banned from disclosing the results of their clinical trials, including early phase studies. Companies routinely

---

605 Since 1997, the United States has relaxed this rule. *See* O'Reilly & Dalal, *supra* note 429, at 295 (explaining how § 401 of the 1997 Food and Drug Administration Modernization Act ("FDAMA") (Pub. L. 105– 115) loosened the 1962 requirement that pharmaceutical manufacturers prove efficacy before marketing their products).

606 In the United States, only the label intended for *physicians* is mandatory. Patients' notice of use are not always compulsory, except for contraceptives or particularly dangerous drugs. *See, e.g.,* OIG (FDA Review), *supra* note 20, at 46. The United States plans on soon aligning its practice on that of other developed countries and make patients' notice of use mandatory too.

607 The label includes among others the approved therapeutic indications, the recommended dosages, the precautions of use, the identified contraindications and safety warnings.

608 *See* OIG (FDA Review), *supra* note 20, at 17-18. See also with respect to labels for pediatric patients, GENERAL ACCOUNTING OFFICE ("GAO"), PEDIATRIC DRUG RESEARCH, SUBSTANTIAL INCREASE IN STUDIES OF DRUGS FOR CHILDREN, BUT SOME CHALLENGES REMAIN, at 9 (GAO-01-705T) (May 8, 2001), ("In some cases, FDA officials said they have had substantial difficulty in getting drug manufacturers to incorporate unfavorable pediatric research results into drug labels.") at http://www.gao.gov/new.items/d01705t.pdf [hereinafter GAO (Pediatric)].

609 *See* Press Release, Schering-Plough, Schering Laboratories Begins Clarinex DTC Education Program, (Mar. 4, 2002), at http://www.schering-plough.com/schering_plough/news/release.jsp?releaseID=264909.

610 Claritin was Schering's former blockbuster until it lost its Rx-only status and its patent protection. Many have argued that Claritin and Clarinex are in fact almost identical compounds. *See* Rita Rubin, *Claritin to go OTC next spring, Clarinex to replace it*, USA TODAY, (Apr. 4, 2002), at http://www.usatoday.com/news/health/drugs/2002-04-23-claritin.htm.

611 According to Article 5.1. OPMéd, advertisement to health care practitioners must be limited to therapeutic uses recognized by Swissmedic.

present such results. Publicly-traded companies may even be obliged to do so in accordance with securities laws, given that clinical trial results heavily affect stock prices.

These opportunities to present clinical trial results influence the sales of the not-yet approved drug/therapeutic indication. On the basis of this information, physicians often start to prescribe the drugs "off-label."[612] Hence, clinical trials help companies cash in on a new treatment before it has been approved.

Sometimes, the clinical trial is not even intended to support a new therapeutic use, but is only meant to bolster the sales of the existing drug use. Sham trials, often organized as phase IV trials, have come under heavy criticisms (see subsection 6.1.4.2. below).[613]

4.1.4.2. After marketing approval

If the sponsor makes use of clinical data in its advertisement, it must do so fairly. In particular, if the advertisement refers to a published clinical study, the reference should be clear so as to enable readers to find the publication.[614] Under Swiss law, advertising must refer only to studies that were conducted according to Good Clinical Practices (GCP).[615] In addition, the studies must be either already or soon to be published. Lastly, the studies must be available to interested parties.[616]

4.1.5. Minimizing liability

The agency's grant of a marketing authorization does not protect pharmaceutical manufacturers against product liability actions.[617] When a drug found safe and effective by the drug agency nonetheless causes injury to a patient, its manufacturer faces liability

---

612 This requires, of course, that the drug be already legally sold on the market for some other therapeutic indication. *See, e.g.,* William F. Clark et al., *Effect of Awareness of a Randomized Controlled Trial on Use of Experimental Therapy*, 290 JAMA 1351-1355 (Sept. 10, 2003), at http://jama.ama-assn.org/cgi/reprint/290/10/1351.pdf.

613 *See, e.g.,* Frank Davidoff et al., *supra* note 603, at 825.

614 *See generally* decision of the Swiss federal appeal commission for therapeutic products, JAAC 66.102, at point 4.b. (Apr. 17, 2002), at http://www.vpb.admin.ch/franz/doc/66/66.102.html*;* International Federation of Pharmaceutical Manufacturers Associations ("IFPMA"), Code of Pharmaceutical Marketing Practices (last revised Jan. 2000), at http://www.afpmbg.org/info/IFPMA%20Code%20of%20Pharmaceutical%20Marketing%20Practices.doc.

615 Article 5.5 of the Federal Council's Ordinance on publicity for pharmaceuticals of October 17, 2001; in French: "*Ordonnance sur la publicité pour les médicaments*"; abbreviated (from the French): OPMéd; RS 812.215.5; text in French at http://www.admin.ch/ch/f/rs/8/812.212.5.fr.pdf. *See also* Valerie Junod, *La publicité pour les médicaments, Difficultés et faiblesses de la réglementation actuelle*, RSDA 5/2005, at 235-43.

616 *Id.* The 2004 revision of the OPMéd reinforces this requirement, by specifying that health care professionals are entitled to ask for the full report of the clinical trial referred to in the advertising.

617 According to sixth Circuit, "FDA approval [does not preempt] state product liability claims based on design defect. … The jury may weigh FDA approval as it sees fit …." Tobin v. Astra Pharmaceutical Products, Inc., 993 F.2d 528, at 537 and at 538 (6th Cir. 1993) (a case where the plaintiff successfully argued, despite FDA approval, that the manufacturer should not have launched its product on the market given its lack of effectiveness and its serious side effects).

suits. In the United States, liability claims are very common and the amounts awarded can be incredibly high.[618]

To fend off liability suits, the manufacturer must prove that it took all possible precautions before deciding to place its product on the market. This creates a separate obligation to test drugs. Only if the manufacturer can show that it thoroughly tested its product can it escape liability in case of patients' injury.

4.1.6. Intellectual property ("IP")

4.1.6.1. Getting IP rights ("IPR")

Clinical trial results may also be used to support a patent application. A patent will, for example, cover a new drug use discovered in the course of a clinical trial (e.g., Viagra was originally designed as a drug against angina, not impotence[619]). However, under most jurisdictions, patent applicants can obtain a patent even if their supporting evidence is far less exacting than that required by drug agencies.[620] Preclinical evidence of utility usually suffices.[621] Hence, clinical trials are not an absolute necessity for a patent to be granted.

In fact, by the time a compound enters clinical trials, it has *already* received substantial patent protection. Sponsors do not incur the risk of using unpatented compounds in clinical trials, since trade secret protection (the alternative to patent protection) is insufficient: Too many people involved in the trial are to receive access to the compound for secrecy to be maintained. Moreover, publication of clinical trial results would destroy the novelty of any invention disclosed therein.[622]

Widespread use of a compound in clinical trials may also invalidate the (yet) unpatented invention under the public use bar.[623] Under U.S. law, use by the inventor (or under his control) which is strictly limited to testing the viability, functionality, or quality of an invention does not, however, fall under the public use bar. These tests fall under the experimental use exception, an exception to unpatentability or invalidity.[624] In the case of clinical trials, it is unlikely that the sponsor can invoke the experimental use exception.[625] First, for most inventions, the sponsor should already have applied for a

---

618 Pharmaceutical companies regularly argue that high jury awards in product liability lawsuits have the effect of raising drug prices for all patients.

619 *See* Jim Kling, From Hypertension to Angina to Viagra, 1(2) Modern Drug Discovery, 33-34, (Nov.-Dec. 1998), at http://pubs.acs.org/hotartcl/mdd/98/novdec/viagra.html.

620 *See* In re Wesley Gale Irons, 340 F.2d 974 (C.C.P.A. 1965).

621 *See, e.g.*, In re Georges Jolles, 628 F.2d 1322 (C.C.P.A. 1980).

622 In other words, if the publication or any other release of information to unauthorized third party reveals an invention for which a patent has not yet been requested, the invention will no longer be patentable, because one of the conditions of patent protection is complete novelty. Novelty requirements in Europe are even stricter than those in the United States. In the United States, see 35 U.S.C. § 102(a).

623 In the United States, 35 U.S.C. § 102(b). *See* Shashank Upadhye, *To Use or Not to Use: Reforming Patent Infringement, the Public Use Bar, and the Experimental Use Doctrine as Applied to Clinical Testing of Pharmaceutical and Medical Device Inventions*, 4 MINN. INTELL. PROP. REV. 1, at 3 (2002).

624 *See* Upadhye, *supra* note 623, at 10-13.

625 *See id.* at 14-15.

patent on the basis of preclinical studies only. Second, clinical trials cannot fulfill the limitations associated with the experimental use exception.[626]

However, the clinical trial stage may constitute the opportunity to apply for *additional* patents, covering, for example, aspects related to the drug's manufacturing process.[627]

In addition to patents, many countries extend marketing exclusivities as a reward for clinical research[628]. Although exclusivities linked to research activities do not last as long as patent protection, these can be helpful when the main compound is not under patent (e.g., patent has expired or could not be obtained in the first place). In such cases, clinical trials are one of the conditions to secure this extra term of protection, typically starting with the grant of marketing authorization. For example, in the United States, approval of a new therapeutic indication based on clinical trial evidence is rewarded by a 3-year marketing exclusivity.[629] Trials on pediatric populations are rewarded by a six-month exclusivity.[630]

Countries also grant patent extension to compensate the period of patent life lost during clinical trial and authorization processes. In the United States, the period of restored protection is calculated based on the duration of the testing phase and the regulatory approval phase;[631] the maximum extension is five years and the maximum total patent life (with the extension) is 14 years.[632]

4.1.6.2. Defending patent infringement claims

The launch of a clinical trial carries the risk that the sponsor be accused of patent infringement by another party claiming patent rights on the compound being tested. While preclinical development is mostly done in the sponsor's facilities, clinical research is done "in the open." Hence, third party patent owners have a first opportunity

---

626 Too many people have access to the invention to maintain the exception. Moreover, the sponsor may be already engaging in early commercialization efforts.

627 It is indeed at this stage that the pharmaceutical sponsor must settle on the way its final product will be manufactured. *See* Bruce Rubinger & Howard Davis, *Protecting IP Throughout the Product Lifecycle*, PHARMEXEC.COM (Aug. 1, 2003), at http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=64069&pageID=1.

628 Article 39.3 of the TRIPS Agreement mandate *some form* of protection for clinical trial data. The text of the agreement is available at http://www.wto.org/english/docs_e/legal_e/27-trips.pdf. For further information about marketing exclusivities in the United States and in the European Union, see my article: *Drug Marketing Exclusivity*, 59(4) FOOD & DRUG L. J. 479-518 (2005).

629 See also in Switzerland, Article 17.2&3 OMéd (indirectly granting a 3 to 5-year exclusivity for new therapeutic uses and significant variations to the original marketing authorization).
The European Union offers a 10-year orphan drug exclusivity. *See* Article 8.1. of Regulation No. 141/2000/EC, *supra* note 44.

630 *See* 21 U.S.C. § 355a(a) and (c), at http://www4.law.cornell.edu/uscode/21/355a.html (Jan. 19, 2004). On other conditions that must be met, see Mark A. Schreiner, *Paediatric Clinical Trials: Redressing the Imbalance*, 2 NATURE REVIEWS, DRUG DISCOVERY 953-54 (Dec. 2003), at http://www.nature.com/cgi-taf/DynaPage.taf?file=/nrd/journal/v2/n12/full/nrd1253_fs.html&filetype=pdf. *See also* FDA, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry, (Sept. 1999) at http://www.fda.gov/cder/guidance/2891fnl.pdf.

631 *See* 35 U.S.C. § 156 and 21 C.F.R. § 60.22.

632 *See* FDA, Frequently Asked Questions on the Patent Term Restoration Program, (last updated Dec. 8, 2003), at http://www.fda.gov/cder/about/smallbiz/patent_term.htm.

to learn if the sponsor exploits their intellectual property ("IP"). The duplication or use of a patented compound in a clinical trial (by someone else than the patent owner) typically amounts to patent infringement. There are some exceptions.

First, if the third party sponsor buys the patented drug on the market, it can use it in its clinical trial, for example to compare it against its own compounds; in this case, the patent owner's IP right was exhausted by the sale.

Second, many jurisdictions admit that the manufacture and use (by a third party sponsor) of a patented compound is permissible if limited to the gathering of clinical information necessary for the sponsor to submit a marketing application to a drug agency.[633] This concerns mainly generic companies that must test their copies of brand-name products. The generic marketing authorization will however only become effective once the patent on the brand-name drug has expired or been invalidated. In the United States, this is referred to as the *Bolar exemption**, because the statute that awarded this right overturned a prior Court decision in Roche v. Bolar.[634] After some hesitations, the European Union has followed suit and introduced its own version of the Bolar exemption.[635]

Recently, the U.S. Court of Appeals for the Federal Circuit ("CAFC") had to decide whether (U.S.) patent law admits a broader exemption for other experimental uses.[636] The answer was no, even when the third party user is a university.[637] Hence, the use of a patent in research (beyond the scope of the Bolar exemption) can form the basis of an infringement lawsuit. The only admissible exception, according to the Court, is when the experimental use is limited to "actions performed 'for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.'"[638] This strict condition is no longer fulfilled when use "is undertaken in the 'guise of scientific inquiry' but has 'definite, cognizable, and not insubstantial commercial purposes.'"[639] Universities and other interest

---

633 *See* William L. Warren et al., *Experimental Uses and Research Tool Licensing Alternatives*, (Apr. 2003), Sutherland, Asbill & Brennan LLP, at 11-14, at http://www.sablaw.com/files/tbl_s47Details%5CFileUpload265%5C2552%5CExperimentalUsesResearchToolLicensing.pdf (on the notion of "activities reasonably related" to the development of information for the FDA).

634 Roche Products v. Bolar Pharmaceutical, 733 F. 2d 858 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 856 (1984). This exception does not apply to patents covering biotech research tools. *See* Integra Lifesciences I, v. Merck, 2003 WL21299392 (Fed. Cir. 2003), *at* http://www.ll.georgetown.edu/federal/judicial/fed/opinions/02opinions/02-1052.html.

635 *See* amendment to Article 10.4 of Directive 2001/83/EC; *also* Draft Opinion of the Committee on Industry, External Trade, Research and Energy, (May 27, 2002), at http://www.europarl.eu.int/meetdocs/committees/itre/20020603/469561EN.pdf.
Until the European Union introduced its own legislation in 2004, each Member State had its own regime. For example, in Germany, clinical trials of patented drugs fell under the experimental use exception (i.e., patent rights are not infringed). The United Kingdom had a restricted view of the experimental use exception. *See* Morrison & Foerster, Europe to Join Japan and the US – a Bolar Exemption in Europe (June 2003), at http://www.mofo.com/tools/print.asp?/mofo_dev/news/updates/files/update1031.html.

636 *See* Madey v. Duke University, 307 F.3d 1351 (Fed.Cir. 2002), decision available at http://biotech.law.lsu.edu/cases/IP/patent/madey_v_duke_ca.htm.

637 "[T]he profit or non-profit status of the user is not determinative." *Id.* at 1362.

638 *Id.* at 1362.

639 *Id.* at 1362.

groups are hoping that the Supreme Court will take up this case and reconsider the lower court's decision.[640]

Swiss courts would probably adopt a similarly rigorous, if not stricter, position.[641]

4.1.7. Obtaining reimbursement status

After securing marketing approval, the sponsor's next step is to obtain reimbursement by insurance companies.[642] In European countries, the decision to reimburse a given drug is usually taken by public authorities different from those granting marketing authorizations. In the United States, insurance companies reimbursing drugs are private bodies, except for a few federal and state programs covering only specific segments of the population (e.g., Medicare, Medicaid). These private companies have considerable latitude to decide whether or not to reimburse a drug.[643]

Pharmaceutical firms thus use clinical trial data to convince social insurance authorities and private drug buyers (e.g., HMOs in the United States[644]) to reimburse the drug.[645] Third party payers are increasingly rigorous as to which drugs are reimbursed. They may reassess the drug's efficacy data to make sure that it offers sufficient therapeutic benefits to offset its cost.

Drug companies must therefore take care to design their clinical trials so that they will yield helpful positive information for these third party payors.[646] While a slight therapeutic benefit over placebo* may be sufficient to secure a marketing authorization, insurance agencies look for more than that when accepting to reimburse the drug.[647] Comparative or head-to-head trials (see below subsection 6.3.3.3.) are certainly an attractive but risky way to convince insurance agencies.

---

640 *See* Jennifer Miller, *Sealing the Coffin on the Experimental Use Exception*, 2003 DUKE L. & TECH. REV. 0012, at 1-2, at http://www.law.duke.edu/journals/dltr/articles/PDF/2003DLTR0012.pdf; Warren et al., *supra* note 684, at 8-9.

641 The only partly relevant provisions in the context of experimental use are Articles 32 and 40 of the Federal Law on patents; June 25, 1954; RS 232.14; at http://www.admin.ch/ch/f/rs/2/232.14.fr.pdf.

642 Nowadays, pharmaceutical companies may even approach drug reimbursement authorities before obtaining marketing approval, because there can be a delay of several month between the application (for reimbursement status) and the final decision of the authority. Therefore, companies need to coordinate the two procedures (marketing approval and reimbursement approval), if they want to avoid the undesirable situation where patients have to buy the product at their own expenses (i.e., "out-of-pocket").

643 A drug which is approved for reimbursement is generally placed on the insurance plan's approved formulary. Drugs which "did not make it" on the formulary are not reimbursed.

644 About a quarter of the U.S. population is enrolled in an HMO system of health insurance. *See* National Center for Health Statistics, ("NCHS"), HHS, United States, 2003, at 12, at http://www.cdc.gov/nchs/products/pubs/pubd/hus/highlits.pdf (emphasis omitted) [hereinafter NCHS (Health Statistics)].

645 However, reimbursement of drugs prescribed *off-label* is increasingly accepted. *See* Tabarrock, *supra* note 433, at 35-36.

646 *See* Tufts Center, *Influence of pharmacoeconomics in drug R&D decisions is growing*, 2 IMPACT REPORT 2 (May 2000).

647 *See, e.g.,* Kulynych, *supra* note 541, at 139.

In Europe as in the United States, the consequence of not obtaining a good reimbursement status is the same: The total sales and revenues for the manufacturer will be significantly lower if the patient has to pay for the drug himself.[648] Since drug companies obviously want consumption to increase, they push strenuously for their drugs to be fully reimbursed.

To convince decision-makers (whether private or public bodies) to pay for the drug, pharmaceutical companies can present them with studies showing that their drugs yield benefits and/or savings that are greater than the cost of the drugs themselves.[649] For example, a sponsor will show that patients treated with product x against influenza return to work earlier or that they do not suffer from aggravating conditions that lead to costly hospitalizations. In other words, these studies endeavor to prove that reimbursement of the drug is *cost-effective*.

There are many methods to demonstrate such benefits. For example, the sponsor can gather information on the cost of its drug treatment and compare it to the expenses that would be borne if patients were not treated with the drug. Costs included in these two categories often vary. For instance, costs may include, besides the direct price of the treatment, the cost of a visit to the prescribing physician, the cost of failed treatments, of hospitalization, as well as expenses related with work absenteeism, early mortality, incapacity, or diminished quality of life ("QoL").[650] The sponsor may also focus its analysis on two comparable drugs for the same therapeutic indication.[651] In such a case, the efficacy and the prices of two treatments (intended for the same indication) are compared. While the (direct) price of the two treatments is a known factor, their comparative efficacy needs to be assessed (see also subsection 6.3.3.3. below).

Good cost-effectiveness (also called pharmacoeconomic) studies are organized according to a protocol and resemble a clinical trial in that sources of bias are duly minimized.[652] A therapeutic clinical trial (e.g., a phase III trial) and a cost-effectiveness study may also be organized in parallel.[653] Cost-effectiveness studies involving subjects should entail the subjects' consent.[654] Presently, studies that only focus on cost-effectiveness data are not regulated, since they present no special health risks.

Governments do not – yet – systematically mandate cost-effectiveness comparisons before deciding whether to reimburse a new drug. There is, however, a clear trend to-

---

[648] The diminution in demand will depend on the price elasticity of demand. When the product is entirely reimbursed, the elasticity is generally equal to 0, meaning that an increase in price will have no effect on the demand.

[649] According to PhRMA, "[f]or each additional $1 spent on newer pharmaceuticals, $6.17 is saved in total health spending, $4.44 of which comes from savings in reduced hospital costs." PhRMA, Annual Report 2003-2004, at 8-9, (Oct. 2003), at http://www.phrma.org/publications/publications//2003-11-20.870.pdf.

[650] *See* Nicole Vogt & Pierre Dayer, *Comment lire un essai pharmaco-économique?*, 53 MED. ET HYG. 878 (Apr. 19, 1995).

[651] For a review of the different types of pharmacoeconomic studies, see *id.* at 877-80.

[652] However, not all pharmacoeconomic studies are clinical trials. Pharmacoeconomic studies can be conducted simply by analyzing already available data (i.e., retrospectively collected data); if the data does not indicate or otherwise reveal the identity of patients or subjects, it does not require an authorization (compare with subsection 3.4.6.3. above).

[653] *See* Vogt & Dayer, *supra* note 650, at 880 (discussing the problems in combining these two studies).

[654] See for examples of such studies: Joshua A. Salomon et al., *Cost-effectiveness of Treatment for Chronic Hepatitis C Infection in an Evolving Patient Population*, 290 JAMA 228-237 (July 9, 2003), at http://jama.ama-assn.org/cgi/reprint/290/2/228.pdf.

ward imposing such a requirement.[655] This is sometimes referred to as the "fourth hurdle."[656] For example, drugs reimbursed through the English National Health Service ("NHS"[657]) must be found cost-effective through assessment conducted by the National Institute for Clinical Excellence ("NICE").[658] In the United States, a 2003 bill would have the government pay to perform similar studies on costly and widely prescribed drugs.[659]

Pharmacoeconomic studies have been criticized for not being impartial.[660] Indeed, the sponsor has a clear economic interest in favoring its own drug. Thus, the study may be designed so as to prejudice the other product. For example, the sponsor's drug will be administered at a higher dosage than the other drug. The industry also complains that cost-effectiveness studies are requested too early, i.e., at a point in time when insufficient data are available to fully appreciate the medical contribution of the new drug.[661] On the other hand, the industry could also benefit from a requirement to produce pharmacoeconomic studies since – once again – it would create a barrier to entry against smaller firms.[662] Moreover, positive pharmacoeconomic studies can boost the drug's uptake with prescribers.[663]

4.1.8. Getting investors interested

Obviously pharmaceutical companies sell drugs to make money. Although executives like to know that their drugs are alleviating patients' suffering, they remain primarily accountable to their shareholders. These shareholders want to see growing profits, reflected in paid-out dividends or in stock value increases.

---

655 As Richard Smith puts it, a clinical data not accompanied by an economic evaluation is "like a shop window without prices." Richard Smith, *New BMJ policy on economic evaluations*, 325 BMJ 1124 (Nov. 16, 2002), at http://bmj.bmjjournals.com/cgi/content/full/325/7373/1124 [hereinafter Smith (BMJ policy)].

656 The first three hurdles are quality, safety and efficacy. *See* Ian Dodds-Smith & Grand Bagley, *Cost effectiveness – the fourth hurdle to market entry*, Life Sciences 2003, Cross-border, at 43, at http://www.arnoldporter.com/pubs/files/Cost_Effectiveness.pdf.

657 *See* webpage at http://www.nhs.uk/.

658 For a review of the NICE's activity, see WHO, Technology appraisal programme of the national institute of clinical excellence. A review by the WHO (June-July 2003), at http://www.nice.org.uk/pdf/boardmeeting/brdsep03itemtabled.pdf. *See also* Dodds-Smith & Bagley, *supra* note 656, at 46-49.
For an example of NICE's review, see that of Genentech's Herceptin: NICE, A rapid and systematic review of the clinical effectiveness and cost-effectiveness of trastuzumab for breast cancer, in particular at 52-59 and 61-62 (Oct. 4, 2001) at http://www.nice.org.uk/pdf/trastuzumabassessmentreport.pdf.

659 *See* Ray Moynihan, *US politicians want federal funding to discover cost effectiveness of new drugs*, 327 BMJ 642 (Sept. 20, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7416/642?etoc. The text of the 2003 Prescription Drug Comparative Effectiveness Act, H.R. 2356, is available from http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_bills&docid=f:h2356ih.txt.pdf.
Funding for comparative studies – which now have a legal basis in the new Medicare Prescription Drug, Improvement and Modernization Act – is presently lacking.

660 *See* Smith (BMJ policy), *supra* note 655, at 1124.

661 *See* Dodds-Smith & Bagley, *supra* note 656, at 43.

662 *See* CMR, Market Access for New Medicines: Are Companies Changing their Strategies, 33 R&D Briefing 6, at http://www.cmr.org/pdf/r&d33.pdf.

663 *See id.*

Future profits depend on future innovation, because existing drugs are only protected against competition during the duration of their patents and because new therapeutic discoveries may at any time displace market shares. Hence no research-based company can afford to rest on its laurels and cease its R&D efforts. On the contrary, all pharmaceutical companies need to push actively their development efforts. Likewise, they need to convince their investors that their research is indeed going to pay off and result in hefty profits. This is why all annual reports claim that the company's pipeline is robust, broad and deep, and preferably will address unmet medical needs.[664]

Investors pay careful attention to the projects in the pipeline. They follow each clinical trial closely. Clinical trial results affect the stock price of the company immediately, even if the drug is still years away from marketing approval. It follows that drug companies must also design their clinical trials keeping their investors in mind.

4.1.9. Getting a pharmaceutical firm interested in a biotech company

The majority of biotech companies still lack the resources, particularly the financial resources,[665] to conduct clinical development until its completion (through phase III studies). They typically turn to pharmaceutical companies to fund and lead their late stage clinical trials, especially the expensive phase III.[666] For pharmaceutical companies, this is a great opportunity to complement their own and sometimes below-par pipelines. Partnerships between pharma and biotech companies take different forms. Usually, in exchange for milestones payments, the pharmaceutical company acquires an exclusive license to sell the future drug on most, though not necessarily all, markets.[667] The pharmaceutical company may also request an equity stake in the biotech company. In other cases, the pharmaceutical company will simply acquire the entire biotech firm.

Deals are triggered by early successes in clinical development. The best time for licensing and acquisition deals is on completion of the first phase II trials, when there is preliminary evidence of efficacy.[668] This evidence lowers the risk attached to the compound and hence enhances the value of the biotech firm. The clearer the evidence, the higher the firm's valuation. It follows that biotech firms must take particular care in the

---

664 The pipeline contains all the compounds in development, from late preclinical stage to clinical phase III trials until marketing approval. There is an average of 24 new active substances in the pipeline of large pharmaceutical companies. *See* Malcolm Ogg, *Major Challenges for the Pharmaceutical Industry in the New Millenium*, CMR BRIEFING (2000), at http://www.cmr.org/pdf/CMR00-137R_PIO_99_Briefing.pdf. However, even large pharmaceutical companies only succeed in launching one or two new chemical entities (NCEs) each year. *See* Deutsche Bank, *supra* note 537, at 37.

665 Aside from cash to conduct clinical trials, biotech firms may lack the skills and expertise to conduct efficient clinical trials. They also look to their pharmaceutical partner for the regulatory expertise in securing marketing approval once the trials have been successfully completed. Finally, pharmaceutical partners have a much better sale network to market the drug to doctors and patients.

666 Pharmaceutical companies also typically take care of the marketing application process, given that they have more expertise in handling drug agencies' requests.

667 The exclusivity may be limited to certain territory since the biotech company usually wants to retain control over its own national market.

668 *See* James Kalamas & Gary Pinkus, *The optimum time for drug licensing*, 2 NATURE REVIEWS 691 (Sept. 2003), (arguing however that it would be in the pharmaceutical partner's interest to acquire the license earlier, i.e., already at the preclinical stage) at http://www.nature.com/cgi-taf/DynaPage.taf?file=/nrd/journal/v2/n9/full/nrd1181_fs.html&filetype=pdf.

design of their phase I and phase II clinical trials if they want to attract large pharmaceutical backers.

4.1.10. Factors in deciding to launch a clinical trial

The decision to launch a clinical trial is normally taken based on a detailed assessment of the *market* for the future drug. Drugs that address the need of only a small number of patients may not be developed, because their expected revenues might not recoup the sponsor's investment.[669] Ideally, sponsors want to accumulate blockbuster* drugs.[670]

To understand the market for their future drugs, pharmaceutical firms look for feedback from physicians working in the relevant field. These physicians may point to unmet medical needs (e.g., pediatric formulation for a given drug) and explain how this need can best be addressed (e.g., syrup at dosage of x mg).

Although financial considerations are most important, other factors may be taken into account. For example, an important factor in the decision process to fund a clinical trial is the difficulty of *proving* the efficacy of the investigational compound to the drug agency. Depending on the disease, the drug and the endpoints* studied, a simple or complex clinical trial design may be necessary.[671] Pharmaceutical companies are disinclined to invest in a product when its efficacy can only be demonstrated by complex – and hence risky – trials. For example, clinical trials that require each subject's treatment to be tailor-made (e.g., certain cancer trials) are viewed as problematic because comparisons of efficacy and safety within the subject pool are made very difficult.[672]

Not uncommonly, the decision to go ahead with a clinical trial may depend on unforeseen *emotional* factors. Pharmaceutical companies' business and marketing departments must often compromise with their own scientists who will insist on seeing their research efforts translate into a marketed product.

> A company's decision to proceed with the clinical development of a drug is always a source of tension, part of what the biotechnology world calls normal pharma business. Scientists invariably believe their idea will pan out while the company officials in clinical affairs, ever aware of the staggering costs and risks

---

669 *See, e.g.*, VASELLA, *supra* note 127, at 13-16 (explaining how Novartis reached the decision to develop Gleevec).

670 A blockbuster drug is one whose sales exceed $1 billion. The ten bestselling drugs in 2003 were Lipitor (sales in 2003 of $10.3 billion), Zocor ($6.1 billion), Zyprexa ($4.8 billion), Norvasc, Erypo (Procrit), Ogastro/Prevacid, Nexium, Plavix, Seretide, Zoloft ($3.4 billion). See IMS Health, *Lipitor leads the way in 2003*, (Mar. 18, 2004) at http://open.imshealth.com/webshop2/IMSinclude/i_article_20040317.asp [hereinafter IMS Health (Lipitor)]. *See also* Deutsche Bank, *supra* note 537, at 27 (indicating that the sales of Lipitor alone account for some 2% of the entire pharmaceutical industry's revenues).

671 "[P]otential drug candidates for more complex and degenerative diseases require more time to study, and they are often more difficult to evaluate than drugs for simpler diseases and acute illnesses. An example of the growing complexity of drug development is the average number of clinical procedures incorporated into the design of the clinical trial protocols for various types of diseases. An analysis of Phase III clinical trials by disease type and procedures shows a dramatic increase in highly complex disease types (as measured by procedural complexity) in just the past few years from 28 percent of overall projects in 1995 to 49 percent in 2000." PhRMA (Industry Profile 2003), *supra* note 601, at 3.

672 *See* RICK MURDOCK & DAVID FISHER, PATIENT NUMBER ONE, 62 and also at 130 (Crown Publishers 2000).

of human trials, regard the researchers as starry-eyed idealists whose exuberance must be contained.[673]

In the case of both CellPro[674] and Genentech[675], that decision was influenced by the fact that the investigational treatment could be used to save the life of the CEO and of a family member of a high-ranking executive.

Faced with the escalating cost and difficulties in securing marketing approval, some firms have occasionally taken an alternative approach. Instead of conducting robust clinical trials as a basis for a marketing application, they orchestrate flimsier studies that they use as marketing tools to promote *off-label use* by doctors.[676] As we already saw, customary practices allow physicians to prescribe drugs for therapeutic indications not approved by a drug agency ("off-label use").[677] Hence, a pharmaceutical firm may make considerable profits out of such sales.[678] For the firm, the main disadvantage is that patients buying the drug for the unapproved indication may not be reimbursed by their insurance companies,[679] thus limiting the size of the market.

---

673 ROBERT BAZELL, HER-2, THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER, 49 (Random House 1998).

674 *See* MURDOCK & FISHER, *supra* note 672, at 115-16 (Crown Publishers 2000). Rick Murdock, author of the book and CEO of CellPro, was diagnosed with an aggressive lymphoma. When chemotherapy failed, he embarked on an investigational treatment of stem cell transplant, assisted by an even more investigational device invented by his own firm. The combination of these two treatments was successful. He wrote: "Most science is dispassionate. At CellPro we rarely had any direct contact with the human beings who might benefit – or die – from the success or failure of our work. In the development of the Ceprate system [their investigational device], patients were simply the end product, statistics we needed to move forward with out clinical trials or to get final FDA approval to go to market. None of those people had a name or a face, we didn't know anything about their families or their hopes and dreams. The doctors conducting our clinical trials sent us reports – this many patients showed improvement, that many patients failed to respond to treatment. It's easier to go home at night when you don't know the patients' names. I was changing the rule." *Id.* at 116-17.

675 BAZELL, *supra* note 673, at 51. At Genentech, Bill Young, a vice president in charge of manufacturing, pushed for clinical trials to be conducted on Her-2 when his mother was diagnosed with breast cancer. Brazell notes that: "Genentech presented itself as a sophisticated corporation that had outgrown the rashness of an upstart and made rational decisions based on sound business principles. But the truth was that passionate interest in a project, especially from someone with a voice in the financial decisions, was critical to the equation [whether or not to fund a trial]."

676 *See, e.g.*, Melody Petersen, *Court Papers Suggest Scale of Drug's Use*, N.Y. TIMES, May 30, 2003, at http://www.nytimes.com/2003/05/30/business/30DRUG.html?pagewanted=2&tntemail1 ("Warner-Lambert paid dozens of doctors tens of thousands of dollars each to speak to other physicians about how Neurontin, an epilepsy drug, could be prescribed for more than a dozen other medical uses that had not been approved by the Food and Drug Administration. The top speaker for Neurontin, Dr. B. J. Wilder, a former professor of neurology at the University of Florida, received more than $300,000 for speeches given from 1994 to 1997, according to a court filing. Six other doctors, including some from top medical schools, received more than $100,000 each. Other doctors were paid to write reports on how Neurontin worked for a handful of their patients, the court papers said. Still others were paid to prescribe Neurontin in doses far exceeding the approved levels as part of a clinical trial that Warner-Lambert created to market the medicine, according to the court papers, which are new documents filed in the lawsuit by the whistle-blower.").

677 See subsection 3.4.4. above. Usually, the drug has at least one approved use, allowing it to be sold legally on the market.

678 "Some observers have estimated that approximately half of all prescriptions represent uses not approved by the FDA." Noah, *supra* note 4, at 397 (listing also the reasons behind legislative acceptance of off-label uses).

679 However, insurance companies may be unable to tell whether or not a drug is prescribed for an approved use without implementing far-reaching controls. For more details as to when drugs *not* on the FOPH's List of Specialities are to be reimbursed, see ATF 130 V 532.

4.2. Economic issues in clinical trials

4.2.1. Costs of clinical trials

4.2.1.1. Number and length of trials

Each year in the United States, an estimated 50,000 to 80,000 clinical trials take place;[680] they enroll between 700,000[681] and 20 million subjects.[682] According to a 1996 survey, 41 pharmaceutical companies had a total of 350 new active substances in advanced clinical trials.[683] A 2002 survey found that 371 biotech drugs were in various stages of development in the United States.[684] In contrast, the European Union had only about 100 biotech medicines under clinical trial, most of them in early phase trials.[685] For the last 10 years or so, U.S. pharmaceutical R&D figures far exceed those of the European Union.[686]

There is no set number of clinical trials necessary to support the marketing application of a new drug; the average varies between 14 and 37.[687] The average number of

---

680 *See* Jill Wadlund, *Heading Off a Clinical Trial Liability Lawsuit*, APPLIED CLINICAL TRIALS at 51 (Apr. 2003), at http://www.chubb.com/businesses/cci/chubb1165.pdf. *See also* Diana L. Anderson, *The Patient Recruitment Market, An Overview of Today's Issues,* APPLIED CLINICAL TRIALS, (Nov. 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=77707.
According to FDA statistics, the agency received 2120 original INDs (Investigational New Drug applications) in 2003. *See* FDA, Original INDs Received, *supra* note 596. However, this high figure also includes use of investigational drugs outside clinical trials, for example in the context of a "Treatment IND." *See* FDA, Investigational New Drug Application, at http://www.fda.gov/cder/handbook/indbox.htm.

681 According to a CenterWatch analysis for the United States territory, out of 2,8 million that complete the initial screening to determine eligibility, only 700,000 can be enrolled. CenterWatch, a word from study volunteers, sample at http://www.centerwatch.com/bookstore/samples/wordstudy.pdf [hereinafter CenterWatch (Word from)].

682 There are no official statistics and estimates vary widely. Slater indicates that the "number of participants in federally funded research increased from 7 million to almost 12 million" from 1997 to 2000. Eve E. Slater, *IRB Reform*, 346 NEW. ENG. J. MED. 1402-1404 (May 2, 2002), at http://content.nejm.org/cgi/reprint/346/18/1402.pdf. See *also* Daniel D. Federman, *Minimizing Risk in Clinical Research*, Editorial, 139 ANN. INTERN. MED. 71-72, (July 1, 2003), at http://www.annals.org/cgi/reprint/139/1/71.pdf ("Published figures for the United States range from 2 000 000 to 20 000 000.").
In France, according to one source, at least 800,000 subjects participated in research in 1996. *See* CCNE N°58, *supra* note 117, at 12.

683 IBM Business Consulting Services, Pharma 2005, An Industrial Revolution in R&D, at 6, at http://www-1.ibm.com/services/au/igs/pdf/gw510-9220-pharma-2005-industrial-revolution.pdf (referring to a study of Phase II and III clinical trials by CMR International). *See also* PhRMA (Industry Profile 2003), *supra* note 601, at 16-17.

684 *See* PhRMA, 2002 Survey, New Medicines in Development, Biotechnology, at http://www.phrma.org/newmedicines/resources/2002-10-21.93.pdf.

685 *See* European Parliament, Committee on Industry, External Trade, Research and Energy, Report on the Future of the Biotechnology Industry, (Feb. 28, 2001), (A5-0080/2001; PE 297.119), at 19, at http://www.botanischergarten.ch/debate/PurvisReportProv.pdf [hereinafter E.U. (Future)].

686 *See, e.g.,* PhRMA (Industry Profile 2003), *supra* note 601, at 10.

687 These figures include small exploratory trials. According to a study by Toigo et al., for the 185 new molecular entities (i.e., wholly new drugs) approved between 1995 and 1999, there were a corresponding 2,581 clinical trials. *See* Evelyn B. Toigo et al., Women's Participation in Clinical Trials and Gender-Related Labeling: A Review of New Molecular Entities Approved in 1995-1999, Office of Special Health issues at the FDA, at http://www.fda.gov/cder/reports/womens_health/women_clin_trials.htm.
According to CMR International, a submission for marketing approval for a new active substances contains an average of 37 clinical trials, most of them (21) being Phase I studies. *See* CRM International, *Describing Dossiers: Characterising Clinical Dossiers for Global Registration*, 25 R&D BRIEFING, (Jan. 2000), at

subjects throughout the drug's development is about 4,000.[688] The pharmaceutical industry has been blaming the drug agencies, particularly the FDA, for being ever more demanding. According to the industry, the FDA insists on longer and larger clinical trials. Partly for this reason, clinical costs are said to have soared since the 1970s (multiplied by an 8.6 factor).[689]

The industry complains because the trial's length is a strong determinant of clinical costs. Yet, the true length of clinical development is also a controversial subject.[690] Over 2000 and 2001, the average duration of clinical development was of about 5 year.[691] Besides, the length of a given trial may influence either the length of other trials required to secure regulatory approval or the duration of the regulatory review. If trials submitted to the drug agency did not monitor the drug during a sufficiently long period, the agency may require additional trials. Performing these additional trials will lead to significant delays. The review of the application by the drug agency may also be slowed down if it has to examine partly overlapping studies.[692]

Unforeseen delays are dreaded, since, "[f]or each day's delay in gaining FDA approval of a drug, the manufacturer loses, on average, $1.3 million."[693] Even if this figure seems inflated, delays have multiple adverse consequences, including on the company's stock valuation (see also subsection 4.1.8. above).[694] Therefore, the extra time spent on devising a strong clinical trial may ultimately save time on other aspects of the drug development process.

---

http://www.cmr.org/pdf/25.pdf [CRM (Describing Dossiers)]. However, the number of clinical trials per application may be decreasing. *Id.* at 2-3.

688 *See id*. *See also* Joseph A. DiMasi et al., *The price of innovation: new estimates of drug development costs*, 22(2) J. HEALTH ECONOMICS 151, at 177, n.41 (Mar. 2003).

689 *See* Tufts Center for the Study of Drug Development, Total Cost to Develop a New Prescription Drug, News Release, (May 13, 2003), at http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29 [hereinafter Tufts (May 13, 2003)].

690 *See, e.g.,* Roy Levy, *The Pharmaceutical Industry*, *A Discussion of Competitive and Antitrust Issues in an Environment of Change,* Bureau of Economics Staff Report, Federal Trade Commission, at 184 (Mar. 1999), at http://www.ftc.gov/reports/pharmaceutical/drugrep.pdf.

691 In the United States, the exact figure for new small-molecule drugs (excluding proteins and monoclonal antibodies) is 63.9 months in 2000 and 2001. *Janice M. Reichert*, Trends in development and approval times for new therapeutics in the United States, 2 NATURE REVIEWS 695, 697 (figure 2) (Sept. 2003), at http://www.nature.com/cgi-taf/DynaPage.taf?file=/nrd/journal/v2/n9/full/nrd1178_fs.html&filetype=pdf. Since 1980, the duration of clinical development has varied from a low of 42.7 months (1980-1981) to a high of 92.5 months (1994-1995). *Id. See also* OIG (FDA Review), *supra* note 20, at 2 (stating that FDA review time for new drug applications is now under 20 months).

692 The pharmaceutical sponsor is often the source of the delays, for example because the application initially submitted was incomplete and had to be amended. *See* OIG (FDA Review), *supra* note 20, at 15-16.

693 Thomas Bodenheimer, *Uneasy Alliance – Clinical Investigators and the Pharmaceutical Industry*, 342 NEW. ENG. J. MED. (May 18, 2000), at http://content.nejm.org/cgi/reprint/342/20/1539.pdf. *See also* Janice Cruz Rowe et al., *A Cure for Clinical Trials*, THE MCKINSEY QUARTERLY, 2002, Number 2, at 134, at http://www.caplix.com/pdf/Clinical%20Trials.pdf (evaluating the loss to "at least $800,000 a day … for a niche medication … and as much as $5.4 million for a blockbuster like Prilosec").

694 For instance, Swiss biotech company Actelion lost 60% of its stock market value when it had to announce that its Phase III clinical trial had not demonstrated efficacy. *See* François Mutter, *L'annonce d'essais cliniques décevants fait plonger Actelion de plus de 60%*, [*Notice of disappointing clinical trials brings down Actelion more than 60%*], LE TEMPS, Apr. 21, 2001, at 29; Actelion's press release of April 20, 2001, at http://www.actelion.com/uninet/www/www_main_p.nsf/Content/me+20+Apr+2001.

4.2.1.2. Estimates of total costs

To be sure, clinical trials are very expensive. Before a compound can be approved as a marketable drug, we saw that it has to be tested on thousands of subjects (see also subsection 6.1.3. below).[695] The medical care that these subjects receive is paid, at least in part, by the sponsor – typically, a pharmaceutical company. Average costs *per subject* for phase III trials are between $10,000 and $24,000.[696] The sponsor must also pay the researchers conducting the trial; it must pay for the costs of manufacturing the investigational compound; it must pay to have a report written on the outcome of the study. As a result, clinical trials represent more than half the total out-of-pocket expenses of drug R&D.[697] Out-of-pocket costs for clinical trials have been estimated at $282 million (with cost of capital at $467 million).[698] However, as signaled above, estimations vary widely.[699] The cost of a single clinical trial is subject to important variations, contingent upon its objectives and size among other things; there are no consensual estimates.[700]

Cost estimates for the *entire* drug development range between a low $100 million and a high $897 million. The low figure comes from a prominent left-wing pro-consumer group.[701] The second figure is given by an equally prominent pro-business

---

695 For example, Taxol, a blockbuster anti-cancer drug first approved against ovarian cancer, was tested on 28,882 research subjects. *See* GAO, Technology Transfer, NIH-Private Sector Partnership in the Development of Taxol, at 3, Report to the Hon. Ron Wyden, U.S. Senate, GAO-03-829 (June 2003), at http://www.gao.gov/new.items/d03829.pdf [hereinafter GAO (Taxol)].

696 *See* Global Alliance for TB Drug Development, The Economics of TB Drug Development, at 54, (Oct. 2001), at http://www.tballiance.org/pdf/Economics%20Report%20Full%20(final).pdf. *But see* Public Citizen, at http://www.cptech.org/ip/health/taxol/ ("the average cost of a clinical trial was $169,789 to $310,563, depending upon the year, with an average per patient cost of $3,861 to $6,202 (depending upon the year)").

697 The cost, taking into consideration cost of capital, can be lower because clinical trials are initiated towards the end of the R&D process. Since a dollar paid at time "t" costs more than a dollar paid at time "t+10," clinical trials expenses "cost less" than earlier pre-clinical expenses.

698 These estimates include the cost of failed projects. *See* DiMasi et al., *supra* note 688, at 165 and also at 171-72.

699 *See* James Love, *How much does it cost to develop a new drug*, CONSUMER PROJECT ON TECHNOLOGY, (Apr. 2000) [draft paper], at http://www.cptech.org/ip/health/econ/howmuch.html. *See also* James Love, *A Free Trade Area For The Americas, A Consumer Perspective On Proposals, As They Relate To Rules Regarding Intellectual Property*, Comments for the Working Group On Intellectual Property Rights, Third Trade Ministerial and Americas Business Forum, Belo Horizonte, Brazil, May 1997, James Packard Love, Center for Study of Responsive, http://www.cptech.org/pharm/belopaper.html#novartis.

700 *See, e.g.*, Jeff Gerth & Sheryl Gay Stolberg, *Drug Companies Profit From Research Supported by Taxpayers*, NEW YORK TIMES, Apr. 23, 2000, at http://www.nytimes.com/library/national/science/health/042300hth-drugs2.html. *See also* Grow, *supra* note 249, at 113.
Estimates of pediatric clinical trial costs also vary considerably. "[The NICHD] estimated that a safety and efficacy study may cost between $1 million and $7.5 million, while the cost of a pharmacokinetic study can range from $250,000 to $750,000 per age group. Limited data provided by PhRMA suggested higher study costs, ranging from under $5 million to more than $35 million. Another study indicated that, based on a survey of drug companies, the cost of pediatric studies averaged $3.87 million per written request." GAO (Pediatric), *supra* note 608, at 4-5.

701 *See* Public Citizen, Rx R&D Myths: The Case Against The Drug Industry's R&D "Scare Card," at 3, (July 2001), at http://www.citizen.org/documents/ACFDC.PDF (the figure corresponds to the after-tax cash outlays). Moreover, based on data from the U.S. Orphan Drug Tax Credits, "US pre-tax expenditures on clinical testing, including the costs of failures, was only $7.9 million per approved orphan drug, before tax, and $3.9 million after the benefits of the tax credit." Consumer Project on Technology ("CPTech"), Costs of Human Use Clinical Trials: Surprising Evidence from the US Orphan Drug Act, (Nov. 28, 2001), at http://www.cptech.org/ip/health/orphan/irsdata9798.html. *See also* James Love, Novartis Outlays on R&D for Glivec, CPTech, (Sept. 22, 2003), at http://www.cptech.org/ip/health/gleevec/glivec-RND-costs.doc.

and pro-pharma institution.[702] One important difference is that the industry's figure *compounds* the out-of-pocket expenses with the interest rate on opportunity cost. Moreover, the rate selected is quite high at around 11% per year.[703] Cost of preclinical studies and phase IV trials are also included.[704] Also added to this is the quite significant cost of failure, corresponding to investments on compounds that failed to reach the market.[705] Tax deductions for R&D expenditures are not always deducted in the same way in the various estimates.

Member companies of the U.S. PhRMA trade association are reported to have invested $32.1 billion in drug R&D in 2002; this would represent a "24-fold increase in just 25 years."[706] Pharmaceutical companies reinvest between 15% and 20% of their revenues in R&D.[707] An equal, if not higher, share of revenues goes to drug advertising and marketing.

4.2.2. Risks of clinical trials

Clinical trials are not only costly, they are also very risky endeavors. Out of ten compounds that are tested in clinical trials, only one or two will make it to the market as an approved drug.[708] In general, if 10 compounds were to start phase I clinical trials, 7

See also the low estimate of costs related to the development of a new antituberculosis drug as calculated by the Global Alliance for TB Drug Development, *supra* note 696.

[702] *See* DiMasi et al., *supra* note 688, at 161 and at 163-64; Tufts (May 13, 2003), *supra* note 689.

[703] *See, e.g.,* Henry Grabowski et al., Returns on R&D for 1990s New Drug Introductions, at 5-6, (Mar. 2002), at http://www.dklevine.com/archive/grabow-randd_returns.pdf. "One of the authors undertook an informal survey of six pharmaceutical firms in mid-2001 with respect to the hurdle rates that drug firms utilize in their R&D investment decisions. The survey of these firms yielded (nominal) hurdle rates from 13.5% to over 20%." *Id.*

[704] The other commonly cited figure, also from the Tufts Center, is $802 million, including $403 million in out-of-pocket costs. This estimate does not include phase IV studies. *See* A. DiMasi et al., *supra* note 688*, at* 151-85. *See also* PhRMA (Industry Profile 2003), *supra* note 601, at 2 and 5.

[705] *See* Tufts Center for the Study of Drug Development, A Methodology for Counting Costs for Pharmaceutical R&D, (Nov. 30, 2001).

[706] PhRMA (Industry Profile 2003), *supra* note 601, at 10. This $32.2 billion investment was divided between U.S.-based R&D activities ($26.4 billion) and foreign activities ($5.7 billion). *Id.*
In comparison, the total budget of the NIH (the U.S. National Institutes of Health) budget was $24 billion. *Id.* at 11.
According to other estimates, about $6 billion are spent each year for clinical trials. *See* Dolorez Ruiz Ibarreta et al., Industry-funded clinical trials in developing countries, background paper prepared for the EGE, at 191 (Oct. 2002), at http://europa.eu.int/comm/european_group_ethics/docs/avis17_complet.pdf [hereinafter Ibarreta et al. (Industry)].

[707] *See also* PhRMA (Industry Profile 2003), *supra* note 601, at 10.

[708] "Research scientists start with ten thousand natural substances or synthetic molecules, which they then check with the help of automatic testing systems such as ultra-high-throughput screening to determine whether they influence or change specific disease-related reactions in the body. Those lacking a desirable pharmacological effect are weeded out, leaving only about a hundred candidates in the field. In further selection steps, the remaining hopefuls are tested in cell or organ cultures, e.g. for harmful biochemical properties (toxicology). And then there were 20. … Tests on animals then determine whether and in what amounts the substance actually acts in a complex organism and at what dose it exhibits toxic effects. … And then there were ten. … . The molecules that are still in the race are now tested for the first time in humans. At the end of the first two clinical test phases only three candidates remain, and after phase III probably just one – the new drug." Roche, When new drugs have to show what they're made of, at http://www.roche.com/pages/facets/18/pharmadeve.htm.

would finish it, 3 would finish phase II trials, 2 would finish phase III trials, and only one would reach the market (on the phase division, see subsection 6.1. below). This rate of failure may seem tolerable compared with the much higher rates for preclinical development (i.e., one drug out of 5,000 or 10,000 compounds).[709] However, because clinical trials are so much more expensive than preclinical studies, this 10% chance of success represents a huge hurdle for pharmaceutical companies.

The high percentage of drugs abandoned during clinical trials is explained in part by the *increase in costs* of each consecutive phase of clinical development (i.e., phase III trials are much more expensive than phase II and phase I studies). Since it would be ruinous to replicate phase III trials for a dozen potentially interesting compounds, drug companies have to retain only one or two among their best candidates.[710]

4.2.3. Implications of clinical trial costs

High drug R&D costs carry consequences on the industry, on patients, and on society in general.

4.2.3.1. Consequences on the industry

The industry regularly complains that the costs (both in time and in money) of conducting clinical trials in compliance with the elaborate Western (especially U.S.) regulatory requirements are so high as to *stifle innovation*.[711] High costs also force companies to concentrate on fewer pharmaceutical compounds and therefore to give up other potentially interesting substances. Indeed, available evidence supports this view as the number of new molecular entities (absolutely novel drugs) submitted to drug agencies has been waning over the past five years;[712] increased investments do not appear to be rewarded by corresponding productivity.

See also DiMasi et al., *supra* note 688, at 162 (stating a 71% probability of a phase I-compound entering phase II and 31% probability of entering phase III); FDA Commissioner Mark B. McClellan, Speech before the First International Colloquium on Generic Medicine (Sept. 25, 2003), at http://www.fda.gov/oc/speeches/2003/genericdrug0925.html (criticizing harshly other developed countries for not contributing their fair share) [hereinafter McClellan Speech]; FDA, Challenge and Opportunity on the Critical Path to New Medical Products, at 8, (Mar. 2004), at http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf [hereinafter FDA (Critical Path)] (mentioning an 8% probability of a drug entering phase I ever reaching the market).
See also Tufts (May 13, 2003), *supra* note 689 (indicating that only 21.5% of drugs that enter Phase I trials reach the market); Dror Ben-Asher, *In Need of Treatment? Merger Control, Pharmaceutical Innovation & Consumer Welfare*, Discussion Paper No. 270, 12/99, Harvard Law School, at 17 n. 57.
According to Jan Leschly, former CEO of SmithKline Beecham, "only 3 percent of compounds make the journey from preclinical studies to pre-registration and only 1 percent actually emerges as a drug." Ernst & Young, European Life Sciences 2001: Integration, at 2-3, from http://www.ey.com/GLOBAL/content.nsf/UK/HS_-_Library_-_Integration.

709 *See, e.g.,* PhRMA (Industry Profile 2003), *supra* note 601, at 3. Preclinical studies account for about a third of drug R&D expenses. *See* Deutsche Bank, *supra* note 537, at 32.

710 This choice is made on the basis of phase II results.

711 *See* Ton J. Cleopha & Aeilko H. Zwinderman, *Limitations of randomized clinical trials, Proposed Alternatives designs*, 38(12) CLIN CHEM LAB MED 1217-23 (Dec. 2000).

712 *See, e.g.,* FDA (Critical Path), *supra* note 708, at 2-3.

Similarly, researchers complain that the amount of "red tape" has escalated so much as to make clinical trials unworkable.[713] They lose valuable time in following procedures they consider to be inefficient. These barriers operate to delay the arrival of new products on the market. Patients die while waiting for life-saving drugs to be approved.[714]

Even so, the cost of clinical trials is not without its benefits for the industry. First, high costs create a barrier to the disadvantage of small and less experienced companies – plainly, to the advantage of large and well-established firms. Small or foreign companies face greater obstacles to bring their drugs to the market by themselves. These companies have to enter into alliances with larger pharmaceutical firms, whereby the latter manages clinical trials and attends to the regulatory process.

Second, stringent regulatory requirements reduce the risk that a marketed drug be suddenly pulled out from the market because it has been found unsafe.[715] Because of these requirements, there are good chances that a drug, once approved, will remain on the market. Likewise, they hedge against lawsuits initiated by injured patients against the sponsor-manufacturer (see subsection 4.1.5. above). Greater legal security is beneficial for business planning.

4.2.3.2. Consequences for patients

For years, the FDA has been accused of being responsible for the proverbial "*drug lag*." Starting in the mid-1970s, the industry held the FDA responsible for the fact that drugs are first marketed on European markets and enter the U.S. market only later.[716] As a result, American patients were last to benefit from innovations. The drug lag mostly disappeared as the FDA committed to stricter deadlines (thanks to fees collected from the industry based on the 1997 Modernization Act) and as Europe moved to adopt stringent requirements based on the U.S. model.[717]

---

713 *See* Owen Dyer, *Red tape is stifling research, charity says*, 327 BMJ 640 (Sept. 20, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7416/640-d?etoc.

714 "Gieringer (1985) estimates that a one-year delay in new drug benefits costs between 37,000 and 76,000 lives per decade in the U.S. population. Relative to the number of lives saved by the avoidance of unsafe drugs, he finds that the cost of the policy outweighs the benefit by a margin of at least 4 to 1." Sobel, *supra* note 247, at 1. Needless to say, this point of view is controversial. Sobel also argues that, at least when there is no truly effective treatment available, drugs whose effects are only that of a placebo should be allowed on the market. In his view, patients should be able to enjoy the real therapeutic benefits of placebo drugs.

715 *See* In re Baycol, 218 F. R. D. 197 (D.C. Minn. 2003) (where the claimants argued that Bayer's drug Baycol had only been tested on a comparatively small number of subjects – 3,000).

716 *See* BRODY, *supra* note 447, at 164-67 (commenting studies by Sam Peltzman, William Wardell, the GAO, and the McMahon group), at 181-82 (commenting a study by Kaitin), at 168-69 (reviewing later evidence on the drug lag), at 189 (commenting the 1983 Cullen study).

717 The new drug lag is said to operate in the reverse: drugs reach the European markets later because they need to go through lengthy reimbursement procedures in Europe. *See* Patricia M. Danzon et al., *The Impact of Price Regulation on the Launch Delay of New Drugs – Evidence from Twenty-Five Major Markets in the 1990s*, (2003) at http://hc.wharton.upenn.edu/danzon/PDF%20Files/Final%20Launch%20Manuscript%207.14.03.pdf; CMR International, *The Impact of the changing regulatory environment on review times*, 35 R&D BRIEFING 1-7, at http://www.cmr.org/pdf/r_d35.pdf; CMR International, *Profile of Performance (3): Review Times – Is there Still Room for Improvement?*, 31 R&D BRIEFING 1-6, (Feb. 2001), at

Comprehensibly, drug agencies faced with the dilemma of either approving dangerous drugs or not approving helpful ones would rather opt for the second alternative. Being particularly careful may prevent patients from benefiting from innovative therapies, but is not as conspicuous as having an approved, but unsafe, drug withdrawn from the market.[718] This represents the classic distinction between type I* and type II* errors.[719] A "type I error" resides in rejecting (as false) a hypothesis that is in fact true.[720] A "type II error" is admitting a hypothesis that is in fact false. In the case of drug safety assessment, the agency is said to commit a type I error, when it reaches the conclusion that the new drug is effective and safe when it is not.[721] Conversely, it commits a type II error when it falsely concludes that the new drug is ineffective and unsafe, although in reality it is.[722] In this context, type I errors are also called "false-positive" results or "alpha error," while a type II errors are akin to "false-negative" results (also called "beta error").

Finding the right balance between type I and type II errors involves painful trade-offs. No foolproof mechanism has been devised to overcome the natural reluctance of drug agencies to engage in a path laden with type I errors.[723]

4.2.3.3. Consequences on price levels

The cost of clinical trials has an undisputable impact on the final cost of drugs. Although not all drugs are expensive to develop, the average cost of drug R&D is the central explanation advanced by the industry to justify the high prices of its medicines. These steep prices have generated heated controversies at least since the 1960s. The controversy affects all countries, rich and poor alike. The debate gathered renewed momentum in the late 1990s, with the forceful involvement of AIDS activists and NGOs advocating for developing countries.

Patients – joined, more and more, by governments – criticize pharmaceutical companies for pricing their drugs too high; they complain about price increase for old drugs well above the inflation rate. They call attention to the outstanding profitability of the

---

http://www.cmr.org/pdf/r_d31.pdf. *See also generally* Kenneth I. Kaitin, *Don't turn back the clock on drug regulatory reform*, Editorial, Tufts Center for the Study of Drug Development, (Sept. 2000), at http://155.212.10.127/InfoServices/ImpactReportPDFs/ImpactEditorialSept2000.pdf.

718 In the United States, between 1997 and 2001, 13 drugs were withdrawn because of problems pertaining to safety. *See* OIG (FDA Review), *supra* note 20, at 2 and also at 35-36.

719 *See* Primer on Type I and Type II Errors, 4 EFFECTIVE CLINICAL PRACTICE 284 (Nov./Dec. 2001), at http://www.acponline.org/journals/ecp/novdec01/primer_errors.pdf.

720 In the strict version of statistics, this hypothesis is always the *null hypothesis*, that is the assumption that there is *no difference* between the two treatments being compared. However, investigators sometimes set the *experimental* hypothesis (i.e., the investigational drug has positive effects) as the null hypothesis. On the first notion, see also BRODY, *supra* note 447, at 12. *See also* Tabarrok, *supra* note 433, at 39.

721 The risk of type I error is diminished if the researcher sets a very high level of evidence necessary to reject the (null) hypothesis; this requires setting a low p-value as a cutoff point. On this notion, see subsection 6.3.10.3. below.

722 Type II errors can generally be avoided by increasing the sample size, that is the number of enrolled subjects.

723 *See generally* Daniel P. Carpenter, *The Political Economy of FDA Drug Review: Processing, Politics and Lessons for Policy*, 23(1) HEALTH AFF 52-63 (2004), at http://www.medscape.com/viewarticle/466261_print.

pharmaceutical industry.[724] They scoff at the money "wasted" on expensive advertising campaigns.

The industry retorts that the therapeutic and social benefits of drugs still far exceeds their associated cost.[725] It rectifies the way its profitability ought to be calculated in order to minimize it.[726] It points out that only a small number of marketed drugs are really profitable (chiefly the so-called blockbusters).[727] It counters that drug prices would not be so high if each country contributed its fair share to R&D expenses. Presently, patients in a handful of industrialized countries (mainly the United States) shoulder most of the costs of drug R&D.[728] In 2003, the Head of the FDA called for a better distribution of this financial burden;[729] he proposed that drug prices be set in proportion to each country's income.[730] European countries are unlikely to find this proposal attractive – to say the least…

4.3. Regional harmonization of clinical trial requirements

In the not-so-distant past, each drug agency required that at least part of the clinical development take place on its own territory. For example, the Japanese drug agency would not approve a drug that had been tested only on American patients.[731] Furthermore, the format in which a marketing application was presented to one national drug agency would not satisfy another country's agency.

Obviously, this exacerbated the burden (in time and money) borne by sponsors. Moreover, duplicative testing needlessly jeopardized subjects' health. Patients also suffered because they had to wait longer before drugs were marketed. In addition, drug prices had to reflect the extra cash outlay made necessary by these mandatory, but wasteful, clinical trials.

---

724 "Since 1990, industry net income has increased by an average of 15% annually. In the same period, pharmaceutical earnings per share increased by an average of 12%, which compares very favorably with an average of 7% for the Standard and Poor Index overall." Gabby Ashton & Faiz Kermani, *Getting to grips with Attrition Rates*, 20 (1) CMR INTERNATIONAL NEWS 8 (2002), at http://www.cmr.org/pdf/springnews2002.pdf. Total worldwide sales for pharmaceutical products were $491.8 billion in 2003. *See* IMS Health (Lipitor), *supra* note 670.

725 *See, e.g.,* Ronald Bailey, *The New Global Villains, Drug Companies and 'Obscene Profits,'* 17(3) POLICY 6, at (Spring 2001), at http://www.cis.org.au/policy/Spring01/polspr01-2.pdf. For a cost-benefit analysis of the introduction of treatments for five medical conditions, see David M. Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?*, 20(5) HEALTH AFF. 11-29 (2001), at http://www.medscape.com/viewarticle/409797_print.

726 *See* Bailey, *supra* note 725, at 7.

727 *See, e.g.,* Grabowski et al., *supra* note 703, at 23.

728 Because drug prices in Europe are generally set or controlled by governments (and thus set at a low level) and because developing countries can only afford to pay very low prices for drugs, pharmaceutical companies rely chiefly on the U.S. market (i.e. American patients) to recoup their clinical costs and earn benefits.

729 *See* McClellan Speech, *supra* note 708.

730 "It seems fair that the average price of a new treatment ought to bear some relation to a nation's income. Developing nations should pay little; rich nations would pay more to support the research and development. If all of the developed countries share this burden together, none need be struck with very high prices." *Id.*

731 Today, the Japanese authority is still reluctant to accept non-Japanese clinical trials as adequate support for a marketing application. *See* ASCO/FDA, *supra* note 572, at 17. *See also* Rachel F. Ochs, *Pharmaceuticals: The Battle for Control in the 21st Century*, 10 J. L. & HEALTH 298, at 330 (1995/1996).

4.3.1. International Harmonization Conference

Beginning in the late eighties, the International Conference on Harmonization (ICH) started to address this problem.[732] Since then, it has been at the forefront of the harmonization effort, issuing dozens of widely followed guidelines. Above all, the ICH has succeeded in aligning clinical trial requirements. Not only are ICH guidelines applicable in the three ICH regions (the United States, the European Union and Japan), but they are also followed by many other countries, including Switzerland (see subsection below).

Most recent harmonization efforts aim at defining clinical *study reports* and *marketing applications* that can be submitted, in one uniform version, to all drug agencies.[733] The ICH has issued several guidances to outline such an application (the Common Technical Document or CTD).[734] Given the efforts that go into the preparation of a marketing application, let alone several different applications, this harmonization is particularly welcome by the pharmaceutical industry. The ICH also encourages electronic applications.[735]

---

[732] On its website, the ICH comments its history: "Harmonisation of regulatory requirements was pioneered by the European Community, in the 1980s, as the EC (now the European Union) moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible. At the same time there were bilateral discussions between Europe, Japan and the US on possibilities for harmonisation. It was, however, at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to materialise. Soon afterwards, the authorities approached IFPMA to discuss a joint regulatory-industry initiative on international harmonisation, and ICH was conceived. The birth of ICH took place at a meeting in April 1990, hosted by the EFPIA [European Federation of Pharmaceutical Industries and Associations] in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the USA met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH." ICH webpage titled History and Future of ICH, at http://www.ich.org/Main.jser?@_ID=524.
See also M. Miller, *supra* note 83, at 227-28. On early harmonization efforts in the European Union, see Bernard Dupuis, *Le dossier clinique*, *in* L'EUROPE DU MÉDICAMENT: RÉALITÉS ET AMBITIONS, at 199-200 (Inserm 1990); Eigill F. Hvidberg, *Good Clinical Practice: the REC Document 1990*, at 201-205, in the same publication.

[733] In the European Union, see for example Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC, OJ L 159, 27.6.2003, p.46, at whereas (3), at http://pharmacos.eudra.org/F2/eudralex/vol-1/new_v1/direct_comm_2003_63_en.pdf.

[734] In the European Union and in Japan, the CTD is the mandatory format for regulatory submissions; in the United States, it is strongly recommended; the CTD allows drug sponsors to focus exclusively on the content of their application. See also the many guidelines proposed by ICH on its website at http://www.ich.org/Main.jser?@_ID=520, in particular ICH Guideline M4 on the Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (Nov. 8, 2000) (Step 4 of ICH Process), at http://www.ich.org/MediaServer.jser?@_ID=554&@_MODE=GLB (this Guideline sets forth the content of the standard 5 modules of a marketing application; efficacy data are found in Modules 2 and 5).

[735] Soon, the U.S., E.U. and Japanese drug agencies will electronically receive the same application. Already in the United States, "about 70 percent of NDAs [new drug applications] have some electronic component and one-third are completely electronic." OIG (FDA Review), *supra* note 20, at 8.

4.3.1.1. The ICH E6 Guideline

The ICH E6 Guideline has already been mentioned several times in this thesis.[736] First put forward in August 1995, it represents a very important step in the harmonization process as it contends with perhaps the most central aspect of clinical trials: Good Clinical Practices (GCP). Practically all facets of clinical trial regulations can be made to fit the GCP definition. Although it is not the only ICH guidelines to deal with clinical trials, the GCP E6 Guideline is at the core of the entire clinical trial system. It defines the obligations of all key participants in a clinical trial, from the sponsor and the investigator to the data safety monitoring boards (see, on DSMB, subsection 5.8. above). The role of public authorities, in particular drug agencies and ethics committees, is also discussed.

Contrary to ethics guidelines, the ICH E6 Guideline's primary focus is not on the protection of research subjects. Although it does contain detailed provisions on informed consent, the main thrust of the Guideline is to achieve regulatory harmonization to facilitate drug registration across the three ICH regions. Thus, for instance, informed consent is treated as one subsection in the chapter listing the investigator's responsibilities.[737] Although the Helsinki Declaration is explicitly mentioned, the Guideline leaves it to the ethics committees to lay down applicable ethical principles. The process by which the Guideline was prepared was certainly not conducive to ground-breaking bioethical opinions: consumer or patient groups were not invited to participate in the drafting process,[738] whereas the three regional pharmaceutical trade associations are full-fledged members of the ICH.

Although the ICH E6 Guideline does not revolutionize subject protection, it is nonetheless an exceptional document. With its 53 pages, it was – and still is – the most comprehensive and detailed regulations of clinical trials. The fact that an agreement could be reached between the three regions on so many positions is a tribute to the ICH and its imperfect – yet effective – regulatory process.

4.3.1.2. The ICH E5 Guideline

The ICH E5 Guideline stresses the importance of selecting the *right subject population* for clinical studies whose results will be submitted to different drug agencies.[739]

---

736 *See* subsection 2.2.1.5. above.

737 Chapter 4.8 of ICH E6. Admittedly, it is a long subsection, with 15 sub-paragraphs.

738 *See* M. Miller, *supra* note 83, at 236.

739 ICH Harmonized Tripartite Guideline, Ethnic Factors in the Acceptability of Foreign Clinical Data, E5, Step 4 of ICH Process, (Feb. 5, 1998), at http://www.ich.org/cache/compo/475-272-1.html#E5 [hereinafter ICH E5].

4.3.1.2.1. What role do ethnicity and race play?

The ICH E5 Guideline starts with the historical,[740] but largely outdated,[741] assumption that drugs have different effects contingent on the patient's *ethnicity*. Ethnic factors are broadly defined as they include cultural and environmental characteristics (so called extrinsic factors), in addition to the usual genetic and physiologic factors (the intrinsic factors[742]). Examples of extrinsic cultural factors include use of tobacco, pattern of compliance with prescribed treatments and socio-economic status;[743] environmental factors can refer to pollutants to which the patient population is exposed.[744]

This concept of ethnicity and the related concept of race are controversial. The fact that, in the past, racial classification, including racial classification for pseudo-medical purposes, has been used to discriminate against racial minorities contributes to a passionate debate. Today, people disagree on whether race is at all relevant in medicine.[745] Some believe that racial classification should be replaced by a more accurate classification based on genetic makeup.[746] Others argue that race is a practical factor helpful to take many medical decisions.

There is only weak evidence that drugs have different effects in patients of different races.[747] Example of such drugs include antidepressants, antipsychotics, and beta blockers.[748] Also in 2003, VaxGen, a company trying to develop an AIDS vaccine, found that its experimental product appeared to show a degree of efficacy only on a subgroup

---

740 According to the Guideline, "[h]istorically, this [concern about ethnic differences pertaining to the drug's safety, efficacy, dosage and dose regimen] has been one of the reasons [for] the regulatory authority in the new region [to request] that all, or much of, the foreign clinical data in support of registration be duplicated in the new region. Although ethnic differences among populations may cause differences in a medicine's safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions." *Id.* at 1.2.

741 Today, at best, race is used as a proxy "for a mix of genetic, disease, social, behavioural, or clinical characteristics." Saif S. Rathore & Harlan M. Krumholz, *Race, ethnic group, and clinical research*, 327 BMJ 763 (Oct. 4, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7418/763.pdf. *See also* Susan Mayor, *Responses of black patients and white patients to antihypertensive drugs are similar, study shows*, 328 BMJ 602 (Mar. 13, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7440/602-b?etoc.

742 Intrinsic factors include "age, gender, height, weight, lean body mass, body composition and organ dysfunction." A factor which now attracts considerable interest is genetic polymorphism, that is distinct versions of a gene found in different people, in particular people of different race or origin. *See* ICH E5.

743 *See id.*

744 *See id.* at appendix A.

745 See the very good article by Esteban González Burchard et al., *The Importance of Race and Ethnic Background in Biomedical Research and Clinical Practice*, Sounding Board, 348 NEW. ENG. J. MED. 170-1175 (2003), at http://content.nejm.org/cgi/content/full/348/12/1170. *See also* Judith B. Kaplan & Trude Bennett, *Use of Race and Ethnicity in Biomedical Publication*, 289 JAMA 2709-2711 (May 28, 2003), at http://jama.ama-assn.org/cgi/reprint/289/20/2709.pdf.

746 Genetic traits may be distributed differently among races; they are better predictor than race itself. "Race and ethnicity … are social constructs that change according to time and place" and are therefore considerably less reliable than genetic traits. Victoria Stagg Elliott, *Color-blind? The value of racial data in medical research*, AMN News (Jan. 5, 2004), at http://www.ama-assn.org/amednews/2004/01/05/hlsa0105.htm [hereinafter Elliott (Color)].

747 ICH E10 Guideline indicates that "[f]or example, blacks usually respond poorly to the blood pressure effects of beta blockers and angiotensin-converting enzyme inhibitors." ICH E10 Guideline on Choice of Control Group and Related Issues in Clinical Trials, at section 1.4.3.2 (p.7), (Step 4 of the ICH Process, July 20, 2000), at http://www.ich.org/cache/compo/475-272-1.html#E10 [hereinafter ICH E10].

748 *See* FDA, FDA Issues Guidance for Collection of Race and Ethnicity in Clinical Trials for FDA Regulated Products, FDA Talk Paper, (Jan. 23, 2003), at http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01193.html.

of enrolled subjects: black patients.[749] The company was later criticized for "having jumped the gun."[750]

More likely, the ethnicity argument is invoked to force pharmaceutical firms to conduct part of their drug R&D in the country. As we will see in subsection 4.4. below, clinical trials bear economic and strategic significance and countries are in competition to retain as much clinical research business as possible. Alleged ethnic differences have been used as a trade weapon in this fight. In particular, Japan has long maintained an intransigent approach, by insisting that at least some studies be performed on its territory before a "foreign drug" could be approved.[751]

Ideally, the sponsor should consider ethnic factors early on, that is when designing its first clinical trials. If the sponsor plans on marketing the drug in different regional markets, it should start by assessing the ethnic sensitivity of the compound.[752] This may lead the sponsor to the conclusion that international multicentric tests are more appropriate so as to dispense with the need for later bridging studies.

4.3.1.2.2. Bridging studies

Despite these possible but unlikely ethnic differences, the ICH seeks to promote acceptance of foreign data so as to avoid needless and costly duplicative studies made to satisfy the local requirements of each national drug agency.

According to ICH E5, drug agencies remain free to clarify what kinds of studies are needed to demonstrate safety and efficacy[753] (e.g., one or two randomized phase III trials), but they should not automatically require that the study be conducted within their own geographic territory. Instead, an agency should determine whether the findings of a foreign study conducted on foreign subjects can be *extrapolated* to the local patient population.

If there are reasons to fear that ethnic factors preclude extrapolation, the agency should not ask the entire set of studies to be duplicated. Rather, it must request smaller *bridging studies* that demonstrate that the "foreign" clinical findings will be equally applicable locally.[754] The need for bridging studies is assessed based on an analysis of the pharmacokinetic*[755] and pharmacodynamic*[756] properties of the drug tested or of simi-

---

749 *See* Elliott (Color), *supra* note 746.

750 *Id.*

751 *See, e.g.,* CMR International, *The impact of the ICH E5 Guideline on global drug development*, 36 R&D BRIEFING 1-7 (Oct. 2002), at http://www.cmr.org/pdf/r_d36.pdf. According to a survey of pharmaceutical companies conducted by CMR International, 73% of respondents "believe that Japan continues to request scientifically invalid clinical development." *Id.* at 6.

752 *See* ICH E5, at 4.

753 Section 2 of the ICH E5 Guideline gives a general description of the kind of clinical trials typically required to support a marketing application.

754 In addition, of course, the agency will determine whether the foreign clinical trial met the other regulatory requirements which are not geographically related. When a sponsor needs to conduct an additional study to meet these other requirements, it can take this opportunity to incorporate a bridging study based on ethnic factors into this additional study. *See id.* at 1.3.

755 The ICH defines a pharmacokinetics (abbreviated "PK") "as the study of how a medicine is handled by the body, usually involving measurement of blood concentrations of [the] drug and its metabolite(s)." Such a study focus on the "absorption, distribution, metabolism and excretion [abbreviated "ADME"] of [the] drug, either in blood or in other pertinent locations." ICH E5, at glossary.

lar compounds whose properties having been previously ascertained.[757] When a bridging study is found necessary, the ICH anticipates that a single additional trial will be enough to demonstrate extrapolation.[758] Bridging studies can be designed so as to compare the pharmacodynamic and pharmacokinetic effects of the drug in the two distinct ethnic populations.[759] They can also start by comparing the drug's efficacy and/or safety between those populations.[760]

A drug can be characterized as "ethnically insensitive" if there is no reason to believe that its effects will differ depending on the patient population.[761] Similarly, a drug can be ethnically sensitive but the two populations considered in the two distinct regions are ethnically related (e.g., Western Europeans and Northern Americans).[762] In these two situations, bridging studies are usually not necessary. However, the ICH admits an exception to this rule, as "regions with little experience with registration based on foreign clinical data" can still ask for bridging studies … even if the drug is known to be ethnically insensitive.[763]

The inclusion of *extrinsic* ethnic factors and the *exceptions* contained in the Guideline betray the difficulties in convincing drug agencies to renounce local studies. To understand this reluctance, one has to take into account the scientific, economic and therapeutic importance of clinical trials. Countries act in their best interest when they try to attract as many local clinical trials as possible (see subsection 4.4.2. below). Local trials have multiple benefits. First, they create employment for a highly skilled local workforce, including university hospitals and private clinics.[764] They bring scientific renown to those institutions and to the investigators who participate in the trial. They help patients who receive earlier access to promising new therapies. Large clinical trials may also accustom health practitioners (recruited as investigators) to a novel treatment, thus reducing risks of subsequent medical errors once the drug is approved.

---

[756] Pharmacodynamics (abbreviated "PD") is "the branch of pharmacology that studies reactions between drugs and living structures, including the process of bodily responses to pharmacological, biochemical, physiological, and therapeutic effects." Pharmaportal at Applied Clinical Trials, Glossary of Terminology, at http://www.actmagazine.com/appliedclinicaltrials/static/staticHtml.jsp?id=2451. Another definition approved by the ICH is the "study of a pharmacological or clinical effect of the medicine in individuals to describe the relation of the effect to dose or drug concentration." ICH E5, at glossary.

[757] *See* ICH E5, at 3.

[758] *See id.* at 3.2.2.

[759] *See id.* appendix C.

[760] *See id.* at 3.2.2 to 3.2.4.

[761] A drug is more likely to be ethnically insensitive if it exhibits the following features: "lack of metabolism or active excretion, a wide therapeutic dose range, and a flat dose response curve." *Id.* at 3; for more details, see appendix D of this Guideline.

[762] *See id.* at 3.2.3.

[763] *See id.* at 3.2.2.

[764] In the United States, "[t]he industry is one of this country's largest employers, with approximately 223,000 employees nationwide." PhRMA (Industry Profile 2003), *supra* note 601, at 17. In Switzerland, together the chemical and pharmaceutical industries employ over 63,000 people. *See* Swiss Society of Chemical Industries, L'industrie chimique et pharmaceutiques suisse [The Swiss chemical and pharmaceutical industry], at 14 (2003), at http://www.sgci.ch/plugin/article/sgci/10136.

4.3.2. Recognition by Swissmedic of foreign clinical trials

The 2002 Federal Regulations recognize the importance of international harmonization. As the following table makes clear, several provisions call for incorporating international standards.

Provisions	Rules
4.2 LPTh	The Federal Council may, by decree, distinguish between the terms used in this law as well as those used in paragraph 1, define them in greater detail, and may provide for exceptions based upon new findings in science and technology as well as on **international developments**.
7.2 LPTh	The Federal Council shall define the principles of good manufacturing practice. In doing so, it shall take into consideration **internationally recognized guidelines and standards**.
9.1 LPTh	Ready-to-use medicinal products and veterinary medicinal products intended for the manufacture of medicinal foodstuffs (premixed medicinal products) may only be placed on the market if authorized by the Agency. This shall be subject to **international agreements** on the recognition of marketing authorizations.
11.2.a LPTh	The Federal Council shall: a. lay down, taking into account the **recognized international guidelines and standards**, the requirements for organizing, carrying out and recording the pharmacological and toxicological tests referred to in paragraph 1g, […]
14.1 LPTh	The Agency shall make provision for simplified procedures for the authorization of certain categories of medicinal products where this is compatible with the quality, safety and efficacy requirements, and where there is no conflict with Swiss interests or **international agreements**.
17.1 LPTh	If the manufacture of a medicinal product requires special measures to be taken, in particular to guarantee safety, then a release authorization must be obtained from the Agency for each batch before distribution. This shall be subject to **international agreements** on batch release.
29.2 LPTh	The Federal Council shall specify the recognized principles of good wholesale trade practice. In doing so, it shall take into account **internationally recognized guidelines and standards**.
37.3 LPTh	The Federal Council shall specify the recognized principles of good manufacturing practice. In doing so, it shall take into consideration **internationally recognized guidelines and standards**.
45.4 LPTh	The Agency shall designate the technical standards which are appropriate for fulfilling the fundamental requirements. It shall designate, as far as possible, the **internationally harmonized standards**.
53.2 LPTh	The Federal Council shall specify the recognized principles of good clinical practice. In particular, it shall lay down the obligations to which the investigator and the sponsor are subject and shall adopt provisions concerning the control procedure. In doing so, it shall take account of **internationally recognized guidelines and standards**.
60.3 LPTh	It shall delegate the inspections referred to in Articles 6, 19 and 28 in all other sectors to the cantonal inspectorates insofar as they satisfy the requirements of federal law and **international law** applicable in Switzerland.
4.1 OClin	« Les essais cliniques de médicaments doivent être conformes aux Directives des bonnes pratiques cliniques de la Conférence **internationale** sur l'harmonisation (Directives ICH) dans la version du 1er mai 1996. »
26.1 OClin	« L'institut édicte des directives techniques sur le système d'autorisation et d'annonce ainsi que sur la documentation; ce faisant, il tient compte des **normes internationales harmonisées** correspondantes. »

The LPTh also acknowledges the importance of foreign clinical trials. According to Article 13 LPTh: "If a medicinal product or procedure is *already authorized* in a country having equivalent medicinal product control, the *results of tests* carried out for this purpose shall be taken into account."[765] However, the rationale behind this provision is unclear. It seems obvious that clinical trial *results* submitted to the Institute will always be taken into consideration; this is true whether or not these results have already been presented to another drug agency and whether or not the agency has granted marketing approval.

Apparently, the Swiss legislator did not dare state that the *assessment* by a foreign drug agency of these clinical trial results should be taken into account. Such a rule was stated, in some vague terms, in the LATh project,[766] but the LPTh of the Federal Council toned it down.[767] The proposition to adhere to assessments by foreign drug agencies has resurfaced in 2003 following reports of disorganization and inefficiencies at Swissmedic.[768]

In its comment of Article 13, the Federal Council wrote that approval by another authority creates a presumption that the drug meets the requirement of quality, safety and efficacy under Swiss law[769]. How exactly this provision will be interpreted by the Institute remains to be seen. In a 2002 appellate decision, a Swiss commission stressed that decisions from foreign drug agencies are never binding on Swissmedic.[770] Hence, approval of a drug by the FDA and the EMEA does not compel Swissmedic to authorize it too.

---

765 Translation by Swissmedic, see *supra* note 7 (emphasis added). In the French text: "*Si un médicament ou un procédé a déjà été autorisé à la mise sur le marché dans un pays ayant institué un contrôle des médicaments équivalent, les résultats des essais effectués en vue de l'octroi de l'autorisation sont pris en considération.*" See also Article 9.1 LPTh on (future) international agreements on the recognition of marketing approval decisions.

766 Article 30.2 of the draft Law on therapeutic agents of Feb. 19, 1997 (LAth). *See also* DHA 1997 Explicative Report, *supra* note 7, at 56. See also the comments made during the consultation procedure: DHA 1997 Consultation Report, *supra* note 7, at 20. As a reminder, the LAth was, until 1999, the title of the LPTh project; *see also supra* note 7.

767 *See* the ambiguous comments made by the Federal Council in its Message on the LPTh, FF 1999 3151, at 3196.

768 *See* Stéphane Zindel, *Maladies de jeunesse ou incompétence? Le parlement se penche sur le cas de Swissmedic*, LE TEMPS, Jan. 18, 2003, at 4 ("*Hans Stocker* [director of Swissmedic] *a évoqué publiquement une autre possibilité pour décharger Swissmedic: lui retirer la charge d'admettre de nouveaux médicaments sur le marché suisse, travail d'une utilité très relative dès lors qu'il revient à doublonner pour l'essentiel celui effectué pour l'accès aux marchés de l'Union européenne.*").

769 FF 1999 3151, at 3196; the provision proposed by the Federal Council to the Parliament differed somewhat from the present Article 13 LPTh, since it was the results of analyses and studies ("*des examens et des études*") that had to be taken into consideration and not the results of trials ("*essais*").

770 *See* decision of the Swiss appeal commission for pharmaceuticals, JAAC 67.31, *supra* note 562, at point 9.h.

4.3.3. Recognition of foreign clinical trials in the United States

Since 1994, the FDA accepts clinical trials that were not conducted in the United States.[771] An application may even be approved solely on the basis of foreign clinical trials.[772] It is reported that "75% of clinical trials submitted to FDA to support applications for anti-cancer agents used non-U.S. sites."[773]

FDA-acceptable trials must be scientifically valid; their design and their conduct must match the requirements applicable to U.S. trials.[774] The investigator in the foreign country must hold proper qualifications.[775] If only foreign trials are submitted for drug approval, the characteristics of the subject population tested must match that of the U.S. patient population.[776] Moreover, U.S. medical practice must not be so different from that existing at the foreign study site as to make the foreign study results ungeneralizable.[777] The FDA typically conducts an inspection of the study site to "validate" foreign results.[778]

More and more people doubt that clinical results could vary according to national geographic borders.[779] Not only have populations and medical customs *across* countries become hardly distinguishable, but they are also less and less homogeneous *within* a given country.[780]

Foreign trials submitted to the FDA must also be ethically valid; they must conform at least to the ethical principles set forth in the Helsinki Declaration of 1989.[781] The

---

771 *See* 21 C.F.R. § 312.110(b); FDA, Guidance for Industry, Acceptance of Foreign Clinical Studies, at http://www.fda.gov/cber/gdlns/clinical031301.pdf [FDA (Foreign)].
William DuBois goes over FDA practice regarding foreign clinical trial. "In 1962, the FDA first told the pharmaceutical industry that data from foreign clinical studies would be acceptable; however, at that time the data could be used only as a supplemental demonstration of the drug's safety and efficacy. Foreign clinical studies could not serve as primary evidence of a drug's safety and efficacy until 1975. At that time, the data became acceptable only in unusual cases. In 1984, in response to pressure from the pharmaceutical industry and foreign governments, and in recognition to rising scientific standards abroad, the FDA finally elevated foreign research data to a status similar to that of domestic data." *Supra* at 118, and also at 167.

772 *See* 21 C.F.R. § 314.106(b).

773 This number (apparently) pertains to the years 2001-2002. In addition, "the number of trials conducted exclusively in the United States has declined from a high of 80% to about 24% today." Jill Wechsler, *FDA Politics Encourage Cancer Research*, APPLIED CLINICAL TRIALS 20, at 21 (Aug. 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=80018.

774 *See* 21 C.F.R. § 312.120(b)(3) and (5).

775 *See id.* § 312.120(a) and (b)(1).

776 *See id.* § 314.106(b)(1).

777 *See id.*

778 *See id.* § 314.106(b)(3).

779 "Overwhelming evidence indicates that pharmacogenomic differences between nationalities or ethnic groups are insignificant." ASCO/FDA, *supra* note 572, at 18, see also at 17.

780 *See* Pinco, *supra* note 300, at 117-18 (discussing the "comparability" requirement albeit in the context of OTC products).

781 *See* 21 C.F.R. § 312.120(a) and (c); FDA (Foreign), *supra* note 771. *See also* SPRUMONT, *supra* note 16, at 133. See also NBAC's critical comments: NBAC (Developing), *supra* note 254, at 6.
See also the rule of the European Union at point (8) of the Introduction and general principles of Annex I to Directive 2001/83/EC, as modified by Directive 2003/63/EC ("To be taken into account during the assessment of an application, clinical trials conducted outside the European Community, which relate to medicinal products intended to be used in the European Union, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to

United States refers to the 1989 Declaration and not the 2000 Declaration. The latter version limited the use of placebos,[782] a change which was opposed by the U.S. pharmaceutical lobby.[783] The FDA has not incorporated the 2000 amendments (see subsection 6.3.5.2. below).[784] If the foreign country sets higher ethical standards, the FDA asks that these be followed.[785] Sponsors conducting clinical trials abroad can also elect to follow the IND ("Investigational New Drug" application) route, by filing such an application with the FDA.[786]

4.4. Strategic weight of clinical trials, in particular in Switzerland

4.4.1. Strategic importance of clinical trials

Clinical trials have secondary effects such as training physicians (who participate as investigators or who are part of the medical staff), helping finance public researchers' own projects, stimulating technology transfer and building medical and scientific capacities (notably when the trial takes place in less developed countries). Hence, the question of whether a country is an attractive location for clinical trials is one that worries all governments. Much money is contingent – directly or indirectly – on the good will of the pharmaceutical industry. Hence, all countries are longing for a share.[787] Countries also take pride in having clinical trials taking place on their territory. The

---

the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.").
On the difficulty of deciding whether foreign regulations and foreign practices afford an equivalent degree of protection to research subjects, see generally Dickens, *supra* note 103, at A-3 to A-13.

782 According to paragraph 29 of the Declaration of Helsinki, "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the *best current prophylactic, diagnostic, and therapeutic methods*. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." (emphasis added). A footnote clarifies this point by stating that "in general this methodology [placebo controls] should only be used in the absence of existing proven therapy." The World Medical Association has however allowed some exceptions.

783 The U.S. pharmaceutical lobby is led by the trade association PhRMA. In the budget year 2003-2004, PhRMA plans to spend $150 million for campaigns benefiting the interests of its members. *See* Robert Pear, *Drug Companies Increase Spending to Lobby Congress and Governments*, N. Y. TIMES, June 1, 2003, at http://www.nytimes.com/2003/06/01/national/01LOBB.html?tntemail1.

784 The FDA however indicates that it is "reviewing its regulations … to determine if it should revise [its] regulations to incorporate new or modified standards or requirements." FDA (Foreign), *supra* note 771, at II.

785 *See id.* at I.

786 *See* DuBois, *supra* note 118, at 170. *See* OIG, HHS, The Globalization of Clinical trials, A Growing Challenge in Protecting Human Subjects, (Sept. 2001), at 2 and 5, at http://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf [hereinafter OIG (Globalization)].

787 In the European Union, see for instance whereas (3) of Directive 2001/83/EC; Peter O'Donnell, *Strategy and Tactics for European Clinical Trials*, APPLIED CLINICAL TRIALS 24, (Aug. 1, 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=80022; European Commission, A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient, A Call for Action, Communication, in particular at 18-20, (July 1, 2003), (COM(2003) 383 final), at http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/com/2003com2003_0383en01.pdf; Catrina Reed & Faiz Kermani, *Is the UK losing its competitive edge in the area of clinical research?*, CMR International (2001), at http://www.cmr.org/pdf/uktrials.pdf.

number and the type of clinical trials help measure the country's rank in research. Research is viewed as linked to general economic competitiveness.[788]

Switzerland is no different. Skilled and highly-paid labor positions would be lost if the industry was to shun Swiss clinical sites. Academic centers could lose some of their prestige. There is a permanent debate as to whether Switzerland's clinical research sector is lagging behind (see subsection below). Taking advantage of this attitude, pharmaceutical companies can threaten to move their research activities outside the country as a way to retaliate against higher regulatory standards, excessively low reimbursement prices or IP protections.[789]

The draft OClin even had a provision that implicitly aimed at retaining the goodwill of pharmaceutical companies: the State Secretariat for Economic Affairs ("SECO")[790] would have been consulted whenever a change in Good Clinical Practices could amount to a technical barrier to trade.[791] This clause was not retained in the final text of the OClin, presumably because of consumer groups' resistance.[792] Switzerland is prepared to consent many sacrifices to retain the pharmaceutical companies located on its territory as well as those launching trials there.[793] High drug prices are currently the major cost of this policy (see also subsection 4.2.3.3. above).

4.4.2. Assets and drawbacks of Swiss clinical trials

In Switzerland, estimates place the annual number of *drug* clinical trials at about 500.[794] Swissmedic tracks some 400 clinical trials, of which about 100 are phase I trials, less than 100 phase II trials, some 150 phase III trials, the rest being phase IV studies (for an explanation of clinical trial phases, see subsection 6.1. below).[795] Half of all drug trials taking place in Switzerland are multicentric.

---

788 *See, e.g.,* Amstad (Suche), *supra* note 425, at 2218.

789 *See, e.g., id.* at 2217; Amanda Burls & Josie Sandercock, *How to make a compelling submission to NICE: tips for sponsoring organisations*, 327 BMJ 1446, at 1148 (Dec. 20-27, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7429/1446.pdf.
See also interview with Vito Grimaudo, Swissmedic, Clinical Trial Division (May 8, 2002).

790 *See* website at http://www.seco-admin.ch.

791 *See* Article 35.2 of the 2000 draft OClin, *supra* note 8. *See more generally* Article 1.3.b & c LPTh.

792 *See* Comments by the Swiss Fédération Romande des Consommateurs during the consultation procedure [hereinafter FRC (OClin comments)].

793 *See, e.g.,* Fabio Lo Verso, *Après l'« affaire Lipobay »: haro sur la surveillance des médicaments*, Le Courrier (Feb. 26, 2002), at http://www.lecourrier.ch/Selection/sel2002_139.htm.

794 *See* D. Sprumont et al., *Essais cliniques, responsabilité civile et contrats d'assurance*, 83 BULLETIN DES MEDECINS SUISSES 2092-2096, at 2096 (2002), at http://www.saez.ch/pdf/2002/2002-40/2002-40-881.PDF. There are many other clinical trials aside from those focusing on drugs. Thus, Swiss ethics committees have reviewed over 1500 protocols in 2002. *See* H. Amstad et al., *Die Schweizer Ethikkommissionen reden miteinander*, 84(34) BULLETIN DES MÉDECNS SUISSES 1733-36, at 1733 (2003), at http://www.bullmed.ch/pdf/2003/2003-34/2003-34-722.PDF [hereinafter Amstad (Reden)].
Compare these numbers with the figures given for the United States in subsection 4.2.1.1. above.

795 Interview with Vital-Durand, *supra* note 484. *See also* Swissmedic, Annual Report 2002, at 47, at http://www.swissmedic.ch/files/pdf/Swissmedic_GB_2002.pdf.
The number for 1996, 1997, 1998, and 1999 are respectively, for phase I trials: 107 (1996), 125 (1997), 142 (1998) and 85 (1999); for phase II trials: 75, 77, 91, 66; for phase III trials: 190, 199, 183, 140. There were

Some have voiced reservations that Switzerland is not – or no longer – an attractive place to conduct clinical trials.[796] First, Switzerland is a *small country*.[797] Recruiting enough patients with an uncommon medical condition can be a tall order. Second, Swiss patients get *excellent health care* (through normal channels) and thus have no reason to turn to clinical trials to get access to medical care.[798] Third, the partition along three *different languages* imposes an additional burden: each subject must receive information in his own language; written information has to be translated; collaboration between research centers in different regions may be hampered. Four, general *costs of living* are high in Switzerland, which translate into high payments to investigators, hospitals, clinics and subjects (for their health care).[799] Five, Swiss *medical schools* have not placed the emphasis on clinical research.[800] There may not be enough qualified investigators eager to get involved in clinical trials. Rates of publication of Swiss clinical research papers are low.[801] Hospitals are only gradually introducing Standard Operating Procedures (SOP) to facilitate clinical research.[802] Public funding of clinical research is lacking.[803] Social insurance funds cannot be used to fund health research nor clinical

---

respectively 39 (1996), 34 (1997), 35(1998) and 32 (1999) for phase IV trials reported to the IOCM. *See* OICM, Annual Report 1998, at 69, at http://www.pharmalaw.org/O_rapport%20annuel%201998.pdf and Annual Report 1999, at 71, at http://www.pharmalaw.org/O_rapport%20annuel%201999%20(2).pdf.

796 *See, e.g.,* Peter Kleist, *Patienten dringendst gesucht* !, 81(43) BULLETIN DES MÉDECINS SUISSES, at 2449 (2000), at http://www.saez.ch/pdf/2000/2000-43/2000-43-1065.PDF [hereinafter Kleist (dringendst)]; Paul Dietschy, Werner Stauffacher and Hermann Amstad, *Les essais cliniques souffrent encore de nombreuses lacunes en Suisse*, [Swiss clinical trials are still plagued with many faults], LE TEMPS, Oct. 18, 2002.

797 Interview with Vital-Durand, *supra* note 484. *See also* Conseil suisse de la science et de la technologie [Swiss Science and Technology Council] (SWTR), Recherches cliniques en Suisse [Clinical research in Switzerland], at 10, Recommandations (2002) at http://www.swtr.ch/swtr_fr/pdf/KliFo/Recherche_clinique.pdf [hereinafter SWTR (Recommendations)]. *See also* Kleist (dringendst), *supra* note 796, at 2450; Indermühle, *supra* note 162, at 243.

798 *See, e.g.,* Peter Kleist et al., *Seite 23, oben rechts: « Leiden Sie under allergischem Asthma ? »*, 83(14) BULLETIN DES MÉDECINS SUISSES 656 (2002), at http://www.saez.ch/pdf/2002/2002-14/2002-14-310.PDF [hereinafter Kleist (23)].

799 Interview with Vital-Durand, *supra* note 484.

800 *See* Hermann Amstad et al., *Essais cliniques en Suisse: état des lieux* [Clinical trials in Switzerland: overview of the situation], 83 BULLETIN DES MEDECINS SUISSES 2451 (2002), at http://www.saez.ch/pdf/2002/2002-45/2002-45-1106.PDF [hereinafter Amstad et al. (Lieux)]; SWTR (Recommendations), *supra* note 797, at 7 and 10-14. *See however* P. Kleist et al., *Die (Un-) Abhängigkeit der klinischen Forschung*, 82 BULLETIN DES MÉDECINS SUISSES 2346, at 2348 (2001), at http://www.saez.ch/pdf/2001/2001-44/2001-44-1137.PDF [hereinafter Kleist (Abhängigkeit)] (mentioning a recent advanced training opportunity for doctors wishing to specialize in clinical research).

801 *See, e.g.,* Press Release, Federal Office for Statistics, Les activités de recherche en Suisse sont intenses [Swiss research activities are intensive], at 2, (Feb. 1999), from http://www.bfs.admin.ch/bfs/portal/fr/index/themen/bildung_und_wissenschaft/wissenschaft_und_technologie/blank/medienmitteilungen.Document.

802 *See* Swiss Society of Chemical Industries ("SSCI"), Clinical research in Switzerland: opportunities and challenges, (Feb. 2000), at http://www.sgci.ch/plugin/template/sgci/164/3668/---/Klinische+Forschung+in+der+Schweiz+%28EN%29+%28Internet+Artikel+%28SGCI+Exporter%29%29.

803 *See* SWTR (Recommendations), *supra* note 797, at 7. *See generally* Conseil suisse de la science et de la technologie [Swiss Science and Technology Council] (SWTR), *Evaluation du Fonds national Suisse de la recherche scientifique (FNS) et de la Commission pour la technologie et l'innovation* (CTI) [Evaluation of the Swiss National Science Foundation and the Commission for technology and innovation], (May 30, 2002), at 14, at http://www.swtr.ch/swtr_en/pdf/SNF_KTI_Evaluationen/SNF_KTI_Abschlussbericht_F.pdf.
See however Federal Council, *Message relatif à l'encouragement de la formation, de la recherche et de la technologie pendant les années 2004 à 2007*, [Message regarding the encouragement of education, research and technology during the years 2004 to 2007] (Nov. 29, 2002), FF 2003 2067, at 2088, 2102, 2105, 2123 and 2217, at http://www.admin.ch/ch/f/ff/2003/2067.pdf.

training of physicians.[804] Six, because research ethics committees ("RECs") are organized along cantonal, not national, lines, a sponsor often has to satisfy the requirements of *several RECs*.[805] Each REC can uphold its own views as to the proper conduct of the trial. Not uncommonly, written information provided to subjects has to be adapted for each cantonal study site to satisfy each REC. Clearly, the industry would prefer a more centralized procedure.[806] Seven, the pharmaceutical industry[807] as well as non-profit research centers[808] sometimes complain that *Swissmedic* is particularly exacting, compared to other drug agencies. Whether this is true or not remains to be seen.

On the other hand, many clinical trials still take place in Switzerland. Swiss hospitals and academic centers have a good reputation.[809] Swiss patients are said to make good subjects. Another reason has to do with the good social reimbursement prices offered in Switzerland as compared with other European countries. To stay in the good graces of the FOPH,[810] pharmaceutical companies voluntarily choose to conduct at least part of their clinical trials in Switzerland. Apparently, during later price negotiations, they find an advantage in claiming that part of the development effort took place in Switzerland.

Certain groups are working to maintain, or even enhance, the attractiveness of Switzerland. The Swiss Society of Chemical Industry has organized various training courses to coach physicians about GCP.[811]

---

804 *See, e.g.,* Dayer (Limites), *supra* note 74, at 66-67.

805 *See* Interview with Vital-Durand, *supra* note 484. *See also* Kleist (dringendst), *supra* note 796, at 2449.

806 *See, e.g.,* SSCI, *supra* note 802.

807 *See* Interview with Vital-Durand, *supra* note 484.

808 *See* Swiss Institute for Applied Cancer Research (SIAK), Annual Report 2002-2003, at 9 and 13, (criticizing what it describes as a paralyzing increase in clinical trials administrative burden with no corresponding improvement in the quality of studies or in the safety of patients).

809 *See generally* Michael Batty, *Citation Geography: It's About Location*, 17:16 THE NEW SCIENTIST (Aug. 25, 2003), at http://www.the-scientist.com/yr2003/aug/opinion_030825.html; Kleist (dringendst), *supra* note 796, at 2450.

810 Reimbursement prices were previously set by the Federal Office for Social Insurance. In 2002, jurisdiction was transferred to the Federal Office for Public Health (FOPH).

811 *See* Kleist (Abhängigkeit), *supra* note 800, at 2346. *See* SSCI, *supra* note 802.

4.5. Clinical trials in developing countries

High R&D costs are a reason often put forward to justify doing clinical trials abroad. In the early 1990s, the trend was to move clinical trials from the U.S. to Eastern Europe.[812] Nowadays, more and more clinical trials take place in low to middle-income countries (e.g., South America, Eastern Europe).[813]

Although drug agencies in Western countries do not keep tab of *foreign* clinical trials submitted in marketing applications,[814] available evidence confirms a growing trend.[815] For instance, the FDA has processed data from clinical trials originating from 79 foreign countries in 1999, as compared to 28 in 1990.[816] According to another source, the number of clinical trials conducted in Latin America has increased tenfold between 1995 and 2000.[817] Latin America and Eastern Europe are prized destinations because

---

812 The U.S. NIH proposed a study testing whole-cell and acellular vaccines on pertussis (whooping cough), a serious disease that affects mainly children. "The controversial part of the 1993 experiment was the inclusion of a placebo group of more than 500 infants who got no protection at all, an estimated 5 percent of whom were expected to develop whooping cough, compared to the 1.4 percent estimated risk for the study group as a whole. Because of these risks, the study would not be permissible in the U.S. The NIH, however, insisted on the inclusion of a placebo control, and therefore initiated the study in Italy where there are fewer restrictions on human research trials. Originally, Italian health officials recoiled from these studies on ethical as well as practical grounds, but persistent pressure from the NIH ensured that the study was conducted with the placebo." Human Experimentation: An Introduction to the Ethical issues, Research issues Compendium, Physicians Committee for Responsible Medicine, www.pcrm.org/issues/Research_Issues_Compendium/res_comp_1.html.
See also Elisabeth Rosenthal, *For More Drugs, First Test is Abroad*, N.Y. TIMES, Aug. 7, 1990, at C1.

813 Developing countries are home to 80% of the world population. People from developing countries have an average life expectancy of about 65, as compared to 78 in developed countries (for 1998). *See* World Bank, Data on Poverty, Social Indicators, at http://www.worldbank.org/poverty/data/trends/mort.htm. *See also* Nuffield Council on Bioethics, The ethics of research related to healthcare in developing countries, at 15-21 (Apr. 24, 2002), at http://www.nuffieldbioethics.org/fileLibrary/pdf/errhdc_fullreport001.pdf [hereinafter Nuffield (Developing)]. Yet, as many commentators point out, there are also tremendous differences *within* developing countries. *See id.* at 39.

814 *See* DuBois, *supra* note 118, at 168; OIG (Globalization), *supra* note 786, at 6.

815 OIG, HHS, Recruiting Human Subjects, Pressures in Industry-Sponsored Clinical Research (June 2000), at 14, at http://oig.hhs.gov/oei/reports/oei-01-97-00195.pdf [hereinafter OIG (Recruiting)] ("According to our analysis of an FDA database, the number of new foreign investigators increased from 988 in the 1990-92 period to 5,380 in the 1996-98 period."); OIG (Globalization), *supra* note 786, at 6 ("In 1980, just 41 foreign clinical investigators conducted drug research under an IND. By 1990, that number grew to 271, and by 1999, to 4,458.") and at 8 ("An industry source reports that, in 1992, 61 premarket clinical research protocols were approved in Hungary; by 1998, that number almost tripled to 178 approved protocols. Another industry source reports that the number of multi-site trial protocols in Russia grew from 38 in 1996 to 99 in 1999." *See also* Karen DeYoung & Deborah Nelson, *Latin America is Ripe for Trials, and Fraud*, WASH. POST, Dec. 21, 2002, at A01; Matas A. Loewy, Cancer Drug Trials Questioned in Argentina, Reuters, May 23, 2003, at http://www.xtramsn.co.nz/health/0,,8068-2398643,00.html ("Clinical trials in Argentina have surged over the last few years, driven by the alleged quality of medical professionals and more recently the deep devaluation of the peso against the dollar, which made recruitment of researchers and volunteers far cheaper in Argentina than in the U.S. or Europe. The official number of Argentine patients taking part in clinical trials funded mainly by international pharmaceutical companies has increased from 12,400 in 2000 to 19,500 in 2002.").

816 *See* OIG (Globalization), *supra* note 786, at i. *See also* Ibarreta et al. (Industry), *supra* note 706, at 193-96. According to FDA data, the "number of foreign clinical investigators conducting research on new medicines" increased 16 times between 1990 and 1999. Nuffield (Developing), *supra* note 813, at 22.

817 Ibarreta et al. (Industry), *supra* note 706, at 196.

local investigators are skilled and the regulatory system is mostly up-to-speed.[818] Africa is popular for other reasons, having to do mainly with the prevalence of disease.[819]

The European Union has confronted this trend by choosing to fund a program of clinical trials whose goal is to foster close collaboration between researchers from the European Union and those from sub-Saharan Africa.[820] Another aim is to build up the research capacities of developing countries (also called "host countries" in this context) and to upgrade their clinical facilities.[821]

4.5.1. Advantages and disadvantages of clinical trials in developing countries

There are several reasons that motivate sponsors' choices of host countries.[822]

Poor countries experience *high incidence* rates of numerous diseases. Treatment-naïve patients (i.e., patients who have not received treatment before) can easily be found since many have to go without any treatment.[823] These subjects are particularly sought after because they tend to exhibit better clinical results than patients who have already taken other drugs. Thus, the drug being tested is more likely to be proved effective.

Because of poverty and lack of access to government-subsidized health care, chances are that people in developing countries will readily *accept any treatment*, even in the context of clinical trials.[824] For many, if not most, patients, participating in a study may be the only way to access a treatment that may not even be commercialized in their country – and would anyhow be unaffordable.

Conducting clinical trials in developing countries can be significantly *cheaper*.[825] Both investigators and subjects are paid less than in developed countries.[826] Nonethe-

---

818 *Id.* at 195-96; Nuffield (Developing), *supra* note 813, at 23.

819 According to a survey reported by Ibarreta, 35% of clinical trials occurring in the developing world take place in Africa, 25% in South America. *See* Ibarreta et al. (Industry), *supra* note 706, at 194.

820 *See* Press Release, European Commission, European Commissioner Busquin presents clinical trials programme to African Health Ministers, (Sept. 1, 2003), at http://europa.eu.int/comm/research/press/2003/pr0109en.html.

821 *See* Europe Developing Countries Clinical Trials Partnership (EDCTP), Background note, (Aug. 27, 2003) at http://europa.eu.int/comm/research/info/conferences/edctp/pdf/background_en.pdf.

822 Kass and Hyder conducted a survey among U.S. and international investigators to find out what are the main motivations behind clinical trials in developing countries. They found altruistic reasons to be predominant. Nancy Kass & Adnan A. Hyder, *Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subject Regulations*, *in* ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES, VOLUME II, COMMISSIONED PAPERS AND STAFF ANALYSIS, at B-6, (National Bioethics Advisoy Commission, May 2001).

823 *See also* OIG (Globalization), *supra* note 786, at 8. *See* Ibarreta et al. (Industry), *supra* note 706, at 197.

824 *See* EGE, *supra* note 110, at point 1.32.

825 *See, e.g.*, Dražen Babić & Iva Kučerova, *Benchmarking Clinical Trials Practices in Central and Eastern Europe*, APPLIED CLINICAL TRIALS, at 56 (May 2003), at http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/222003/58187/article.pdf. See also the concrete examples provided by the Global Alliance for TB Drug Development in its economic study of TB drug development, *supra* note 696, at 52 and at 56-59.

less, investigators are very eager to participate in clinical trials as it gives them excellent opportunities to learn about state-of-the-art technologies and advance their careers.[827] The medical infrastructure is less costly to acquire and maintain, often because the legal standards are lower (e.g., the daily cost of hospital stay is lower, there is no requirement to have a lot of expensive medical equipment).

Developing countries can also conduct clinical trials more *rapidly*. Necessary approvals may be faster and easier to obtain.[828] Subject enrollment is swift.[829]

Clinical trials in developing countries also have their *drawbacks*, some of which are explained below.

First and foremost for the sponsor, results of such trials may not be accepted by drug agencies in *developed* countries to support a marketing authorization. For instance, the FDA may be reluctant to accept foreign trials originating from developing countries. Most agencies, including Swissmedic, will look twice at trials done in developing countries. At least in the past, this hostility towards trials in less developed countries was justified since clinical data from such trials were perceived as significantly less reliable (than data obtained from clinical trials in developed countries). Investigators in developing countries have been criticized for a proclivity to "doctor" the data in the belief that it will please the sponsor or that it will hide their mistakes.[830] However, lately, these criticisms have abated as many developing countries have assimilated the know-how necessary to achieve compliance with Western-based GCP.[831]

A second concern relates to the *hidden costs* of conducting trials in developing countries.[832] Sponsors may not be properly adding all costs specific to these countries. For example, the sponsor may need to arrange for infrastructure development, because the hospital lacks some important pieces of equipment.[833] The sponsor also needs to resort to the services of local translators.[834] Less effective means of telecommunications

---

826 According to DuBois, "the per-patient cost of a clinical trial in the United States averages $10,000, in Russia costs average $3,000, and in poor nations the average is much less." *Supra* note 118, at 167-68.

827 Babić & Kučerova, *supra* note 825.

828 *Id.*

829 *See also* OIG (Globalization), *supra* note 786, at 8; Babić & Kučerova, *supra* note 825, at 57. A comparative survey showed that some preconceived ideas about clinical trials in developing countries are not always true. "The average time to get regulatory approval was about the same in CEE [Central and Eastern Europe] (126 days) as in Western Europe (121 days). The average time from HA [protocol review committee approval to health authority approval] approval to FSFV [first subject's first visit] was shorter in CEE countries (38 days) than in Western Europe (68 days). The average recruitment period in CEE countries was 183 days (range 157-218 days). Although recruitment in Western Europe averaged only 129 days (range 17-175 days), sites in CEE countries randomized substantially more subjects." *Id.* at 58.

830 *See* Karen DeYoung & Deborah Nelson, *supra* note 815; Loewy, *supra* note 815.

831 *See, e.g.,* Pyotr G. Platonov et al., *Recruitment Rates and Data Quality, Are They Linked?*, APPLIED CLINICAL TRIALS (Nov. 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=77243 (finding that trials in Eastern European countries did not generate more queries (unfilled data) than trials done in western countries).

832 *See* Mary Stober, *Multinational Clinical Trials, Breaking Language and Cultural Barriers*, APPLIED CLINICAL TRIALS, at 24-30 (Sept. 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=79882.

833 *Id.* at 26.

834 *Id.* at 26.

may require more regular visits from sponsor representatives and monitors to the research site.[835]

A third concern is that clinical trials in developing countries are subject to much *less oversight* than trials in developed countries.[836] Ethics committees delivering prior approval may not follow high standards of ethical review.[837] On the contrary, they may be more sensitive to external influences, including corruption. These committees are subject to little surveillance by local authorities. They also avoid inspections by drug agencies of developed countries.[838] Even the FDA is reluctant to inspect foreign *ethics committees*, invoking "sensitivities associated with national sovereignty" and limited financial resources.[839] Similarly, inspections of clinical *investigators* by the FDA pose problems, including "diplomatic" ones.[840] In Switzerland, the restrictions upon the export of pharmaceuticals, including investigational compound for clinical trials, allow for an indirect control of sponsors' activities abroad.[841] The United States also restricts the exportation of investigational drugs.[842]

One consequence is the perception that sponsors are moving to developing countries studies that would be *unethical* in Western nations (see also subsection 6.3.5.2.2. below). Because developing countries do not regulate scientific research as stringently as Western countries, pharmaceutical companies enjoy more leeway when conducting clinical trials.[843]

4.5.2. Scandals in developing countries

A related drawback of clinical trials in developing countries is the bad reputation that they have acquired following justifiably harsh media reports. In 2000, the Washington Post ran a series of articles on clinical trials in developing countries, exposing horrors and clearly immoral handling of the local population.[844]

---

835 *Id.* at 26.

836 *See, e.g.,* Ganapati Mudur, *Use of antibiotic in contraceptive trial sparks controversy*, 328 BMJ 188 (Jan. 24, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7433/188-a.

837 *See* OIG (Globalization), *supra* note 786, at ii and 15-16 ("In fact, one large pharmaceutical company was concerned enough about the adequacy of ethics boards in some of these regions to contract a U.S. institutional review board to train members of the foreign institutional review boards reviewing its research." *Id.* at 15).

838 *See id.* at ii and 12.

839 *See id.* at 12.

840 *See id.* at 12-13.

841 Articles 18, 21 and especially 22.2 LPTh.

842 In the United States, see generally FDA, Investigational New Drugs: Export Requirements for Unapproved New Drug Products, Proposed Rule, 67 Fed. Reg. 41,642 (June 19, 2002), at http://www.fda.gov/OHRMS/DOCKETS/98fr/061902a.pdf (requiring that either the investigational drug have a valid U.S. IND or that the exporter hold an export authorization delivered by the FDA. There are exceptions for several industrialized countries who import (from the United States) already authorized drugs for clinical trial purposes. The FDA is planning to relax the existing rules to replace the authorization mechanism by a certification process.)

843 *See* DuBois, *supra* note 118, at 194-95.

844 *See* Joe Stephens, *As Drug Testing Spreads, Profits and Lives Hang in Balance*, The Body Hunters, Part 1, WASH. POST, Dec. 17, 2000, at A01, at http://www.washingtonpost.com/wp-dyn/articles/A11939-

In 1997, a dozen U.S.-sponsored clinical studies were condemned by a large portion of the scientific community, because they had knowingly let pregnant women transmit AIDS to their babies,[845] even though the sponsor and the investigator had the therapeutic (i.e., the drug nevirapine) and financial means to prevent this.[846] The researchers involved in these trials were apparently acting in good faith, aiming to prove the efficacy of a cheaper course of anti-AIDS treatment; this affordability would in turn make the treatment more readily accessible in developing countries.[847]

In 1996, Pfizer tested its antibiotic Trovan on Nigerian children.[848] Pfizer was accused of deliberately endangering the health of the children.[849] First, it was known that Trovan had dangerous side effects for children. Second, children in the control group were given a low and hence sub-effective dose of the alternative treatment. According to the plaintiffs, Pfizer had failed to obtain informed consent from the subjects and their parents. The company did not arrange for follow-up of the children.[850] The plaintiffs charged the company with conspiring with the Nigerian government to organize the trial.

2000Dec15.html; Mary Pat Flaherty, Deborah Nelson & Joe Stephens, *Overwhelming the Watchdogs*, The Body Hunters, Part 2, WASH. POST, Dec. 18, 2000, at A01, at http://www.washingtonpost.com/wp-dyn/articles/A11986-2000Dec15.html; Sharon LaFraniere, Mary Pat Flaherty & Joe Stephens, *The Dilemma: Submit or Suffer, 'Uninformed Consent' Is Rising Ethic of the Drug Test Boom*, The Body Hunters, Part 3, WASH. POST, Dec. 18, 2000, at A01, at http://www.washingtonpost.com/wp-dyn/articles/A22893-2000Dec18.html; John Pomfret & Deborah Nelson, *In Rural China, a Genetic Mother Lode, Harvard-Led Study Mined DNA Riches; Some Donors Say Promises Were Broken*, The Body Hunters, Part 4, WASH. POST, Dec. 20, 2000, at A01, at http://www.washingtonpost.com/wp-dyn/articles/A26797-2000Dec19.html; DeYoung & Nelson, *supra* note 815, at A01; Mary Pat Flaherty & Doug Struck, *Life by Luck of the Draw In Third World Drug Tests, Some Subjects Go Untreated*, The Body Hunters, Part 4, WASH. POST, Dec. 22, 2000, at A01, at http://www.washingtonpost.com/wp-dyn/articles/A37168-2000Dec21.html.

845 In at least one HIV trial, the sponsor tried to avoid the "placebo-controlled label" by administering a dose of nevirapine known to be ineffective. *See* EFGCP, The EFGCP News, at 3 (Summer 2002), at http://www.efgcp.org/webitems/doc/newsletters/2002_Summer.pdf [hereinafter EFGCP (Summer 2002)].

846 *See* Marcia Angell, *The Ethics of Clinical Research in the Thirld World*, 337 NEW. ENG. J. MED. 847 (Sept. 18, 1997); Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 NEW. ENG. J. MED. at 853-856 (Sept. 18, 1997).
But see the response of NIH, Harold Varmus & David Satcher, *Ethical Complexities of Conducting Research in Developing Countries*, 337 NEW. ENG. J. MED. 1003-1005 (Oct. 2, 1997).
See generally Dolorez Ruiz Ibarreta et al., Study on the ethical controversy over the use of placebo in clinical trials in developing countries: Impact on international research Guidelines and scientific literature and on industry-funded clinical trials in developing countries, study initiated by the EGE, at 165-166 (Aug. 2002), at http://europa.eu.int/comm/european_group_ethics/docs/avis17_complet.pdf [hereinafter Ibaretta et al. (controversy)]; Nuffield (Developing), *supra* note 813, at 8; NBAC (Developing), *supra* note 254, at 2.
Somewhat similar studies (AZT versus placebo) were even repeated after 1997. *See, e.g.,* Tawee Chotpitayasunondh, et al., *Safety of late in utero exposure to zidovudine in infants born to human immunodeficiency virus-infected mothers*, 107 PEDIATRICS (Jan. 2001), at http://pediatrics.aappublications.org/cgi/reprint/107/1/e5.pdf; see also the three HIV studies published in 353 LANCET 773-92 (Mar. 6, 1999) and the one published in 359 LANCET 1178-86 (Apr. 6, 2002).

847 *See* EFGCP (Summer 2002), *supra* note 845, at 8.

848 *See* Abdullahi v. Pfizer, 2002 U.S. Dist. LEXIS 17436 (D.C.N.Y. 2002). *See, e.g.*, DuBois, *supra* note 118, at 163 and 168-69 (telling the story of Pfizer's testing of Trovan in Nigeria and other dubious foreign clinical trials).

849 "Eleven children died in the study, and others suffered severe injuries including deafness and lameness." DuBois, *supra* note 118, at 164.

850 *See id.*

Studies have suggested that true informed consent might be impossible to secure in developing countries.[851] Even when investigators go through the stage of fully informing subjects, the latter often do not grasp the basic components of the trials and their most fundamental rights. In Bangladesh, researchers found that less than half of the women enrolled were aware of their right to withdraw consent and quit the trial.[852]

4.5.3. Reactions to scandals

The scandals described above, as well as several others, underscored the need to develop a more ethical approach to clinical trials in developing countries.[853] In the United States, the National Bioethics Advisory Commission ("NBAC") published in 2001 an extensive report on the topic and articulated 28 recommendations.[854] The U.S. Office of Inspector General ("OIG") issued its own recommendations.[855] In England, the Nuffield Council on Bioethics published a two hundred page report.[856] The CIOMS has revised its guidelines, adapting them to the situation of clinical trials in developing countries.[857] In Europe, the Group on Ethics in Science and New Technologies ("EGE") issued an opinion to the attention of the European Commission.[858] Lively discussions were reported in medical journals.

The general consensus is that sponsors carrying out trials in developing countries should not only follow all ethical principles applicable in developed countries, but should also implement *additional safeguards* in favor of poor patient population.[859] Thus, higher standards are set for trials in developing countries. The intended, but still largely theoretical, effect is that subjects in developing countries should be even better pro-

---

851 See the very good account of difficulties encountered in obtaining informed consent in Nigeria, by Patricia A. Marshall, *The Relevance of Culture for Informed Consent in U.S.-Funded International Health Research*, *in* ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES, VOLUME II, COMMISSIONED PAPERS AND STAFF ANALYSIS, at C-10 to C-24 (National Bioethics Advisory Commission, May 2001).

852 *See* Niels Lynöe et al., *Obtaining Informed Consent in Bangladesh*, 344 NEW. ENG. J. MED. 460-461, at 461 (2001), at http://content.nejm.org/cgi/reprint/344/6/460-a.pdf.

853 See also, several years earlier, the opinion of the French CCNE, *La coopération dans le domaine de la recherche biomédicale entre équipes françaises et équipes de pays en voie de développement économique*, [Cooperation in biomedical research between teams from France and teams from developing countries], Advice N°41 (Dec. 17, 1993), at http://www.ccne-ethique.fr/francais/pdf/avis041.pdf [hereinafter CCNE N°41].

854 *See* NBAC (Developing), *supra* note 254.

855 *See* OIG (Globalization), *supra* note 786, at 17-21. These recommendations focus on improving data collection by the FDA regarding foreign clinical trials, on strengthening monitoring by sponsors, and on building capacity in developing countries.

856 *See* Nuffield (Developing), *supra* note 813. *See also* J.R. McMillan & C. Conlon, *The ethics of research related to health care in developing countries*, 30 J. MED. ETHICS 204-206 (2004), at http://jme.bmjjournals.com/cgi/content/full/30/2/204 (commenting the Nuffield report).
See also Michel B. Vallotton, *L'éthique de la recherche dans le domaine des soins de santé dans les pays en développement*, 83(46) BULLETIN DES MÉDECINS SUISSES 2513-15 (2002), at http://www.saez.ch/pdf/2002/2002-46/2002-46-1104.PDF.

857 See for example its Guidelines 10, 20 and 21, *supra* note 103. *See also* U. Schüklenk, *The standard of care debate: against the myth of an "international consensus opinion,"* 30 J. MED. ETHICS 194, at 195 (2004), at http://jme.bmjjournals.com/cgi/content/full/30/2/194 (harshly criticizing the CIOMS consultation process).

858 *See* EGE, *supra* note 110.

859 *See* Shapiro & Meslin, *supra* note 245, at 139.

tected than those in developed countries. An example: subjects in developing countries should, according to ethical judgments,[860] be covered against trial-related injuries, even though U.S. law does not require such coverage for U.S. trials.

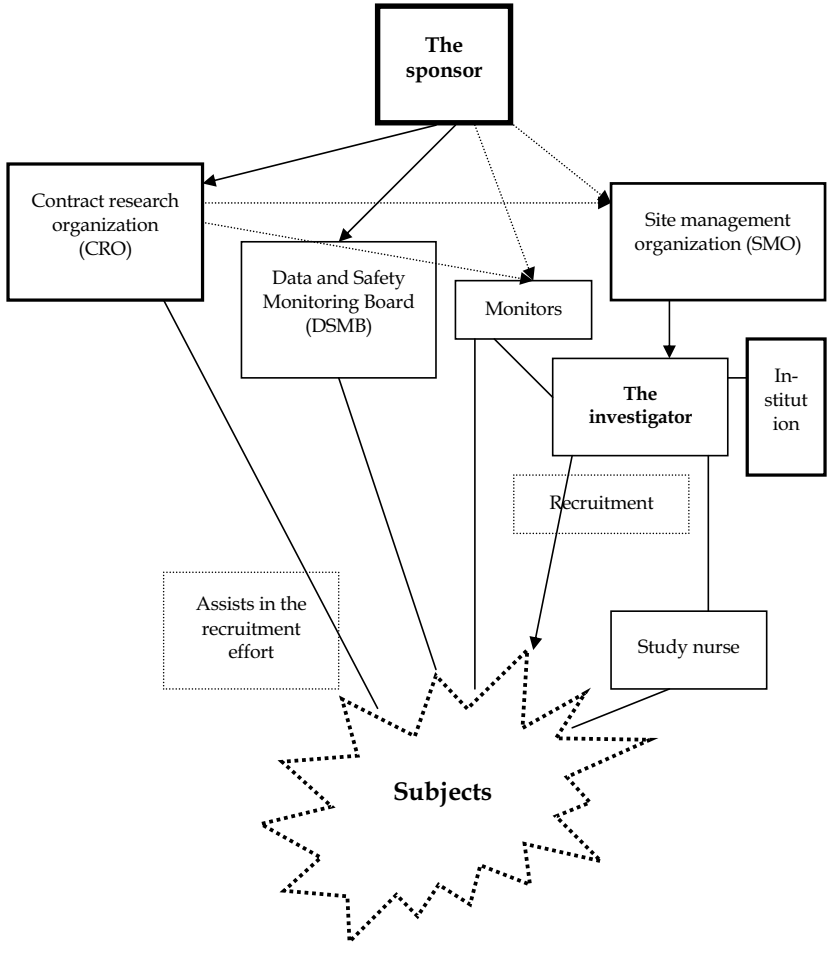
The above-mentioned recommendations, which are further explored in subsection 8.6. below, could profoundly change the face of clinical trials throughout the world; they put forward innovative rights benefiting both subjects and their country of residence. Perhaps, they might even have an impact on developed countries !

[860] *See, e.g.,* Guideline 19 of CIOMS.

Part II

5. The professional participants in a clinical trial

Clinical trial call for the participation of several professionals, such as the sponsor, the investigator, the monitor, the contract research organization, the site management organization. This subsection discusses their role. The recruitment, enrollment and rights of research subjects are analyzed in a different section (section 8). The diagram below attempts to represent the respective position of these participants.



5.1. The sponsor

5.1.1. Legal requirement pertaining to the sponsor

According to Article 5.a OClin,[861] the sponsor is the entity that takes responsibility for launching, financing or managing a clinical trial. In other words, endorsement of one of these responsibilities determines who the sponsor is.[862] Anyone ready to bear the ensuing responsibility can be designated as sponsor. Thus, there is no *material* requirement regarding who the sponsor must be.

This definition is not very satisfactory. First, it suggests that the sponsor can choose to assume responsibility for one *or* the other aspect mentioned in Article 5.a OClin. For example, the sponsor could choose to be responsible only for the initiation of the trial, and then disregard entirely the way it progresses. Or the sponsor could just provide financing, and not care about what happens next.[863] This is misleading considering that, sponsors, at least commercial sponsors, are usually held to a much higher standard.

Second, this definition as well as the other provisions of the OClin minimizes the role of the sponsor. In practice, sponsors tend to assume an active and important role.[864] By comparison, the former IOCM 1995 Regulation contained an explicit clause listing the sponsor's obligations.[865] For instance, the sponsor was responsible for taking all necessary measures to guarantee the safety of the research subjects.[866]

Therefore, it would have been more appropriate to describe the duties of the sponsor in the OClin, and replace the ambiguous definition of Article 5.a OClin by one that refers to the voluntary acceptance of all these duties.

---

861 Article 5.a OClin reads in French: "*promoteur: toute personne ou organization qui assume la responsabilité du lancement, de la gestion ou du financement d'un essai clinique*." In German, it is "*Sponsor: Person oder Organisation, die für die Einleitung, das Management oder die Finanzierung eines klinischen Versuchs die Verantwortung übernimmt*."
See also section 1.53 (p.7) of ICH E6.
In the European Union, see Article 2(e) of Directive 20021/20/REC.
In the United States, see for example 21 C.F.R. § 50.3(e), § 56.102(j) and § 312.3(b).

862 The U.S. FDA observes that the manufacturer of the drug does not qualify as a sponsor simply because it is supplying it. FDA, Information for Sponsor-Investigator Submitting Investigational New Drug Applications (INDs), at http://www.fda.gov/cder/forms/1571-1572-help.html.

863 This is of course not entirely true, since the sponsor is liable for injuries incurred by subjects, even if it did not cause them by its own actions (see subsection 8.6.5. below). This liability justifies the fact that the sponsor is to supervise closely what the other parties involved in the trial, and most notably the investigator, are doing. *See* Article 7.1. OClin.

864 *See, e.g.,* Kleist (Abhängigkeit), *supra* note 800, at 2348.

865 *See* Article 9 of the (former) IOCM 1995 Regulation; Articles 2.1 to 2.3 of the accompanying Good Clinical Practices.

866 *See* Article 9.2.e) of the (former) IOCM 1995 Regulation.

5.1.2. Who becomes sponsor?

The sponsor can be an individual or a legal entity. Generally the sponsor is the pharmaceutical firm that studied the compound during the preclinical phases. The same party will then submit the marketing application and commercialize the drug.[867]

Most drug clinical trials and, above all most phase III trials, are funded by large pharmaceutical firms. Relatively to these private firms, *public* bodies (e.g., governments, academic institutions) have reduced their financial support to clinical research.[868] According to some U.S. figures, the public sector funds 48% of clinical trial, while the private sector sponsors 52%.[869] In the United States, the NIH is the most important public funding source for clinical trials, spending about $6.4 billion on clinical research in 2001.[870] It sponsors several of its own trials as well as extra-mural research.[871] However, it rarely follows a compound through its marketing approval, preferring instead to enter into license agreements or cooperative R&D agreements ("CRADA") with pharmaceutical firms.[872] This tendency to hand the last stage of drug development over to commercial firms is well established. However, in 2003, three major U.S. universities announced that they would launch their own clinical trials to test their inventions.[873]

Biotech firms are also hard-pressed to pay for large and lengthy clinical studies.[874] Sponsoring clinical trials, especially large ones, also requires a great deal of experience. Given the expenses involved, no sponsor wants to fail in the design or conduct of a trial. This also explains why, under collaborative agreements, "Big Pharma" often

---

867 According to Thomas Bodenheimer, "Of the $6 billion in industry-generated money for clinical trials worldwide yearly, about $3.3 billion goes to investigators in the United States. Seventy percent of the money for clinical drug trials in the United States comes from industry rather than from the National Institutes of Health (NIH)." Bodenheimer, *supra* note 693. *See also* Bodil Als-Nielsen et al., *Association of Funding and Conclusions in Randomized Drug Trials*, 290 JAMA 921-28 (Aug. 20, 2003), at http://jama.ama-assn.org/cgi/reprint/290/7/921.pdf ("Eighteen percent of trials [in their sample of 370 randomized drug trials from 1971 to 2000] were funded by nonprofit organizations and in 29% funding was not reported. Fourteen percent of trials were funded by both nonprofit and for-profit organizations and 39% by for-profit organizations alone." *Id.* at 923)

868 Drug agencies (e.g., the American FDA, the European EMEA) do not sponsor clinical trials.

869 *See* ECRI, Should I Enter a Clinical Trial?, A Patient Reference Guide for Adults with a Serious or Life-Threatening Illness, at xv, (Feb. 2002), at http://www.ecri.org/Patient_Information/Patient_Reference_Guide/prg.pdf [hereinafter ECRI (Guide)]. It is not quite clear what ECRI includes under the term "clinical research."

870 *See* U.S. GENERAL ACCOUNTING OFFICE ("GAO"), CLINICAL RESEARCH, NIH HAS IMPLEMENTED KEY PROVISIONS OF THE CLINICAL RESEARCH ENHANCEMENT ACT, at 2 (Report to Congressional Committees, GAO-02-965) (Sept. 2002) at http://www.gao.gov/new.items/d02965.pdf [hereinafter GAO (NIH)]. These $6.4 billion represent 32% of the NIH "total research dollars." *Id.* at 2 and also at 8. The total budget of the NIH in fiscal year ("FY") 2002 was $23 billion. *See also* GAO (Taxol), *supra* note 695, at 6.

871 *See* GAO (NIH), *supra* note 870, at 10. "In fiscal year 2001, NIH estimated that it spent about $529 million, or 27 percent of its intramural research expenditures, on clinical research." *Id.* at 10. *See also* SPRUMONT, *supra* note 16, at 135.

872 *See, e.g.,* GAO (Taxol), *supra* note 695, at 3-5 and at 7.
See also for a description of non-commercial clinical trials conducted in England, Ian Chalmers et al., *Descriptive survey of non-commercial randomised controlled trials in the United Kingdom, 1980-2002*, 327 BMJ 1017 (Nov. 1, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7422/1017.pdf.

873 *See* Andrew Pollack, Three Universities Join Researcher to Develop Drugs, N.Y. Times, July 31, 2003, at C1.

874 "Given the expense of the phase III trials and their importance as the principal criterion for FDA approval, they can make or break small biotechnology companies." *See* BAZELL, *supra* note 673, at 31.

overtakes this task for less experienced biotech firms.[875] When large pharmaceutical companies are not willing to fund late stage clinical trials and assist in the regulatory approval process, small biotech firms have very few alternatives. Only rarely, do non-pharma companies or philanthropic foundations get involved in drug clinical research.[876] Hence, it is estimated that "pharmaceutical companies sponsor about 80 percent of all drug trials."[877]

The situation in Switzerland is much worse than in the United States. There is almost no *non-commercial* funding for Swiss drug clinical trials.[878] The SNSF is among the few institutions that occasionally fund non-commercial clinical trials.

5.1.3. Number of sponsors

In most situations, there is *only one* sponsor per drug clinical trial.[879] Cooperative efforts among pharmaceutical companies to conduct joint clinical trials have so far been rare (with the exception of the classic biotech-Big Pharma collaborative agreements). These joint endeavors could multiply in the future, especially for serious diseases such as cancer and AIDS. In 2003, for instance, several companies agreed to pool their resources and share the risks in order to find better cancer treatments.[880] Similarly, HIV vaccine trials often require the pooling of resources of many sponsors, both from the commercial and the public sector.[881]

Swiss law does not explicitly prohibit *multiple* sponsors. However, the OClin only mentions the sponsor in the singular form. Moreover, several provisions are formulated in a way that presupposes a single sponsor (e.g., reporting rules). But if two entities are willing to undertake the sponsor's obligations *jointly and severally*, there should be no

---

875 *See id.* at 134.

876 *See id.* at 73-76 (describing the involvement of the cosmetic firm Revlon in the development of Genentech's Herceptin).

877 *See* U.S. GENERAL ACCOUNTING OFFICE ("GAO"), NIH CLINICAL TRIALS, VARIOUS FACTORS AFFECT PATIENT PARTICIPATION, at 4, (Report to Congressional Requesters, GAO/HEHS-99-182) (Sept. 1999), at http://www.gao.gov/archive/1999/he99182.pdf [hereinafter GAO (Factors Affect)].
See also OIG, HHS, Institutional Review Boards: A Time for Reform, (June 1998), at 7, at http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf [hereinafter OIG (Reform)] ("For decades, under the fee-for-service system, research expenditures were subsidized by patient-care revenues; under managed care, however, traditional financial support for research activities has been diminishing. In the process, commercial sponsorship has become increasingly important. At the academic health centers we visited, commercial sponsorship accounted for as much as 50 percent of research funding.").

878 *See* urgent question of Parliament member ("MP") Franco Cavalli to the Swiss Federal Council of June 13, 2002, and answer by the latter of July 2, 2002, at http://www.parliament.ch/afs/data/f/gesch/2003/f_gesch_20031076.htm.

879 *See however* O'Donnell (Squeezing), *supra* note 169.

880 *See* Andrew Pollack, *Companies May Cooperate on Cancer Drugs*, N.Y. TIMES, May 13, 2003, at C1, abstract at http://query.nytimes.com/gst/abstract.html?res=FB0D12FB3B5B0C708DDDAC0894DB404482; Susan Warner, *Collaborators Against Cancer*, 17(13) THE SCIENTIST p.48 (June 30, 2003), at http://www.the-scientist.com/yr2003/jun/prof2_030630.html.

881 *See, e.g.,* UNAIDS, Ethical considerations in HIV preventive vaccine research, UNAIDS Guidance Document, at 8, (May 2000), at http://www.unaids.org/html/pub/publications/irc-pub01/jc072-ethicalcons_en_pdf.pdf.

reason to deny them this choice as this should not harm subjects. On the contrary, there would be two parties liable instead of just one.[882]

There is however a debate in the European Union as to whether the 2001/20/ Directive (whose language is similar to the OClin) permits multiple sponsors (for example a consortia of public or non-profit entities).[883] Public entities, in particular, are worried academic centers will no longer be able to act as sponsors.[884] However, once again, there is no reason to insist on a single sponsor as long as the responsibilities of all parties involved are clearly defined and that the situation of research subjects is not prejudiced.

Another question to be confronted is whether the OClin should automatically apply to anyone who meets the conditions of Article 5.b. OClin (see subsection 5.1.1. above). For example, if several institutions have provided adjunct funding, while a commercial company is supplying the investigational product, should *all* these parties be designated "sponsors" and thus be obliged to abide with the corresponding requirements of the OClin (e.g., the liability clause of Article 7 OClin)? In my opinion, the OClin was not drafted with this purpose in mind. If one party agrees to undertake the sponsor's obligations, this should exempt other eligible parties. It is only where no one has moved forward to assume these obligations that Article 5.b OClin can be applied to any or all parties that meet the conditions.

5.1.4. The sponsor's duties

The sponsor's obligations are spread across different articles of the OClin.[885]

In practice, these obligations fluctuate significantly since the sponsor is allowed to delegate most of them to either the investigator or other parties (e.g., CROs). Thus, in certain cases, the sponsor may not do much more than provide the initial funding, all other tasks being allocated to third parties.

Nonetheless, the sponsor should be obliged to exercise a minimal oversight over the investigator. It is regrettable that the OClin does not state this obligation explicitly. The OClin only focuses on one main attribute of the sponsor: its liability for any damages occurring in relation with the trial (see subsection 8.6.5. below). Undeniably, this should create an incentive to ensure that the trial is well-managed.

---

882 *See* Article 7 OClin.

883 *See* Rory Watson, *Research bodies lobby EU governments over trials legislation*, 327 BMJ 1010 (Nov. 1, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7422/1010.

884 Researchers affiliated with public institutions also fear that the European Directive places an excessive legal burden on public-sector sponsors, in particular with respect to liability rules. *See* Rory Watson, *Scientists beg EU to repeal new rules for clinical trials*, 328 BMJ 187 (Jan. 24, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7433/187. See however the 2005/28/EC Directive laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, available at http://pharmacos.eudra.org/F2/eudralex/vol-1/DIR_2005_28/DIR_2005_28_EN.pdf.

885 *See* Article 6.3, 7, 13.1, 19-23, and 25 OClin. Compare with Article 9.2 of the (former) IOCM 1995 Regulation.

5.2. The investigator

Usually, the sponsor does not conduct the trial itself. Instead, it appoints one or several investigators who will actually carry out the studies described in the protocol.[886] An agreement must be signed between the sponsor and the investigator and/or between the sponsor and the institution with whom the investigator is affiliated.[887]

Investigators cannot be legal entities; if an investigator is employed by an institution, for example a university hospital, the institution will not be the investigator.

The law allows for the sponsor and the investigator to be the same person. That person must be an individual, not a legal entity.[888] In such a case, the individual bears the responsibilities of both the sponsor and the investigator. Such a person is referred to as sponsor-investigator.[889]

The relationship between the sponsor and the investigator is to be qualified, under Swiss law, as one of mandate:[890] The investigator is bound by a best effort duty, not by the obligation of producing given results.

The LPTh and the OClin only target the investigator, and do not regulate her institution.[891] This distinguishes them from U.S. regulations that are also aimed at institutions.[892] This lack of federal provisions regarding Swiss research sites is regrettable. Institutions play a key role in supervising investigators and enforcing uniform guidance pertaining to the conduct of clinical trials.[893] For instance, institutions should be responsible for investigating, at least at the preliminary stage, claims of impropriety raised against investigators by human research subjects. Of course, RECs can verify whether the existing cantonal requirements are met[894] and can go beyond these requirements to impose stricter rules. However, a federal statutory provision would have been preferable.

---

886 *See* section 1.34 (p.5) and 5.6.1 (p.22) of ICH E6.
In the United States, 21 C.F.R. § 312.3(b), § 312.50 and § 312.60.

887 See for example the template investigator-sponsor agreement prepared by the University of North Carolina at Chapel Hill, at http://research.unc.edu/oct/clinical_trial_research_agreement.pdf [hereinafter UNC (Agreement)].

888 Similarly, if a pharmaceutical company funds a clinical trial conducted by its own employees as investigators, the company is the sponsor and the main individual in charge of the research is the investigator. *See* SPRUMONT, *supra* note 16, at 131.

889 *See* section 1.54 (p.8) of ICH E6; in the United States, 21 C.F.R § 312.3(b), § 50.3(f) and § 56.102(k). The role of the investigator is however the dominant one. *See* Article 5.c OClin.

890 *See* Article 394 of the Swiss Code of Obligations ("CO").

891 There may be other federal laws that govern the activities of these institutions, but most are cantonal. However, under the OClin, institutions have no obligations to monitor or control the activities of employees-investigators. *See generally* SPRUMONT, *supra* note 16, at 93.

892 *See* Glantz, *supra* note 83, at 187. For example, institutions can duplicate the review of ethics committees/IRBs. Thus, a project approved by an IRB can still be turned down by the institution. *See* 21 C.F.R. § 56.112. Institutions are also responsible for the operations of their IRBs. *See* 21 C.F.R. § 56.120(c). *See also* SPRUMONT, *supra* note 16, at 140.

893 *See, e.g.*, U.S. GENERAL ACCOUNTING OFFICE ("GAO"), VA RESEARCH, ACTIONS INSUFFICIENT TO FURTHER STRENGTHEN HUMAN SUBJECT PROTECTIONS, at 6, (Testimony before Subcommittee on Oversight) (June 18, 2003), at http://www.gao.gov/new.items/d03917t.pdf [hereinafter GAO (Insufficient)].

894 See subsection 7.1.1.3.5. below.

5.2.1. Investigators' motivations

There are several reasons why investigators are interested in participating in clinical trials.[895]

First, participation enables doctors to have an early *access* to promising and fascinating new treatments and this clearly benefits their patients. This is especially true for medical conditions for which no effective therapy is available (e.g., several forms of cancer).[896]

Second, participation in clinical trials serves to advance the *career* of investigators, especially academic investigators. A clinical trial is the occasion to publish study findings in medical journals.[897] In turn, the number of publications determines in good part which researcher receives government grants: Researchers with long lists of clinical papers are more likely to receive public funding.[898] In turn, well-funded researchers are more likely to achieve outstanding career. A less desirable consequence is the competition among researchers to participate in clinical trials and to publish the corresponding medical articles.[899]

Third, participating in a clinical trial is a way for academic scientists to get *private funding for their own research*. Since, government funds are insufficient to finance all desirable academic research projects, academic researchers have turned to the industry. Academic researchers take advantage of a commercially sponsored clinical trial to incorporate their research agenda within the trial. Contacts between an investigator and a pharmaceutical company can also open sponsorship opportunities for the former. Medical schools regularly solicit the pharmaceutical industry to finance educational programs or research projects. These schools have gradually become more dependent on these private funding sources.[900] For governments, collaborations between medical schools and the industry offer a nearly irresistible relief for already over-stretched public budgets.

---

895 *See* BAZELL, *supra* note 673, at 60-61.

896 *Id.* at 144.

897 Brazell reports that "[t]he physicians carrying out phase III cancer-drug trial often work a notch below the superstars at large academic medical centers. More prominent physicians prefer to attach their names to the more prestigious phase I and phase II trials, which provide greater opportunity for publishing important research papers even though they do not prove definitively whether a drug works." *See supra* note 673, at 143.
See also Pieter Sauer, *Why is the medical profession interested in good clinical practice?* THE EFGCP NEWS, at 6 (Spring 2001), at http://www.efgcp.org/webitems/doc/newsletters/2001_Spring.pdf.

898 *See* Marcia Angell, *Editorial Responsibility: Protecting Human Rights by Restricting Publication of Unethical Research*, *in* THE NAZI DOCTORS AND THE NUREMBERG CODE 276, 279 (Oxford University Press 1992) [hereinafter Angell (Publication)].

899 *See further* Bernard Barber et al., *Experimenting with humans: problems and processes of social control in the biomedical research community*, *in* THE CHALLENGE OF LIFE, BIOMEDICAL PROGRESS AND HUMAN VALUES, ROCHE ANNIVERSARY SYMPOSIUM, BASEL SWITZERLAND, at 362, (Birkäuser Verlag, 1972) (finding that under-recognized researchers are more likely to neglect the rights and safety of research subjects).

900 In Switzerland, see Kleist (Abhängigkeit), *supra* note 800, at 2349.

Fourth, doctors in private practice can maintain contact *with the academic community* through clinical trials.[901] These physicians are often very eager to be included in vast and prestigious research projects.

Fifth, working as an investigator can be *profitable*, especially if the physician is successful in enrolling her patients. As we will see in subsection 5.3. on conflicts of interest, some investigators have derived sizable financial rewards from their relationships with commercial sponsors.

5.2.2. Sponsor's selection of investigators

Sponsors are mainly interested in investigators who are able to *recruit rapidly* the required number of patients.[902] As reported by the U.S. Office of Inspector General (OIG):

> Asked what sponsors are looking for from sites, one investigator responded, 'Number one – rapid enrollment. Number two – rapid enrollment. Number three – rapid enrollment.'[903]

Even the ICH gives emphasis to this ability to recruit subjects "within the agreed recruitment period."[904] One can wonder whose interests the ICH is protecting here.

Sponsors also seek investigators who, by conducting the trial properly, produce *clean and reliable data*. Given the money invested in clinical trials (see subsection 4.2.1. above), even a tiny mistake can cost millions.

Finally, sponsors have a preference for highly regarded investigators. They hope that the latter's decisions to participate in a trial and then to prescribe the drug will influence other physicians. Pharmaceutical companies often have the same *opinion leaders* participate actively in the subsequent marketing campaigns. Such a practice is now criticized as being inappropriate.[905]

---

901 *See* Brian Vastag, *Clinical Trials to Receive Boost, But How Big?* 286 JAMA 1303 (Sept. 19, 2001), at http://jama.ama-assn.org/cgi/reprint/286/11/1303.pdf [hereinafter Vastag (Boost)]; Timothy Herrick, *Clinical Trials Under the Microscope*, 5(2) CLINICIAN NEWS 1, at 7-9 (2001).

902 *See, e.g.*, PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results, at 8, (July 2002), at http://www.phrma.org/publications/policy/2002-07-18.490.pdf [hereinafter PhRMA (Principles on Clinical Trials)].

903 OIG (Recruiting), *supra* note 815, at 13. "Sponsors and their agents constantly remind sites of the need to expedite recruitment. Sites report numerous phone calls from sponsors, informing them of how their enrollment statistics compare with those of other sites in the trial." *Id.* See *also* VanTx Report, *supra* note 148, at 11.

904 *See also* section 4.2.1 (p.13) of the ICH E6 Good Clinical Practice Guidance. *See also* VanTx report, *supra* note 148, at 19 (approving a requirement similar to the one the IOCM regulation used to stipulate).

905 *See, e.g.,* SAMS, *Recommandations sur la collaboration corps médical-industrie*, [Recommendations on the collaboration between the industry and health professionals], Point I.10, (Sept. 9, 2002), published in 41 BULLETIN DES MÉDECINS SUISSES, at 2174 (2002), at http://www.saez.ch/pdf/2002/2002-41/2002-41-1155.PDF.

5.2.3. Academic and commercial investigators

Traditionally, investigators were selected at first-class hospitals, often *academic* hospitals.[906] Investigators were academic professors-physicians who taught and worked at medical schools. They enrolled their own patients as subjects. Still today, U.S. Medical Schools engaging in clinical trials enter into hundreds of agreements with commercial sponsors each year.[907] In exchange, the industry pays an estimated $1.5 billion to academic institutions.[908]

This tradition is vanishing.[909] Investigators are increasingly recruited among *doctors in private practices*.[910] In the United States, the number of private-practice investigators has quadrupled in a five year span, reaching 11,588 in 1995.[911] The number of *professional* investigators (scientists who specialize nearly exclusively in the conduct of clinical trials) is also on the rise.

The change can be attributed to two interrelated factors. First, the requirements for phase III clinical trials alongside with financial considerations demand *rapid enrollment* of an ever greater number of subjects. Second, it is easier to get access to a *representative set* of subjects through community physicians, as opposed to academic research centers. This was made clear in the early days of AIDS research. AIDS patients lived in poor urban cities, while prestigious universities were located in rich neighborhoods where few residents suffered from the disease. AIDS patients had no contact with the prominent clinics, but saw their community doctors. The response was to delegate more research responsibilities to these doctors.[912]

These primary care doctors are usually appointed co-investigators, the lead investigator still being an academic researcher. In the United States, about 4% of all practitioners have been appointed as (co- or sub-) investigators.[913] Enrolling primary care doctors also ensures their future willingness to prescribe the newly approved drug (see also subsection 6.1.4.2.).[914]

---

906 For Sidney Wolfe, "[w]hereas in 1993, only 20% of pharmaceutical company research was done in the private, for-profit research setting, the fraction has gone up 2.5 times and by 1998, 50% was being done outside of academic medical centers. The number of private practice-based investigators has grown from 3,153 in 1990 to 11,588 in 1995, an increase of almost four-fold." Public Citizen, *Comments on HHS Inspector General's Study Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research*, at http://www.citizen.org/publications/release.cfm?ID=6724. *See also* subsection 5.6. below on CROs.

907 According to a survey led by Schulman, "[t]he median number of site agreements executed in the previous year was 103 (interquartile range, 50 to 210)." Kevin A. Schulman et al., *A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Industry Sponsors*, 347 NEW. ENG. J. MED. 1335-1341 (2003), at http://content.nejm.org/cgi/reprint/347/17/1335.pdf.

908 *See* Mark J. Alberts et al., *Brains, claims and the pharmaceutical industry, Conflict of interest in perspective*, 327 BMJ E107-E109 (Oct. 4, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7418/E107.

909 *See, e.g.,* Davidoff et al., *supra* note 603, at 825 (lamenting this change).

910 *See* Donna T. Chen et al., *Clinical Research and the Physician-Patient Relationship*, 138 ANN. INTERN. MED. 669 (Apr. 15, 2003), at http://www.annals.org/cgi/reprint/138/8/669.pdf.

911 "This growth is in part of the larger influx of investigators into the clinical trials arena. The number of new investigators increased approximately 22% annually between 1992 and 1996." OIG (Recruiting), *supra* note 815, at 12.

912 *See* ARNO & FEIDEN, *supra* note 125, at 111-13.

913 In 1999, this represented 44,000 practitioners. *See* Herrick, *supra* note 901.

914 *See id.*

The second factor relates to the need for speed. Sponsors blame academic investigators for not recruiting subjects and completing clinical trials within deadlines.[915] They trust that *professional* investigators will perform better. As we will see below, CROs have emerged to meet these expectations.

Alternatively, pharmaceutical firms can launch their own in-house clinical trials if subjects can be taken care of outside hospitals. This is the case for early-stage small clinical trials; the investigator is then chosen among the pharmaceutical company's medical staff.

5.2.4. Number of investigators

When several investigators are appointed by the sponsor, there is usually a main investigator, also called the lead or *principal investigator* ("PI"). The PI has responsibilities that go beyond that of the co- or sub-investigators.[916] She is closely involved in the preparation of the trial, including the design of the protocol. She is generally the main author of the study report.

The appointment of more than one investigator is necessary in multicentric clinical trials. Multicentric (multi-centre according to the European and CIOMS terminology) trials are clinical trials conducted in different locations (i.e., research sites), but according to the *same protocol* (i.e., the same document describing the objectives and procedures of all clinical trials taking place). Although the sponsor can choose to have several studies performed under separate but similar protocols, multicentric studies are favored if the objective is to secure marketing approval (see subsection 4.1.1. above).[917] When studies are conducted at several different locations, the sponsor needs at least one investigator per location.[918]

Trials involving several investigators normally require a *coordinating investigator* to organize communication.[919] Coordinating investigators are also indispensable in multicentric trials.[920] Such trials may also set up committees to supervise the different investigators and take over certain important tasks (e.g., preparation of study reports).[921]

---

915 Bodenheimer observes that "… pharmaceutical firms are frustrated with academic medical centers. … Slow review of industry proposals by academic research offices and institutional review boards delays the starting dates of trials. Since academic physicians have multiple responsibilities in teaching, research, and patient care, trials may proceed more slowly than the pharmaceutical firms desire." Bodenheimer, *supra* note 693.

916 When the PI herself appoints other investigators, for example medical staff under her supervision, these are called *sub-investigators*. When it is the sponsor that hires several investigators, those are referred to as *co-investigators*. *See* point 1.56 (p.8) of ICH E6; in the United States, 21 C.F.R. § 312.3(b) ("In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Sub-investigator' includes any other individual member of that team."). *See also* VanTx Report, *supra* note 148, at 15 and 24 (distinguishing between co-investigators and associated investigators).

917 When studies, though very similar in nature, are not conducted under the same protocol, the pooling of their data to draw broader inferences is generally not reliable.

918 For a definition, see Article 10.3 OClin in Switzerland; Article 2(b) of the European Directive 2001/20/EC for the European Union; section 1.40 of ICH E6.

919 *See* section 1.19 (p.4) of ICH E6.

920 Some clinical trials also have steering committees composed of the main investigators and representatives of the sponsor. *See* FDA, Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees, Draft Guidance, at 4 (Nov. 2001), at

5.2.5. Qualifications of the investigator

The investigator selected by the sponsor must have appropriate scientific qualifications in line with the type of studies.[922] In Switzerland, she must be a *licensed physician*.[923]

The investigator must also have enough practical and theoretical *experience* to carry out the clinical trial under the best conditions. The VanTx Working Group suggested that investigators have at least two years of relevant experience.[924] However, neither the LPTh nor the OClin contains any requirement as to the amount of past experience. [925] Formal education of Swiss physicians in the area of clinical research has been criticized. Medical schools lack programs properly focusing on clinical research.[926]

Investigators should have the appropriate *training* to comply with regulations.[927] Part of the duty to impart this training falls upon the industry which contracts trials out to investigators. When investigators are affiliated with medical schools or other research centers, the responsibility may rest on the latter. However, in Switzerland, investigators are apparently not receiving sufficient training.[928]

In Switzerland, universities and pharmaceutical companies are being solicited to undertake a concerted effort in favor of clinical researchers' continuing education.[929] By improving investigators' training upstream, the industry would reap downstream benefits, such as better quality clinical data.

In the United States, web-based training programs have flourished in recent years. Many academic and governmental centers make the completion of such programs mandatory for anyone doing research involving human research subjects.[930]

---

http://www.fda.gov/cber/gdlns/clindatmon.pdf [hereinafter FDA (DMC)].

921 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).

922 Article 8.1 OClin. *See also* paragraph 15 of the WMA's Declaration of Helsinki; sections 2.8 (p.9) and 4.1.1 (p.12) of ICH E6; Principle 12.1 of the Council of Europe's R(90)3 Recommendation, *supra* note 115; Article 8 of the Nuremberg Code; 21 C.F.R. § 312.53(a) in the United States.

923 Article 8.2 OClin. *See* DHA (Ordinance Comments), *supra* note 522, at 45; VanTx Report, *supra* note 148, at 15 (where even the principal investigator at VanTx did not fulfill this basic requirement).
For clinical trials of *medical devices*, other specializations or qualifications are acceptable if they offer similar assurance that the investigator will be in a position to give subjects the best medical care. The requirements appears to be looser for clinical trial with medical devices. Article 8.1, second sentence OClin. Because the OClin only applies to clinical trials of therapeutic products, other types of qualification (e.g., medical students, biologists, psychologists, sociologists) are not envisioned. Compare with paragraph 31 of the COE Explanatory Report, *supra* note 417, at 8.

924 *See* VanTx Report, *supra* note 148, at 23 and 24 (asking that this two-year requirements extend to both the principal and the co- investigators). *See also* SPRUMONT, *supra* note 16, at 91-92.

925 See however Article 9.2.l OClin added in September 2004 (requiring that ethics committees control the GCP training and experience of investigators).

926 *See* Amstad et al. (Lieux), *supra* note 800, at 2453.

927 See, in the United States, CenterWatch, *The Choice for More Training*, 8(3) CENTERWATCH 1-6 (Mar. 2001), at http://www.centerwatch.com/careers/CW0803-Training.pdf.

928 *See, e.g.,* Sprumont & Béguin, *supra* note 134, at 903.

929 *See, e.g.,* M. Trutmann, *Das Heilmittelgesetz und klinische Forschung [The LPTh and clinical research]*, 83(18) BULLETIN DES MÉDECINS SUISSES 863 (2002), at http://www.saez.ch/pdf/2002/2002-18/2002-18-536.PDF.

930 *See, e.g.,* GAO (Insufficient), *supra* note 893, at 8.

The investigator must have personal *time and staff* on hand to perform the study.[931] Of course, she will not do everything herself. In reality, she may only lead her team and oversee the general performance of the trial. Frequently, junior physicians and nurses do the bulk of the work; they administer the product, treat subjects and record the appropriate observations.

Under the previous intercantonal system, the investigator had also to be renowned for her *ethical* qualities and her professional integrity.[932] This requirement is no longer explicit under the OClin.

5.2.6. Responsibilities of the investigator

Once contacted by the sponsor to lead a research project, the investigator will read the protocol, suggest modifications, ask questions about additional requirements that are not contained therein, and discuss her remuneration.[933] Often, a meeting takes place between the sponsor and the investigator(s) to convey the necessary information and resolve all issues.[934]

If the clinical trial design and conditions satisfy the investigator, she will accept the sponsor's offer. With her acceptance, she agrees to take responsibility for the actual performance of the trial; in particular, she is *responsible for the welfare of enrolled subjects*.[935] Although the sponsor is legally liable for the clinical trial, the investigator bears the principal responsibility to conduct the trial. She will recruit patients, make sure that they have given their informed consent, administer the drug, provide general care, record her observations, respond to adverse medical reactions.

Naturally, the investigator is assisted by her staff of interns, nurses and other specialists. In large clinical trials taking place in research centers (as opposed to trials performed by private practice physicians hired as investigators), the investigator herself has only few contacts with the subjects. As just said, subjects mainly interact with

---

931 *See* section 4.2.2 (p.12) of ICH E6 Guideline. *See, e.g.*, FDA warning letter to Harry D. Bear, investigator with the Virginia Commonwealth University, (Sept. 27, 2002), at http://www.fda.gov/foi/warning_letters/g3527d.htm.

932 Glossary of the GCPs accompanying the (former) IOCM 1995 Regulation.

933 Ideally, the investigator should scrutinize the protocol with the same attention as an ethics committee would if asked to give (or refuse) its favorable opinion. On ethics committees' review, see subsection 7.1.2. below. Thus, the investigator should not allow inadmissible provisions that endanger the safety of the subjects or limit their rights. Even though her obligation to safeguard subjects starts with her approval of the protocol or, at the latest with the recruitment of the first subject, she should make sure that the protocol contains no obvious flaws that would lead to its rejection by the ethics committee. Thus, she also acts in her own best interests, since her ethics committee might understandably conceive a bad opinion of her if she has submitted a manifestly defective protocol.

934 *See Investigator Meetings*, THE EFGCP NEWS, at 10-11 (Spring 2001), at http://www.efgcp.org/webitems/doc/newsletters/2001_Spring.pdf.

935 Article 5.c OClin. In the European Union, according to Article 2(f) of the Directive 2001/20/EC, the investigator is defined as the person "responsible for the conduct of a clinical trial at a trial site." In the United States, see for example 21 C.F.R. § 50.3(d) and § 56.102(h).

nurses. The research/study coordinator (working for the investigator) is generally the person most closely involved with subjects.[936]

5.2.7. Investigators' institutions

Still today, most investigators work in research centers or academic institutions. While the conduct of the trial is entrusted to the investigator, these centers and institutions may nonetheless have a role to play.[937] However, as we saw at the beginning of subsection 5.2., this role is not particularly apparent under Swiss law. There is only one provision in the Swiss Ordinance – Article 30.2 OClin – that mentions the institution where the clinical trial takes place. Yet, its wording is unfortunate since it suggests misleadingly that the institution is conducting the trial, whereas the conduct of clinical trials is the responsibility of the investigator.

By contrast, in the United States, the role of the institution is much more developed. Many guidelines are targeted at the institutions. This is particularly true of conflicts of interest. Indeed, since institutions are at least as likely to be sued as the investigator (they are after all richer), it is only reasonable that they take all reasonable precautions.

5.3. Conflicts of interest involving sponsors and investigators

When the sponsor entrusts the conduct of a clinical trial to a third-party investigator (as is usually the case), it is important that the latter performs her duties objectively, serving the interest of both impartial science and research subjects. Whenever the interests of the sponsor, the investigator, objective science, and subjects are not perfectly aligned (as is usually the case too), there should be mechanisms guaranteeing that the interests of the latter prevail. Conflicts of interest[938] should be identified, acknowledged, dis-

---

936 The research coordinator is generally a nurse. *See* ECRI (Guide), *supra* note 869, at 9; Arlene M. Davis et al., *The Invisible Hand in Clinical Research: The Study Coordinator's Critical Role in Human Subjects Protection*, 30 J. OF LAW, MED. & ETHICS 411-419 (2002), at http://www.med.unc.edu/soclmed/scob/Davis.web.pdf (describing the qualifications of and tasks entrusted to study coordinators).

937 For example, the institution may have adopted internal regulations that compel investigators to follow a certain procedure before accepting to undertake a clinical trial for an external sponsor. Moreover, when subjects are injured in a clinical trial, they tend to sue *both* the institution and the investigator, rather than only the latter.

938 See for one definition of "conflict of interest": HHS, Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection, Draft Interim Guidance, at chapter 1.1 (Jan. 10, 2001), at http://www.hhs.gov/ohrp/nhrpac/mtg12-00/finguid.htm [hereinafter HHS Interim Guidance]. The HHS is to replace this Interim Guidance by a toned-down Guidance. The replacement Guidance contains a list of questions that participants in clinical research should ask themselves to assess conflicts of interest. *See* HHS, Financial Relationships and Interests in Research Involving Human Subjects, Draft Guidance for Human Subject Protection, 68 Fed. Reg. 15,456 (Mar. 31, 2003), at http://www.fda.gov/OHRMS/DOCKETS/98fr/03-7691.pdf [hereinafter HHS Financial Guidance] and 69 Fed. Reg. 26,393 (May 12, 2004) at http://www.hhs.gov/ohrp/humansubjects/finreltn/finalguid.pdf; BEAUCHAMP & CHILDRESS, *supra* note 16, at 318.

closed, and either minimized or eliminated. As the U.S. Association of Universities pointed out, "the problem is rarely a particular conflict itself – rather it is the question about what is done with the conflict."[939]

Addressing conflicts of interest is particularly important when the investigator is affiliated with a *public* or semi-public institution, such as a university or a hospital. Lack of independence on the part of the investigator can reflect badly on the institution itself and damage its standing towards patients and the public.[940] While this subsection focuses mainly on the relationship between the sponsor and the investigator and its impact on research subjects, conflicts of interest can also intrude in the relationship between the institution and the sponsor[941] or, more rarely, between the investigator and her institution.[942] A different subsection (7.1.1.4.3. below) discusses conflicts of interest within RECs.

Conflicts of interest can take several forms.[943] The first subsection covers the general topic of investigator's impartiality. Subsection 5.3.2. focuses on *financial* conflicts of interest,[944] while subsection 5.3.3. deals with a sub-issue related to confidentiality

---

Also on the definition of conflict of interest, see Jennifer A. Henderson & John J. Smith, *Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls*, 57 FOOD & DRUG L.J. 445 (2002), at http://www.cimit.org/fdli.pdf; Stanford University, Faculty Policy on Conflict of Commitment and Interest, (Apr. 14, 1994), at http://www.stanford.edu/dept/DoR/rph/4-1.html [hereinafter Stanford (Commitment)]; Association of American Universities ("AAU"), Task Force on Research Accountability, Report on Individual and Institutional Financial Conflict of Interest, at 2, (Oct. 2001), at http://www.aau.edu/research/COI.01.pdf [hereinafter AAU (Conflict)]; paragraph 44 COE Explanatory Report, *supra* note 417, at 9; Medical Research Council ("MRC"), Good Research Practice, at 6, (Dec. 2000), at http://www.mrc.ac.uk/pdf-good_research_practice.pdf.

939 *See* AAU (Conflict), *supra* note 938, at i and 1.

940 In Geneva, the most notorious case has been that of Dr. Rylander, a researcher and professor at the University of Geneva, who was doing research on passive smoking, but hided his long-time relationship with a tobacco firm (Philip Morris). On this subject, see the website of prevention.ch at http://www.prevention.ch/rylanderpm.htm and the November 2001 report of the University of Geneva titled Conclusions and measures of the Rector following the denunciation of links between the tobacco industry and the University of Geneva, [Conclusions et mesures du rectorat faisant suite à la dénonciation sur l'existence de liens entre l'industrie du tabac et l'Université de Genève], at http://www.prevention.ch/ryrapuni061101.htm [hereinafter 2001 Rylander-University report].

941 *See* AAU (Conflict), *supra* note 938, at i and at 10-14. The AAU distinguishes between conflicts involving the institution as such and those involving its high-level officials. A conflict of the first category would arise, for example, when a university is promised a milestone payment from a commercial licensee if the trial conducted at the university yields positive results. A conflict of the second category exist, for example, when a Medical School Dean is appointed as board member of a pharmaceutical company that sponsors clinical trials taking place at the Medical School.

942 Such a conflict can arise, for example, when universities hold the right to an invention, whose value would increase if the investigator's trial showed promising results. U.S. universities can retain ownership of inventions achieved by their faculty members. Usually, universities try to license out these inventions, but do not always succeed. When universities retain the right to the invention (e.g., they hold the patent), their position is somewhat similar to that of a commercial firm.

943 *See* Thomas F. Lüscher, *« Conflict of interest » oder Interesse am Konflikt?* 82(40) BULLETIN DES MÉDECINS SUISSES 2137 (2001), at http://www.saez.ch/pdf/2001/2001-40/2001-40-1043.PDF.

944 Financial interests encompass notably the grant or the promise of stakes in a company, stock options, consulting fees, royalty payments, gifts. *See also* AAU (Conflict), *supra* note 938, at 5. When the value of debt instruments varies based on the company's prospect, they should probably be treated in the same way as equity.

clauses. Conflicts may involve yet other areas (e.g., authorship privileges,[945] commitment splits[946]), which are not reviewed here.

5.3.1. Impartiality of the investigator

5.3.1.1. Tension between research and therapy

We saw before that clinical trials need to be distinguished from "ordinary" medical care, but a precise separation line is hard to draw. This demarcation problem also creates down-stream difficulties when a physician engages in clinical research on human research subjects. The investigator must fulfill two role that are partly in conflict: she must gather reliable scientific data, while at the same time taking good care of her subjects-patients.[947] These two objectives can easily clash.[948] Subsection 5.8. below discusses the problem of stopping a clinical trial at the right moment in time, to preserve both the health of subjects and the reliability of study findings. We will study another illustration of this type of conflict in subsection 6.3.5.2. which examines the use of placebo in clinical trials.

While financial conflicts of interest have attracted considerable media attention, the issue of the fundamental tension between the two roles assumed by the investigator-physician has not been scrutinized as much.[949] A possible reason for this neglect is that this strain is almost entirely unavoidable. Financial conflicts of interest can almost be entirely removed, as we will see shortly, but the investigator has to constantly arbitrate between what she owes to science (as well as future patients) and what she owes to her patient-subjects. Moreover, the investigator's loyalty toward "good" science mixes with her sense of obligations toward the sponsor (who is paying her) and her interests in achieving a prominent career (e.g., to publish, get tenure, receive grants).

5.3.1.2. Independence toward the sponsor

When investigators came mainly from the ranks of academia, they gave extensive input as to the design of trials and the contents of protocols (see subsection 5.2.3. above). Nowadays, sponsors prepare the protocol and the role of the investigator at this stage is more

---

945 *See, e.g.*, OIG, HHS, Recruiting Human Subjects, Sample Guidelines for Practice, (June 2000), at 8, at http://oig.hhs.gov/oei/reports/oei-01-97-00196.pdf [hereinafter OIG (Sample Guidelines)]. *See also* ALLHAT Policy Statement, Intellectual Conflict of Interests, at http://allhat.sph.uth.tmc.edu/Documents/ICOI-Policy-20010122.pdf (on intellectual conflict of interests in relation to clinical trials). For who should qualify as an author of an article published in a biomedical journal, see generally International Committee of Medical Journal Editors ("ICMJE"), Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications (Nov. 2003), at section II.A.1., text at http://www.icmje.org [hereinafter ICMJE].

946 Conflicts of commitment (e.g., share of faculty's time devoted to commercial ventures as opposed to students) are a form of conflict of interest drawing renewed attention at universities. *See* Stanford (Commitment), *supra* note 938.

947 *See, e.g.,* Barber et al., *supra* note 899, at 361.

948 *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 319-20.

949 *See, e.g.,* BRODY, *supra* note 447, at 71 and at 144.

limited.[950] Investigators often struggle to convince the sponsor to implement protocol adaptations, a task all the more difficult when the protocol relates to a multicentric clinical trial.[951]

Nonetheless, investigators are still expected to be *independent* from sponsors.[952] The investigator is bound mainly by the protocol that she has accepted.[953] And even this rule has its exceptions; if necessary, the investigator must be able to challenge the protocol, for instance, if subjects taking the experimental substances see their condition deteriorate. In other words, the investigator is no longer bound by the protocol and other instructions of the sponsor if this were to put subjects at risk.

To guarantee independence and patient safety in clinical trials, it is important that the investigator's access to information is not limited.[954] Reports indicate, however, that this is not always the case as sponsors try to retain exclusive control of data (see subsection 5.3.3.2. below).[955] The editors of the most important medical journals have sided with investigators and stated that they would no longer accept papers for publications when the investigators were denied reasonable access to raw data* (also called "source data" or "source documents"[956]) and responsibility for their analysis.[957]

5.3.2. Financial issues

Financial conflicts of interest are those that worry governments, public bodies as well as the public the most.[958] Any hint of an undisclosed financial conflict is a blemish on the reputation of both the researcher and her institution.

---

950 *See* Bodenheimer, *supra* note 693.

951 *See* Lüscher, *supra* note 943, at 2140.

952 Of course, when the investigator and the sponsor is the same person, independence is impossible (on the sponsor-investigator, see subsection 5.2. above). Independence is also very limited when the investigator is the employee of the sponsor, for example when a pharmaceutical first launches an internal early phase trial.

953 The sponsor can give additional "instructions" which are not found in the protocol. However, the investigator can decide to refuse them or only accept them under certain conditions (e.g., supplementary payment).

954 According to E.U. rules, at least the investigator who is responsible for preparing the study report must have "access to the recorded and reported data to ensure accuracy, completeness and timeliness." E.U. Guidance (Ethics Committee), *supra* note 270, at 11. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary); ICMJE, *supra* note 945, at section II.D.2. The ICMJE "is a group of general medical journal editors" whose uniform requirements have been endorsed by many biomedical journals. *See id.* at VI and VII. Even the ICH recommends the use of the ICMJE citation method for marketing applications. *See* ICH M4 Guideline, *supra* note 786, at 2.

955 *See* Kevin A. Schulman et al., *supra* note 907.

956 Source data include "[a]ll information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." Center for the Advancement of Clinical Research ("CACR"), Clinical Research Dictionary, at http://www.med.umich.edu/cacr/dictionary/R-S.htm [hereinafter CACR (Dictionary)].

957 *See* Davidoff et al., *supra* note 603, at 826.

958 *See, e.g.,* Michael M. E. Johns et al., *Restoring Balance to Industry-Academia Relationships in an Era of Institutional Financial Conflicts of Interest*, 289 JAMA 741-42 (Feb. 12, 2003), at http://jama.ama-assn.org/cgi/reprint/289/6/741.pdf; Jerome P. Kassirer, *Financial Conflict of Interest: an Unresolved Ethical Frontier*, 27 AM. J. L. AND MED. 149, at 149 and 153 (2001).

5.3.2.1. Types of financial involvements

Monetary ties that result in financial conflicts of interest can take many different forms.

The most common form is the *payment* made by the sponsor to the investigator to conduct the clinical trial. Sponsors pay investigators to recruit subjects and to administer the treatments called for by the trial. These payments not only compensate the investigators for their time and expenses, but also include some profit margin.[959]

> Over the years we have seen the payments on offer soar to thousands of pounds per completed patient. Well organized British general practices can earn an extra £15 000 annually for three hours' work a week.[960]

Payments or bonuses to the investigator that are calculated based on the number of subjects recruited are particularly suspicious. They create a disproportionate incentive to recruit subjects even if participation in the trial is not in their best interests. For example, the investigator could recruit subjects who do not meet the protocol's eligibility requirements and hide this in order to pocket a higher remuneration. Most ethical guidelines oppose such payment methods or set strict limits so that extra payments only reflect the higher costs for the investigator.

Investigators may have a more *direct* financial interest in the company set to benefit if the clinical product yields positive results. For example, investigators may own *shares or stock options* in the company holding the patent for the drug and sponsoring the trial.[961] Sometimes, investigators are themselves the founder of the company holding the rights to the compound. In the United States, these financial ties have been endorsed by federal legislation, in particular by the 1980 Bayh-Dole Act which encourages universities to patent their inventions and to commercialize them in cooperation with private companies.[962] Similarly, Swiss law aims to promote such technology transfer.[963]

Investigators and sponsors may also be bound by long-term relationships whereby the former are regularly hired by the latter. Investigators can hold appointments as consultants, lecturers or as advisory board members. They may be designated as experts to testify in court for the sponsor. The fear of losing this source of revenue may make the investigator more wary of displeasing the sponsor in connection with the conduct of its clinical trials.[964]

A 2003 literature review revealed that about 25% of academic investigators "receive research funding from the industry," and that about 66% of "academic institutions hold

---

959 In some cases, the payments may not be sufficient to compensate the costs incurred by the investigator. "The American Society for Clinical Oncology (ASCO) estimates that each trial patient costs $3000 or more – in terms of staff time and other overhead. Yet the [U.S.] National Cancer Institute reimburses only $1500 to $2000 for each of the 20000 patients enrolled in its trials each year." Vastag (Boost), *supra* note 901, at 1304. *See also* BRODY, *supra* note 447, at 151-52 (proposing that all elements of profits be removed).

960 Jammi N. Rao & L. J. Sant Cassia, *Ethics of undisclosed payments to doctors recruiting patients in clinical trials*, 325 BMJ 36 (July 6, 2002), at http://bmj.com/cgi/reprint/325/7354/36.

961 *See, e.g.,* BEAUCHAMP & CHILDRESS, *supra* note 16, at 319.

962 *See* Pub. L. No. 96-517, 94 Stat. 3019, codified at 35 U.S.C. 200-212, available from http://www4.law.cornell.edu/uscode/35/pIIch18.html.

963 *See* Article 28a of Federal Law on research of Oct. 7, 1983; in French: "*Loi fédérale sur la recherche*"; RS 420.1; French text at http://www.admin.ch/ch/f/rs/4/420.1.fr.pdf.

964 *See generally* Catherine D. DeAngelis, *Conflict of Interest and the Public Trust*, 284 JAMA 2237 (Nov. 1, 2000), at http://jama.ama-assn.org/cgi/reprint/284/17/2237.pdf.

equity in "start-up" businesses that sponsor research performed by their faculty."[965] However, another study identified a much smaller percentage of investigators who entertain significant financial relationships with commercial sponsors.[966]

5.3.2.2. Possible consequences

Depending on how payments from the sponsor to the investigator are structured or on how much they represent, the former is able to exercise undue influence on the latter. Clearly, if payments were entirely contingent on proving therapeutic efficacy, the investigator could be tempted to alter the data.[967] Similarly, if the investigator is given shares in the sponsor company, the prospect of a stock market windfall may make her stray from exacting research standards. Conflicts of interest may also lead to neglecting subject safety precautions, with the investigator's desire to please her sponsor coming at the expense of subjects.

Even when payments are not made to depend on certain results, a very high remuneration may cause the investigator to "turn a blind eye."[968] Why would an investigator recurrently hired by the industry and offered generous payments choose to "rock the boat" and submit critical comments that could hurt her benefactor? Indeed, studies have found that investigators working for commercial sponsors tend to report results favoring the sponsor's drug.[969] The calcium-channel blockers studies are an edifying illustration of this:

> A 1998 study published in the New England Journal of Medicine reviewed 70 articles on the use of calcium-channel blockers to treat high blood pressure published in 1995 and 1996. There are safety concerns about the use of calcium-channel blockers because of research showing a higher risk of heart attacks. All but one of the authors of articles supporting the use of calcium-channel blockers (96%) had received funding from the manufacturers as compared to 67% of neutral authors and 43% of authors who criticized the safety of these products.[970]

However, one should be careful not to paint an overly bleak picture. The consequences of financial cooperation among researchers and commercial firms are not all negative. This cooperation creates incentives to develop new drugs, incentives that

---

965 Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research*, 290 JAMA at 463 (Jan. 22/29, 2003), at http://jama.ama-assn.org/cgi/reprint/289/4/454.pdf.

966 In a GAO study of five leading universities, "the overall proportion of clinical researchers who disclosed a significant financial relationship averaged 5 percent. At one university [out of the four], these data were not readily available." U.S. GENERAL ACCOUNTING OFFICE BIOMEDICAL RESEARCH, HHS DIRECTION NEEDED TO ADDRESS FINANCIAL CONFLICTS OF INTEREST, at 13, (GAO-02-89) (Nov. 2001), at http://www.gao.gov/new.items/d0289.pdf [hereinafter GAO (HHS)].

967 For other examples of conflicts of interest in clinical trials, *see id.* at 6.

968 *See, e.g.,* DONATINI, *supra* note 127, at 195.

969 *See* Lise L. Kjaergard & Bodil Als-Nielsen, *Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ*, 325 BMJ 249 (Aug. 3, 2002), at http://bmj.com/cgi/reprint/325/7358/249. *See also* Bekelman et al., *supra* note 965, at 456-63.

970 Haiweb, Blurring the Boundaries, Chapter 5: Research or promotion?, at http://www.haiweb.org/pubs/blurring/blurring.ch5.html. Still "[a]nother review looked at the results of 56 industry sponsored studies of NSAIDS published between 1987 and 1990. In all cases the sponsor's drug was found to be either equally or more effective than the comparison drug." *Id.*

would not necessarily exist without the financial support provided by pharmaceutical companies. These companies also guarantee that the promising compounds discovered in academia ultimately reach the market. A researcher may be happy enough to know that he achieved a great discovery and to publish a paper about it. Drug companies take his work to its final conclusion: a product to help patients. They bear the corresponding commercial risks, risks that neither universities nor governments would want to assume.

5.3.2.3. Disclosure of conflicts

Guidelines address conflicts of interest by recommending broad disclosure. For instance, the Helsinki Declaration calls for financial relationships to be disclosed, both to ethics committees and in journal publications.[971] Disclosure allows readers, regulators and the public at large to take financial ties into account when assessing the objectivity of the statements made by the researcher. It sends a warning signal that additional caution is in order. Disclosure of a potential conflict by no means implies that the statement (e.g., a published article, a submission to the REC) is necessarily biased; it is just a reminder of the necessity to critically analyze articles.[972]

Likewise, most medical journals now post statements about the affiliation and conflicts of interest of the authors of articles they publish.[973] Many publications go even further and ask that the role of the sponsor be systematically described.[974] Thus, one now encounters statements such as this one:

> Pfizer Inc participated in the completion of the study protocol based on input from study investigators, monitored the study, produced the statistical output, and assisted in the generation of the manuscript. Final approval of the manuscript content was provided by the principal author and *was not under the control of the sponsor*.[975]

---

971 *See* paragraphs 13 and 27 Helsinki Declaration. *See also* AAU (Conflict), *supra* note 938, at 5. The AAU recommendations also call for conflict disclosure during *oral presentation* of the research. *Id.*

972 *See, e.g.,* decision of the Geneva Court of Justice in the Rylander case, at 16 (ACJP/223/03), (Dec. 15, 2003), at http://www.prevention.ch/ryju151203.htm; *see also supra* note 940.

973 For example, one report of a randomized clinical trial of pediatric depression indicates: "Financial Disclosures: Dr Wagner has received research support from Abbott, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Organon, Pfizer, and Wyeth-Ayerst; has served as a National Institute of Mental Health consultant to Abbott, Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Novartis, Otsuka, Janssen, Pfizer, and UCB Pharma; and has participated in speaker's bureaus for Abbott, Eli Lilly, GlaxoSmithKline, Forest Laboratories, Pfizer, and Novartis. Dr Ambrosini has received honoraria and funds for clinical trials from Pfizer. Dr Rynn has been a consultant to Pfizer, PharmaStar, and Eli Lilly. Drs Wohlberg and Yang, as employees of Pfizer, hold stock options in the company. Dr Donnelly has been a consultant and speaker for Pfizer and has participated in speaker's bureaus for Eli Lilly and GlaxoSmithKline." *See* Karen Dineen Wagner et al., *Efficacy of Sertraline in the Treatment of Children and Adolescents With Major Depressive Disorder, Two Randomized Controlled Trials*, 290 JAMA 1033-1041, at 1040 (2003), at http://jama.ama-assn.org/cgi/reprint/290/8/1033.pdf.
See generally ICMJE, *supra* note 945, at II.D.1.

974 *See* ICMJE, *supra* note 945, at II.D.2.

975 K. D. Wagner et al., *supra* note 973, at 1040 (emphasis added). *See also* K. Squires et al., *supra* note 577, at 316 ("The funding source supported the collection and analysis of the data. The data were interpreted and the decision to submit the manuscript for publication was made in joint consultation between the funding source and the authors. The funding source placed no restrictions on the interpretation of the data or the content of the manuscript.").

Over the last couple of years, medical journals have expanded the scope of their disclosure requirements.[976] A 2004 proposal to broaden transparency advocate that the cost of research be systematically revealed.[977]

Journals also have had to monitor their requirements to disclose conflicts of interest, as authors are sometimes disinclined to comply spontaneously.[978] One study even found that, out of 70 reviews and letters published in medical journals in 1995 and 1996 regarding calcium channel antagonists for cardiovascular diseases, only two had stated conflicts of interest.[979] A 2004 study reported that 8% of all articles recently published in four leading journals failed to properly state conflicts of interest.[980] Furthermore, medical journals have to keep their own conflicts of interest in check. Journals derive substantial funds from advertising paid for by pharmaceutical companies. Displeasing their commercial clients by publishing articles adverse to their products may be detrimental to their finances.[981] Journals may also be intimidated by lawsuits from pharmaceutical firms following publication of articles critical of the latter's products.[982]

---

976 In August 2003, it was revealed that Nature Research Journals only had a narrow disclosure policy, which allowed authors to submit reviews without disclosing serious conflicts of interest. *See* Melody Petersen, *Undisclosed Financial Ties Prompt Reproval of Doctor*, N.Y. TIMES, Aug. 3, 2003, at 1.18. See the subsequent review of Nature's policy: Susan Mayor, *Nature group extends rules on disclosure to review authors*, 327 BMJ 829 (Oct. 11, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7419/829?etoc.

977 *See* Malcolm Potts, *A Modest Financial Proposal,* 18(2) THE SCIENTIST (Feb. 2, 2004), at http://www.the-scientist.com/yr2004/feb/opinion_040202.html ("Knowing the price tag of actual units of work funded by a variety of donors and conducted in a range of settings would be exceedingly useful.").

978 *See* Richard Smith, *Beyond conflict of interest, editorial*, 317 BMJ 291-92 (1998), at http://bmj.com/cgi/content/full/317/7154/291.

979 *See* Henry Thomas Stelfox et al., *Conflict of interest in the debate over calcium channel antagonists*, 338 N ENGL J MED 101-105, at 104 (1998), at http://content.nejm.org/cgi/reprint/338/2/101.pdf. According to this study, there is "a strong association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers." *Id.* at 101. *See also* ICMJE*, supra* note 945, at III.E. (requiring that writers of letters published by biomedical journals also disclose conflicts of interest). *See also* Susan Mayor, *supra* note 976, at 829 (where *Nature* had to broaden its disclosure rule following the publication of a controversial article by an author who, in conformity with *Nature*'s previous policies, had not disclosed his major conflict of interest).

980 *See* Merrill Goozner, *Unrevealed: Non-Disclosure of Conflicts of Interest in Four Leading Medical and Scientific Journals*, Integrity in Science, (July 12, 2004), at http://www.cspinet.org/new/pdf/unrevealed_final.pdf.

981 *See* Owen Dyer, *Journal rejects article after objections from marketing department*, 328 BMJ 328 (Jan. 31, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7434/244-b.

982 *See, e.g.,* Liza Gibson, *Drug company sues Spanish bulletin over fraud claim*, 328 BMJ 188 (Jan. 24, 2004), at http://bmj.bmjjournals.com/cgi/reprint/328/7433/188.pdf.

5.3.2.4. Conflicts of interest in the United States

5.3.2.4.1. Historical background

The first effort to restrain conflicts of interest in U.S. clinical trials dates back to 1989.[983] The National Institutes of Health (NIH) had wanted to introduce conflict-of-interest standards for its researchers.[984] Its initial draft was particularly strict as it deemed that an investigator in a clinical trial could not be doing consulting work for the same sponsor. The NIH guidelines received a "firestorm of protest." [985]. Researchers protested that such guidelines would stifle biomedical research given the important ties linking academia and the private sector. Their protests were successful in shelving the project.[986]

Even though this initial attempt to regulate financial conflicts of interest failed, the issue did not vanish. It resurfaced even more forcefully with the death of Jesse Gelsinger in September 1999, which spawned a flurry of initiatives on this very delicate subject.[987] Gelsinger was a 18-year old man who suffered from a mild form of a rare disease called ornithine transcarboxylase deficiency.[988] He had agreed to participate in an early phase clinical trial at the Institute for Human Gene Therapy at the prestigious University of Pennsylvania. One of the aspects that made his participation unusual was that in no case would he have derived personal therapeutic benefits from the trial.[989] The study's purpose was to find a treatment for the *pediatric* form of the disease.[990] Shortly after being administered the experimental gene through a virus vector, Gel-

---

983 *See* ARNO & FEIDEN, *supra* note 125, at 194-95. *See also* FDA, Financial Disclosure by Clinical Investigators, Guidance for Industry, (Mar. 20, 2001), at chapter IV.1, at http://www.fda.gov/oc/guidance/financialdis.html [hereinafter FDA (Financial Guidance)] (mentioning a June 1991 report by the IOG first identifying material weaknesses in the operation of the FDA due to lack of any mechanism to control conflicts of interest).

984 On the NIH's initiative and its historical background, see BRODY, *supra* note 447, at 69-73, 144 and 149.

985 *See* Drummond Rennie et al., *Conflicts of interest in the publication of science*, 266 JAMA 266 (July 10, 1991).

986 *See* BRODY, *supra* note 447, at 72-73.

987 *See* GAO (HHS), *supra* note 966, at 10; OIG, HHS, Protecting Human Research Subjects: Status of Recommendations, (Apr. 2000), at 18, at http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf [hereinafter OIG (Status)]. *See also* Henderson & Smith, *supra* note 938, at 451; Trudo Lemmens, *Contrôler les conflits d'intérêts dans le temple de la science*, 3 RAPPORT IDS 7-21 (2003).
Gelsinger's death was followed less than two years later (June 2001) by that of 24-year old Ellen Roche. Roche, a healthy volunteer, had participated in a clinical trial for an asthma study at John Hopkins University. An inquiry by the U.S. Office of Human Research Protections ("OHRP") detected several accounts of failure to abide by the legal requirements, including failure to abide by conflicts of interest rule involving IRB members. *See, e.g.,* letter of Edward Miller, CEO of John Hopkins University School of Medicine to Michael Carome, Director of OHRP, July 21, 2001, at http://www.hopkinsmedicine.org/press/2001/JULY/ActionPlanLetter.htm; Hopkins Internal Committee Report, *supra* note 378; Julian Savulescu, *Two deaths and two lessons: Is it time to review the structure and function of research ethics committees?*, 28 J. MED. ETHICS 1-2 (Feb. 2002), at http://jme.bmjjournals.com/cgi/content/full/28/1/1; Robert Steinbrook, *Protecting Research Subjects, The Crisis at John Hopkins*, 346 NEW. ENG. J. MED. 716-720 (Feb. 28, 2002), at http://content.nejm.org/cgi/content/full/346/9/716. See further on the Ellen Roche case *infra* note 3468.

988 Ornithine transcarboxylase deficiency – abbreviated OTCD or OTC – is a rare disease that, in its most serious form, causes the rapid death of affected babies. In its less severe form, it can be controlled by drugs and an adequate diet. *See* Rainsbury, *supra* note 352, at 592, n. 144.

989 *See id.* at 592-95.

990 See point 2 of the complaint filed by the U.S. law firm of "Silverstein, Kohl, Rose & Podolsky" [hereinafter abbreviated SSKR&P] in the case of Gelsinger v. the Trustees of the University of Pennsylvania, (2000) at http://www.sskrplaw.com/links/healthcare2.html. The lawsuit was settled in November 2000.

singer died of multiple organ failure.[991] It was later found that the investigator, James Wilson, had not strictly followed all procedural requirements.[992]

The most serious issue, however, was the pervasive context of conflicts of interest. Both the investigator, James Wilson, and the University had an equity stake in Genevo, a private biotech company founded by Wilson, which (indirectly) financed the trial.[993] If the trial had yielded positive results, the value of the company's stock would have soared for the benefit of its investors.

5.3.2.4.2. FDA regulation on conflicts of interest

In 1998 the FDA adopted its own rules on conflicts of interest.[994] FDA rules apply to clinical trials submitted to secure marketing approval.[995] Before reviewing any marketing application, the FDA requires that the sponsor-applicant[996] disclose any significant amount of money given or promised to any of its investigators.[997] Similarly, investigators are obliged to provide this information to the sponsor. Disclosure requirements extend to the spouse and the children of the investigator.[998] They apply to (U.S. or non-U.S.) investigators carrying out clinical trials outside the U.S. if the study results are submitted to the FDA.[999] However, they do not apply to the investigator's institution,[1000] an omission which introduces a loophole in the regulation.[1001]

The distinct feature of FDA regulations is that they apply (directly) only to sponsors and only once the clinical trial has been completed and submitted to the agency.[1002]

---

991 *Id.*

992 *See* Rainsbury, *supra* note 352, at 593, n.152.

993 The University of Pennsylvania's Institute for Gene Therapy was conducting the study. Dr. Wilson was the head of the Institute. He owned a private company, Genovo Inc., which held the rights to all discoveries made by him at the Institute. In particular, Genovo had a financial stake in the virus vector used in the study. Genovo had an agreement with Biogen, which had paid $37 million to be shared with the Institute (27% of the Institute's budget). *See also* Henderson & Smith, *supra* note 938, at 454.

994 The rules became effective on February 1999. *See* FDA (Financial Guidance), *supra* note 983, at chapter I. *See also* Henderson & Smith, *supra* note 938, at 450.

995 *See* 21 C.F.R. § 54.2(e) (for a definition of the clinical studies covered). *See also* FDA (Financial Guidance), *supra* note 983, at chapter II and chapter IV.8, 13, 21, 23.
As mentioned in subsection 2.3.2., the rules enacted by the FDA differ from the HHS rules applicable to institutions receiving federal funding. Both sets of rules can be concurrently applicable if the clinical trial is to be submitted in the application package to the FDA and if the investigator is receiving federal funding. *See* GAO (HHS), *supra* note 966, at 5, 7, 8. *See* 21 C.F.R. 54.1(b). *See also* Henderson & Smith, *supra* note 938, at 447 and 450.
U.S. clinical trials outside the purview of the NIH or the FDA (i.e., studies that are not funded by federal dollars and which are not submitted for review to the FDA) may escape oversight with respect to financial conflict of interest. *See* GAO (HHS), *supra* note 966, at 9.

996 For a definition, see 21 C.F.R. § 54.2(g)&(h); FDA (Financial Guidance), *supra* note 983, at chapter IV.7-10 & 22.

997 *See* 21 C.F.R. § 54.2(g) and § 54.3; 21 C.F.R. § 312.64(d) and § 312.53(c)(4); FDA (Financial Guidance), *supra* note 983, at chapter IV.12 (defining investigators so as to exclude "hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data"). *See also id.* at chapter IV.13.

998 *See* 21 C.F.R. § 54.2(d). *See* FDA (Financial Guidance), *supra* note 983, at chapter II.

999 *See* FDA (Financial Guidance), *supra* note 983, at chapter IV.20.

1000 *See id.* at chapter IV.25. *See also* Henderson & Smith, *supra* note 938, at 446.

1001 *See* M. M. E. Johns, *supra* note 958, at 742.

1002 *See* Task Force on Financial Conflicts of Interest in Clinical Research, Association of American Medical Colleges ("AAMC"), Protecting Subjects, Preserving Trust, Promoting Progress, Policy and Guidelines, at 5-6

This is explained by the priority traditionally given by the FDA to *reliable study results*, over subject protection.[1003] Nevertheless, the sponsor is advised to start gathering the required financial information at the beginning of the trial.[1004]

According to FDA rules, any compensation (e.g., payments, royalties) dependent upon the (positive) results of the trial must be disclosed,[1005] such compensation being viewed with suspicion.[1006] The disclosure threshold for *equity* interest in a publicly traded company is set at $50,000.[1007] All significant payments or benefits must also be disclosed. The numerical threshold for mandatory notification is $25,000 calculated from the beginning of the study until one year after its end.[1008] Payments can include honorarium or consulting fees offered to the investigators for an activity outside the clinical trial itself. Benefits can be gifts of medical equipment. Excessive hospitality, even in the course of the clinical trial, must also be taken into account to evaluate the threshold.[1009] For example, inviting the investigator for a one-week stay in a luxurious island resort, allegedly to allow her to make a scientific presentation to potential sub-investigators, would fall under the reportable benefits.

In addition,

> The payments include fees provided to investigators for reviewing promotional material, the value of travel to medical conferences, training courses, and associated honoraria. The payments may be made directly to the investigator, the investigator's professional corporation, a research foundation, or the institution where the research is conducted.[1010]

The disclosure statement must describe in detail the equity participation or payment of concern.[1011] Measures taken to minimize the risk of conflict must be explained

---

(Dec. 2001), at http://www.aamc.org/members/coitf/firstreport.pdf [hereinafter AAMC (I)]; GAO (HHS), *supra* note 966, at 5.

1003 *See* GAO (HHS), *supra* note 966, at 23.

1004 *See* FDA (Financial Guidance), *supra* note 983, at chapter IV.6 ("By collecting the information prior to study start, the sponsor will be aware of any potential problems, can consult with the agency early on, and take steps to minimize the potential for bias.").

1005 *See* 21 C.F.R. § 54.2(a). *See* FDA (Financial Guidance), *supra* note 983, at chapter II.2.A&B.

1006 *See* HHS Interim Guidance, *supra* note 938, at chapter 2.1.

1007 *See* 21 C.F.R. § 54.2(b). *See* FDA (Financial Guidance), *supra* note 983, at chapter II.2.D. According to FDA rules, if the equity stake is in a company which is not publicly traded and the value of the participation cannot be readily assessed, the entire participation must be reported, regardless of any threshold. *Id.* at chapter II.2.C.

1008 *See* 21 C.F.R. § 54.2(f). This threshold does not include the costs of carrying out the clinical trial for the sponsor.
The FDA thresholds are higher than those of the Department of Health and Human Services (HHS). The HHS regulation "defines a 'significant conflict of interest' as including income of an investigator or investigator's spouse or dependent child expected to exceed $10,000 over 12 months, or equity interests exceeding $10,000 or 5 percent ownership of a company." *See* GAO (HHS), *supra* note 966, at 8.

1009 *See* FDA (Financial Guidance), *supra* note 983, at chapter IV.26.

1010 Barry Sall, *Clinical trials, Complying With FDA's Financial Disclosure Regulation*, (Jan. 2000), at http://www.devicelink.com/mddi/archive/00/01/014.html. Also 21 C.F.R. § 54.

1011 *See* FDA (Financial Guidance), *supra* note 983, at chapter IV.16.

(e.g., ownership of the stock through a separate trust).[1012] The statement must be updated whenever there are significant changes in the value of the participation.[1013]

As mentioned above, the reporting obligations continue throughout the study and end only one year after its completion.[1014] If there is nothing to disclose (i.e., there are no conflicts of interest), the sponsor-applicant must still file a certification statement.[1015] Sponsors that fail to comply with FDA rules face delay in the processing of their marketing applications until the information is submitted.[1016] If a sponsor is honestly unable to comply with the reporting requirement (e.g., the foreign investigator is not providing the required information[1017]), it must explain to the FDA which (vain) efforts were undertaken to obtain the information. In other words, it must prove that it proceeded with due diligence, but was nonetheless unable to get all the necessary information.[1018]

Furthermore, the FDA can assess the disclosure statement to determine how problematic the conflict is.[1019] Where the conflict is held to have an impact on the reliability of the data, the FDA can choose between various measures. In the worst-case-scenario for the sponsor, the FDA refuses to take into account the results of the suspicious clinical trial;[1020] the sponsor then has to begin the trial anew. Financial interests may also be disclosed to the public in the course of advisory committees meetings.[1021] In less serious cases, the FDA may conduct audits of the dubious clinical data.[1022]

In addition to the 1998 FDA regulations, the HHS has prepared its own draft guidance to help institutional review boards ("IRBs") assess financial conflicts of interest.[1023] Under this Guidance, IRBs are asked to verify that sponsors and investigators are taking steps to either eliminate or, when elimination is not possible, minimize conflict of interest situations.

This HHS Guidance also obliges institutions where clinical research is conducted to review conflict of interest information pertaining to IRB members.[1024] Institutions should educate both investigators and IRB members on conflicts issues.[1025] Institutions should also make sure that they manage conflicts at their own levels.[1026] For example, a

---

1012 *See id.* at chapter IV.28.

1013 See for more details FDA (Financial Guidance), *supra* note 983, at chapter IV.17. The fact that the sponsor-applicant must only submit the information with its marketing application eliminates the burden of regular updates.

1014 *See id.* at chapter IV.15 (pointing out that "anticipation of payments may be as influential as payments already received").

1015 *See id.* at chapters II and IV.2. Certifications are filed using FDA Form 3454 (at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3454.pdf). Disclosure statements are filed using FDA Form 3455 (at http://www.fda.gov/opacom/morchoices/fdaforms/FDA-3455.pdf).

1016 *See* FDA (Financial Guidance), *supra* note 983, at chapter I.

1017 *Id.* at chapter IV.20.

1018 *Id.* at chapter IV.2 & 3.

1019 *Id.* at chapter II.

1020 *Id* at chapters II and IV.27.

1021 Such disclosure to the public should however be a rare occurrence. *Id.* at chapter IV.29.

1022 *Id,* at chapter II.

1023 *See* HHS Interim Guidance, *supra* note 938, at chapter 3.

1024 *See id.* at chapter 1.4.

1025 *See id.* at chapter 1.5.

1026 *See id.* at chapter 1.6.

sponsor's promise to fund a university chair carries risks of undue influence if the funds are in any way tied to specific clinical projects. Similarly, it may be the institution, and not the individual investigator, that owns an equity interest in the company sponsoring a clinical trial.[1027] Under the Guidance, institutions are told to establish special independent oversight committees to assess and manage their own conflicts of interest.[1028]

5.3.2.4.3. Changes in academic research institutions

The Gelsinger public relation disaster showed U.S. universities that even the *appearance* of a conflict of interests is unacceptable if nothing is done to manage and mitigate the perceived risk.[1029] Perceived conflicts erode public trust in research and may lessen the willingness of research subjects to participate in clinical studies.[1030]

Beginning around 1995,[1031] American institutions started implementing a range of policies.[1032] These policies often extend beyond the minimal regulatory requirements set by the FDA or the HHS.[1033]

Universities are advised to *segregate* responsibilities for technology licensing, fundraising, endowments, from those pertaining to clinical trial oversight (the "firewall" method).[1034] Thus, the perspective of patent licensing royalties or donations from industry sponsors does not cloud the judgments of those involved in clinical trials.

Universities are dissuaded from holding *equity interests* in firms which would be set to gain directly if the product studied in the clinical trial were to be found efficacious.[1035] One thinks of equity stake held in a start-up holding the patent for the studied compound.[1036] Some universities impose a rebuttable presumption that clinical trials

---

1027 *See id.* at chapter 1.6.

1028 *See id.* at chapter 1.7.

1029 *See* AAMC (I), *supra* note 1002, at 4. For how risks should be minimized, see for instance *id.* at 9.

1030 *See, e.g.,* David Korn, *Conflicts of interest in Biomedical Research*, 284 JAMA 2234, at 2236 (Nov. 1, 2000), at http://jama.ama-assn.org/cgi/reprint/284/17/2234.pdf; MRC, *supra* note 938, at 7.

1031 *See* 42 C.F.R.§ 50 enacted in 1995 and applicable to federally funded research.

1032 For a list of initiatives regarding financial conflicts of interest, see footnote 6 to the HHS Notice, accompanying the draft Guidance on Financial Relationships and Interests in Research Involving Human Subjects, 68 Fed. Reg. 15,458, at http://www.nacua.org/documents/Financial_Relatnshps_and_Interests_in_Resrch.htm.

1033 "[M]ore than 70 percent of the 89 respondents [among the top 100 NIH-funded research institutions] had written policies that were more extensive than the federal regulation." GAO (HHS), *supra* note 966, at 11 (citing to a 2000 study by Mildred Cho).

1034 *See, e.g.,* Association of American Medical Colleges ("AAMC"), Task Force on Financial Conflicts of Interest in Clinical Research, Protecting Subjects, Preserving Trust, Promoting Progress II, Principles and Recommendations, at 3 (Oct. 2002), at http://www.aamc.org/members/coitf/2002coireport.pdf [hereinafter AAMC (II)]; GAO (HHS), *supra* note 966, at 18; OIG (Reform), *supra* note 877, at 7 ("We found several examples of hospital IRBs that are housed in offices of grants and contracts or in clinical research programs, the very offices geared to bringing in research dollars. Such organizational placements, while not necessarily representing a conflict, certainly can accentuate pressures on IRBs to accommodate institutional financial interests.").

1035 When such a conflict of interest occurs (equity participation in a publicly or non-publicly traded company, "the institution should conduct a specific, fact-driven inquiry into whether the particular financial relationship may affect or reasonably appear to affect human subjects research conducted at or under the auspices of the institution." AAMC (I), *supra* note 1002, at 6.

1036 *Id.* at 6.

should not be conducted by individuals who hold "significant financial interest" in the ongoing trials.[1037]

When a conflict of interest has been identified, there are three possible responses.

A first response is to *disclose* its existence. A majority of commentators considers that disclosure should specifically include research subjects.[1038] This allows subjects to decide knowingly whether to enroll. Without this information, subjects cannot make an informed choice. Failure to inform patients may have liability consequences for the investigator, and possibly for other parties involved in the research.[1039] PhRMA, the trade association of large U.S. pharmaceutical companies, recommends that investigators reveal to subjects the existence of payments related to the clinical trials. This PhRMA recommendation could have been more explicit by describing the types of payments to be disclosed.[1040]

A second option is to *put an end* to the financial relationship, for example, by selling the equity participation or by relinquishing any consulting work. Divesture is evidently not the investigator's preferred choice.[1041] For instance, the University of Chicago forbids payment by sponsors of "special incentives, bonuses or other similar forms of compensation provided to institutions or investigators as a mechanism for enrolling subjects in research, including clinical trials."[1042] This policy bans, *inter alia*, payment rates that vary according to the number of subjects enrolled, finders' or referral fees, milestones payments for retention of subjects, and bonuses for timely or early IRB approval. Also not permitted are "extra-contractual benefits such as unrestricted research gifts, medical or office equipment, authorship rights, journal subscriptions, educational stipends, payment of conference fees, personal gifts, favors or similar inducements provided in exchange for enrolling human subjects."[1043]

The third and middle-ground approach consists in *monitoring* conflicts of interest. Monitoring can be carried out by *ad hoc* committees that oversee the clinical study and

---

1037 AAMC (II), *supra* note 1034, at 7. The presumption can be rebutted by compelling circumstances.

1038 *See* GAO (HHS), *supra* note 966, at 15.
In the European Union, see E.U. Guidance (Ethics Committee), *supra* note 270, at 22.

1039 *See, e.g.*, the complaint filed by the U.S. law firm of SSKR&P in the case of Wright v. The Fred Hutchinson Cancer Research Center, (Mar. 2001), at http://www.sskrplaw.com/gene/wright/complaint1.html.

1040 PhRMA's recommendation reads: "Clinical investigators are encouraged to disclose to potential research participants during the informed consent process that the investigator and/or the institution is receiving payments for the conduct of the clinical trial." PhRMA (Principles on Clinical Trials), *supra* note 902, at 10.

1041 "Of 111 investigators at four of the universities we visited who had significant relationships with industry in 2000, only 3 voluntarily divested their interests; none were told to divest by their universities. Some investigators with significant financial interests may decide not to be involved in conducting the study, but if they are the only ones with a key skill or knowledge for a particular study, they may still want to play a role." GAO (HHS), *supra* note 966, at 16.

1042 University of Chicago, Policy Prohibiting Use of Enrollment Incentives in Human Subjects Research, (Mar, 6, 2002), at http://www.washington.edu/research/osp/enrollment.html. Enrollment incentives are defined as "any form of direct or indirect inducement offered or received in exchange for enrolling subjects in human subjects research: (i) that is paid as reimbursement in excess of the reasonable cost of utilizing human subjects, or (ii) that is paid extra-contractually, including any bonus, reward, award, grant, gift, benefit, or other quid pro quo, or (iii) that creates a financial incentive that the University determines is contrary to the best interests of human subjects participating in the research."

1043 *Id.*

the investigator's activities.[1044] This system relies heavily on spontaneous compliance by the investigators and research personnel as well as education by institutions.[1045] For example, Stanford University appoints independent oversight committees to protect the integrity of the research and the safety of the subjects.[1046]

Results obtained thus far in university centers are far from perfect. A 2000 report found that ethics committees are still confronted by situations of conflict of interests.[1047] Another 2000 survey of leading U.S. medical schools found significant variation among the policies implemented.[1048] Not all schools required disclosure of gifts and loans.[1049] Research staff was often not subject to disclosure requirements.[1050] Out of ten universities, only six called for disclosure of conflicts to Institutional Review Boards ("IRBs").[1051] Research subjects were informed in only two schools,[1052] which is blatantly inadequate![1053] Six schools had banned investigators from holding any stock or stock options in a company having an interest in the clinical trial.[1054] The study authors concluded that medical schools should introduce more severe and homogeneous conflict-of-interests rules.[1055] Another study observed that "universities generally allowed investigators to self-certify compliance with financial conflict-of-interest policies." [1056] It also found that universities were not very systematic in the way they collected and stored information about conflicts.[1057] The conclusion of an OIG study should ring the alarm

---

1044 "For example, at one university, a subcommittee of the medical school conflict-of-interest committee develops a "monitoring plan" for each case, outlining the composition, appointment, and responsibilities of the monitoring committee. … Conversely, monitoring can be informal and involve, for instance, an investigator designing a personal 'self-management' monitoring plan that satisfies the university's requirement for managing the financial conflict of interest." GAO (HHS), *supra* note 966, at 15.

1045 *See id.* at 16.

1046 *See* Stanford (Faculty Policy), *supra* note 938, at chapter 7, p.10-11. Researchers must also submit yearly reports stating all interests that could create a conflict with the interests of research subjects. *Id.* at 11. *See also* Stanford University School of Medicine, Annual Certification of Compliance, at http://www-med.stanford.edu/conflict/Annual_COI_Disclosure_01-02.pdf and http://med.stanford.edu/conflict/documents/ad_hoc_disclosure_form.doc.

1047 "There has been no progress in insulating IRBs from conflicts that can compromise their mission in protecting human subjects." OIG (Status), *supra* note 987, at 3 and also at 15.

1048 *See* Bernard Lo et al., *Conflict-of-Interest Policies for Investigators in Clinical Trials*, 343 NEW. ENG. J. MED. 1616-1620, at 1618, (Nov. 30, 2000), at http://content.nejm.org/cgi/content/full/343/22/1616.

1049 *Id.* at 1617.

1050 "Four policies applied to all research staff, and three other policies applied to selected research staff, generally those with 'responsibility for the design, conduct, and reporting' of research. Only four policies applied to trainees." *Id.* at 1617.

1051 *Id.* at 1617. In certain institutions, a committee distinct from the IRB is given primary responsibility for reviewing conflict of interest notifications. *See, e.g.,* AAU (Conflict), *supra* note 938, at 6.

1052 *Id.* at 1617. *See also* OIG (Sample Guidelines), *supra* note 945, at 9.

1053 *See* AAU (Conflict), *supra* note 938, at 4 (recommending that research subjects be always informed of financial conflict of interest). *See also* ICMJE, *supra* note 945, at II.D.1. ("Investigators must disclose potential conflicts to study participants and should state in the manuscript whether they have done so.").

1054 The scope of the ban varied. *See* Lo et al., *supra* note 1048, at 1618.

1055 *Id.* at 1619.

1056 *See* GAO (HHS), *supra* note 966, at 11, and also at 12.

1057 "Administrative data used to oversee investigators' research activities and financial relationships at all five universities were kept in various offices and in different databases. The universities generally acknowledged a need for better coordination, and several of the universities told us they were taking steps to develop these linkages." *Id.* at 11 and also at 17.

bell: "75 percent of [respondent] IRBs … do not review any financial arrangements between sponsors and investigators."[1058]

5.3.2.5. Conflicts of interest in Switzerland

Switzerland has just begun to tackle the issue of conflicts of interest in general, and financial disclosure in particular.[1059] A deeply ingrained Swiss tradition is to stay "mum" on money-related topics.

5.3.2.5.1. Provisions of the LPTh and the OClin

The former 1995 IOCM Regulation on clinical trials was silent as to conflicts of interest. The OClin is not much more explicit.[1060] It only prescribes that the authorities (i.e., Swissmedic and ethics committees) must receive and peruse the agreements binding the investigator to the sponsor.[1061] However, the words "conflicts of interest" are nowhere to be found. It is unfortunate that the OClin does not order investigators as well as their institutions to report *all* potential conflicts of interest.

The silence of the OClin has not prevented the Swiss Office for Social Insurance from interpreting Article 33 LPTh so as to encompass many different kinds of conflict of interest.[1062] While this provision appears to have a narrow scope – it belongs to the short section of the LPTh pertaining to advertising –, it is now used to fill the gaps in the Swiss regulatory system. The provision restricts the material benefits ("*avantages matériels,*" "*geldwerte Vorteile,*" "*vantaggi pecuniari*") that can be offered to and accepted by physicians. Only benefits of modest value are tolerated, provided however that they entertain some relation with the practice of medicine (e.g., a medical book is acceptable).[1063] The German and Italian texts only refer to benefits connected to the prescription of drugs, while the French text makes no mention of such a relationship.

1058 *See* OIG (Recruiting), *supra* note 815, at 26.

1059 *See* Kleist (Abhängigkeit), *supra* note 800, at 2346; ASSM Bulletin 3/2000 (Sept. 2000) and 1/2001 (Feb. 2001), http://www.samw.ch/content/bulletin/f_Bulletin3_2000.html and http://www.samw.ch/content/bulletin/f_Bulletin1_2001.html.

1060 E.U. regulations are not much more detailed. They contain only general information about financial conflicts of interest. Investigators must inform their REC of any economic interest that could affect their impartiality. Subjects must receive written information about "any financial or other ties [of the investigator] to the sponsor … as well as the name and address of sponsor/sources of funding." *See* Article 6.3(j) Directive 2001/20/EC. *See* E.U. Guidance (Ethics Committee), *supra* note 270, at 8 and 22.

1061 Article 10.2m&n OClin and Article 14.1.c OClin; *see also* subsection 7.1.2.5.7. below.

1062 According to Article 33 LPTh:

> "It shall be prohibited to grant, offer or promise material benefits to persons who prescribe or supply medicinal products or to the organizations which employ them.
> It shall be prohibited for persons who prescribe or supply medicinal products as well as for the organizations who employ them, to solicit or accept material benefits.
> However, the following shall be permitted:
> a. material benefits of modest value and which are related to medical or pharmaceutical practice;
> b. commercially and economically justified discounts which directly reflect on the price."

Swissmedic's unofficial translation, *supra* note 7.
Compare in the European Union with Articles 94 and 95 of Directive 2001/83/EC.

1063 Article 33.3.a LPTh. In addition, the type of benefit must have some connection with the practice of medicine. Thus, scientific books would constitute acceptable gifts, while a watch would not.

Though there is no close connection between clinical trials and drug advertising or the drug prescription decision, the Office for Social Insurance holds that Article 33 LPTh applies to clinical trials.[1064] According to the Office's recommendation, this provision limits the sponsor's freedom to set the remuneration paid to the investigator. Breach of Article 33 LPTh by either or both party is punishable by criminal fines or arrest. Sponsors and investigators must therefore be careful in how they structure their financial relationship.

Even though neither the LPTh nor the Office's recommendation offers any clear indication as to what is permissible and what is not,[1065] the parties should take into consideration the purpose behind Article 33 LPTh, which is to limit conflicts of interest that could lead to irrational prescribing. Unreasonable prescribing would occur if the physician's prescription decision is not based on the patient/subject's best interest, but takes into account the commercial interests of the sponsor. Thus, a phase IV study whose key purpose would be to convince physicians to prescribe the sponsor's newly approved and expensive drug would run afoul of Article 33 LPTh. The provision also prohibits tying an appointment as investigator to the purchase of the sponsor's drugs by the investigator herself or her institution.[1066]

On the other hand, Article 33 LPTh would not prohibit the investigator from holding equity in a firm sponsoring phase I to III trials.[1067] While such a prohibition could rightfully be set by ethics commission as part of their assessment of protocols, Article 33 LPTh does not constitute a sufficient legal basis for such a ban.

1064 The Office's position is not necessary widely shared. *See* Kleist (Abhängigkeit), *supra* note 800, at 2346.

1065 Based on Article 33 LPTh, the Federal Office for Social Insurance has issued detailed recommendations pertaining mostly to rebates on drug purchases. *See Recommandation concernant la promesse, l'acceptation et l'offre d'avantages matériels liés à des médicaments; obligation de répercuter les avantages obtenus*, (Dec. 21, 2001) at http://www.assurancessociales.admin.ch/storage/documents/799/799_1_fr.doc; *Recommandation concernant la répercussion des rabais obtenus dans le domaine hospitalier lors de l'achat de médicaments prêts à l'emploi*, (Mar. 15, 2002), at http://www.assurancessociales.admin.ch/storage/documents/803/803_1_fr.doc*; Recommandation concernant la répercussion des avantages obtenus dans le secteur ambulatoire lors de l'achat de médicaments prêts à l'emploi*, (July 11, 2002), at http://www.assurancessociales.admin.ch/storage/documents/806/806_1_fr.doc; *Recommandation portant sur les avantages matériels dans le domaine de la formation post-graduée et continue* (Dec.20, 2002), at http://www.assurancessociales.admin.ch/storage/documents/808/808_1_fr.doc.
So far, it has not prepared similar guidelines in the area of clinical trials. Swissmedic adopted in December 2003 its own policy on Article 33 LPTh; once again, clinical trials are not directly affected. *See* Swissmedic, *L'admissibilité des rabais dans le cadre de l'article 33 alinéa 3, lettre b de la Loi sur les produits thérapeutiques,* [Acceptability of rebates in the context of Article 33.3 LPTh] (Dec. 6, 2003), at http://www.newsmaker.ch/upload/customers/swissmedic/Publication_l_admissibilité_des_rabais_dans_le_cadre_de_l_article_33.pdf.

1066 *See, e.g.,* Lüscher, *supra* note 943, at 2143.

1067 The situation might be different for phase IV trials since, by that stage, the drug has become a commercial product for which a market exists. Article 33 LPTh can apply to a phase IV trial that aims to advertise the drug.

5.3.2.5.2. Policies of the Geneva University

It is not easy to identify the official policy of the University of Geneva on conflicts of interest.[1068] The University has no official public position set forth in regulations. The 2001 Rylander[1069] and the 2003 NovImmune[1070] affairs may prompt the University of Geneva to adopt more comprehensive policies. For the time being, at least three university institutions have some jurisdiction over conflicts of interest.

Unitec, the Unversity's office of technology transfer, receives most agreements whereby a researcher collaborates with a private entity to develop the former's invention. Unitec takes this opportunity to make sure that possible conflicts of interest between the two parties are recognized and managed. It has three different forms at its disposal to achieve this objective.[1071] These forms are not currently published. The most commonly used form seeks to raise awareness among university researchers of problems raised by conflicts of interest.[1072] The professor signing the form agrees to several obligations, with respect to his position occupied in the private company, time devoted to the company, contracts signed between the company and the university, intellectual property transfer, use of university resources, confidentiality, recordkeeping. It is a unilateral declaration, and not a bilateral contract. There are no explicit sanctions against a professor who runs afoul of these undertakings. The University Rector is entitled to grant exemptions or approve "higher risk" activities; for example, agreements directly between the private company and the University of Geneva require his prior approval.

1068 See Articles 7 to 8 of the Geneva Law on the University, of May 26, 1973, C 1 30, at http://www.geneve.ch/legislation/rsg/f/rsg_c1_30.html. *See also* more generally points 2.5. and 2.6 of the University (unpublished) Guideline D-10-10-05 titled "*Signatures et compétence d'engager l'Université*"; 2001 Rylander-University Report, *supra* note 940, at chapters 1.3 to 1.7.

1069 *See* notes 940 and 972 above.

1070 On this topic, see the detailed report of the Geneva Parliament's Management Control Commission [Commission de contrôle de gestion], (Oct. 6, 2003) (P 1420-A), at http://www.geneve.ch/grandconseil/data/texte/P01420A.pdf.

1071 The first form is titled "Employee's Statement of Economic Interests in Potential Licensees or Partners in a Collaboration." It asks that employees inform Unitec of ownership interest exceeding CHF 15,000.- in share value or 5% of the relevant company's capital. The researcher must also inform Unitec if he receives payments of more than CHF 5,000 from a single private source. However, this form is not systematically used. All university researchers are not asked to complete it; only those who are in contact with Unitec may be asked to sign it.
The second form is titled "*Engagement personnel*" as (co-founder) of a private company; it is not commonly used either because it mainly concerns the rare occurrence of researchers about to leave the university for a private company.
The third form is discussed in more details below.
These three forms are inspired from similar documents prepared by the Ecole polytechnique fédérale de Lausanne (EPFL).
Moreover, the Unitec's website contains this statement: "Contact Unitec before taking a financial interest in a company with which you collaborate. Unitec will advise you so that you avoid difficult conflict of interest situation." In the original French version "*Contactez Unitec avant de prendre un intérêt financier dans une société avec laquelle vous collaborez. Unitec vous conseillera afin d'éviter de vous trouver dans une situation de conflits d'intérêts difficile à gérer.*" Unitec, Conseils aux chercheurs [Advice to researchers], at http://www.unige.ch/unitec/ressources.html.

1072 This third form is titled "*Engagement personnel pris en qualité de professeur de l'Université de Genève engagé à temps complet et ayant des intérêts financiers ou des responsabilités dans une entreprise privée*" [Personal undertaking as a full-time university professor having financial interests or responsibility in a private company]. As this title indicates, this form addresses both financial and non-financial conflicts of interest. Hence, a researcher with no financial stakes in a private company may nonetheless be asked to sign the form.

Unfortunately, it has been decided that agreements between a researcher-investigator and a pharmaceutical company-sponsor pertaining to the conduct of clinical trials do *not* fall within the purview of Unitec. This important aspect of the relationship between the industry and university physicians is thus not covered by Unitec's policy documents.

Furthermore, in 2003, the University of Geneva set up two commissions whose work involves conflicts of interest.[1073] The ethics commission verifies that University activities conform to the general ethical objectives stated in the first chapter of the Geneva Law on the University. The academic freedom commission reviews agreements between the University and the private sector. However, it is not yet known how these two commissions will split up the work between them and Unitec.[1074] They have not yet taken any official stance on conflicts of interest.

5.3.2.5.3. SAMS policies

The Swiss Academy of Medical Sciences (SAMS) issued in 2002 two sets of recommendations touching upon the issue of conflicts of interest.[1075] Many of these recommendations go beyond the principles now stated in the law. For instance, the Academy asks that investigators seek prior *authorization* from their institution if they have any financial interest that could conflict with the conduct of the trial.[1076] Agreements between investigators and sponsors must contain an obligation to publish or disclose the results of the trial.[1077] The sponsor's level of control over research data must be disclosed.[1078] The institution with which the investigator is affiliated must co-sign the agreement between the investigator and the sponsor.[1079] Publications as well as other public disclosures in medical settings (e.g., presentations at medical conferences) must spell out funding sources.[1080]

All the money paid by the sponsor in relation to a clinical trial must be placed in a separate bank account under the control of the investigator's institution.[1081] The institu-

---

1073 *See* Articles 3, 7, 8, and particularly 78 and 79 of the Geneva Law on the University. *See also* the two corresponding webpages: http://www.unige.ch/conseil-uni/COMETH.html and http://www.unige.ch/conseil-uni/COLIB.html.

1074 *See* E-mail of Prof. Robert Roth (member of the University of Geneva's ethics commission), (June 11, 2004) (on file with author).

1075 *See* Swiss Academy of Medical Sciences, Collaboration between the medical profession and the industry, Recommendations, (Sept. 9, 2002), section I., at http://www.samw.ch/content/Dokumente/e_EmpfAeI.pdf [hereinafter SAMS (Collaboration)].
See also SAMS, Integrity in Science, Guidelines of the SAMS for scientific integrity in medical and biomedical research and for the procedures to be followed in cases of misconduct (June 2002), at http://www.smw.ch/pdf200x/2003/03/smw-10145.PDF [hereinafter SAMS (Integrity)]. *See also* Ewald R. Weibel, *Loyauté et honnêteté pour la science*, 2 BULLETIN ASSM (May 2002), at http://www.samw.ch/content/Bulletin/f_bulletin2_2002.pdf.

1076 *See* SAMS (Collaboration), *supra* note 1075, at point I.4.

1077 *Id.* at point I.5.

1078 *See* SAMS (Integrity), *supra* note 1075, at 2.2.

1079 *See* SAMS (Collaboration), *supra* note 1075, at point I.5. According to Lüscher, all payments by the sponsor should be wired to the institution's bank account (as opposed to that of the investigator); these accounts should be audited. *See* Lüscher, *supra* note 943, at 2143.

1080 *See* SAMS (Collaboration), *supra* note 1075, at point I.8.

1081 *Id.* at point I.6.

tion must ensure that the decision to buy drugs from a pharmaceutical company remains wholly independent from the decision to conduct a clinical trial on behalf of the sponsor.[1082] Investigators are barred from participating in the sponsor's marketing efforts.[1083] It is unclear to which extent these recommendations have been taken into account by Swiss medical institutions conducting clinical trials.

5.3.3. Conflicts of interest pertaining to confidentiality requests

5.3.3.1. The Olivieri case

Public confidence in clinical research was shaken when a shocking tale of conflicts of interest surfaced in Canada. The case of Dr. Nancy Olivieri is an enlightening illustration of conflicts over the publication of study results.[1084] The investigator, Olivieri, intended to publish her *negative* findings about the investigational drug deferiprone in a medical journal. Apotex, the commercial sponsor of the clinical trial, tried to stop her. Apotex invoked a confidentiality clause that pertained to an agreement governing a *previous* clinical trial. Olivieri's institutions, the University of Toronto and the Hospital for Sick Children, utterly failed to support her. They were certainly swayed by the prospect of a multi-million donation by Apotex.[1085]

An independent review panel reached the conclusion that Dr. Olivieri had behaved properly while the University, the medical hospital and Apotex clearly had not. The panel issued several important recommendations. First, *confidentiality clauses* in agreements between sponsors and investigators should in no way limit the academic freedom of investigators, and in particular the right to disclose adverse findings.[1086] Ethics committees should control the agreements and forbid such confidentiality provisions.[1087] Academic research centers should actively disallow such restrictions.[1088] The panel stressed "the importance to the public interest that universities and their affiliated teaching hospitals act robustly to protect academic freedom, bringing to bear the full weight of their resources in cases where large private corporations attempt to infringe academic freedom."[1089]

1082 *Id.* at point I.7.

1083 *Id.* at point I.10.

1084 *See* Jon Thompson et al., Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc., (Oct.2001), at http://www.caut.ca/en/issues/academicfreedom/OlivierInquiryReport.pdf [hereinafter Olivieri Report].

1085 *Id.* at 23 and 29.

1086 "As invoked in this case by Apotex [the commercial sponsor], such confidentiality clauses offend public policy." *Id.* at 25, and also at 40.

1087 *Id.* at 18, and also at 42.

1088 *Id.* at 18.

1089 *Id.* at 36.

5.3.3.2. Confidentiality clauses

Pharmaceutical companies tend to consider that every piece of information pertaining to clinical trials is confidential.[1090] A survey found that clinical trials performed in academic settings for commercial sponsors had confidentiality clauses lasting an average of five years.[1091] Documents communicated by the sponsor to the investigator (e.g., the protocol, the brochure) are often marked as "confidential." [1092]

In one U.S. court case, Roche argued that correspondence between itself and an investigator constituted confidential information and a trade secret because it revealed "how one company went about successfully conducting a clinical study to obtain quick FDA approval."[1093] The Court disagreed with Roche's characterization, finding instead that the method of conducting trials, supposing it even existed, was "generally known in the medical profession."[1094] As a result, the investigator was eventually allowed to disclose her documents concerning the clinical trial.[1095]

Possible disputes between sponsors and investigators about the *publication of findings* should be forestalled by embracing appropriate policies in the agreement between the sponsor and the investigator.[1096] The agreement should set deadlines for the sponsor to provide its critical comments about the contents of a planned publication. Nowadays, standard deadlines vary between 30 and 60 days. Deadlines can be extended for an additional 30 to 60 days when the sponsor intends to apply for a patent.

The agreement should also confirm that investigators, or at least the principal investigator, shall have *full access* to all collected data. This right guarantees that subsequent publication of results is based on a comprehensive assessment of all facts.[1097] Yet, in multicentric trials, PhRMA claims the right to restrict individual investigators' access to the study-wide database.[1098] According to PhRMA, the sponsor may distribute to investigators a summary of the multicentric results, instead of providing them with the

---

1090 *See, e.g.,* FDA, Final Rule, Postmarketing Studies for Approved Human Drug and Licensed Biological Products, Status Reports, 65 Fed. Reg. 64,611 (Oct. 30, 2000), at http://www.fda.gov/cber/rules/pstmrkrpt.pdf [hereinafter FDA (Postmarketing Rule)] ("… clinical protocols are highly proprietary in terms of design and analytical plan …").

1091 *See* Schulman et al., *supra* note 907.

1092 For example: "This protocol is the property of X. Data contained herein is confidential and may not be used or disclosed without the prior authorization of X. The investigator is responsible for the protocol's safekeeping and may be asked to return it to X." On the role played by these documents, see subsection 6.2. below.

1093 Hoffmann-La Roche Inc. v. Yoder, 950 F. Supp. 1348, at 1356 (S.D. Ohio 1997). This case centering on an injunctive relief requested by Roche involved the drug Accutane. At the time, Accutane was suspected of causing birth defects. This suspicion would ultimately turn out to be well-grounded.

1094 *Id.* at 1360.

1095 See however the more recent case of Transkaryotic Therapies, Inc. v. Bain & Co., 2002 Mass. Super. LEXIS 73 (Mass. Super. Ct. 2002) (where the sponsor obtained an injunction so as to prevent disclosure of trade secrets by its investigator to a consultant firm acting on behalf of the sponsor's competitor.)

1096 *See* UNC (Agreement), *supra* note 887; G. DuVal, *Institutional ethics review of clinical study agreements*, 30 J. MED. ETHICS 30, at 31-32 (2004), at http://jme.bmjjournals.com/cgi/reprint/30/1/30.pdf.

1097 Articles published in medical journals contain a corresponding statement to the intention of readers, for example: "Author Contributions: Dr Wagner, as principal author of this article, and Dr Yang, as principal statistician for the analyses, had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analyses. All coauthors also had access to the data. " K. D. Wagner et al., *supra* note 973, at 1040.

1098 PhRMA (Principles on Clinical Trials), *supra* note 902, at 22-23.

data generated by other research sites.[1099] In contrast, the Swiss SAMS guidelines ask that investigators be given a right of access to all data necessary to ensure the protection of the subjects.[1100]

Additionally, the agreement should uphold the freedom of the investigator to inform human research subjects of any circumstance material to their health or willingness to participate in the trial.[1101] The investigator is responsible for subjects' safety and is entrusted with the defense of their rights. Hence, she should have discretion to decide what should be disclosed to subjects (e.g., an effective alternative treatment has now become available elsewhere); her decision must prevail over the contrary wishes of the sponsor.

5.4. Monitors

5.4.1. Obligation to monitor the trial

To ensure that the investigator is following the protocol and other applicable rules, the sponsor must monitor the clinical trial. To this end, it appoints one or several monitors.[1102]

The former IOCM 1995 Regulation made monitors mandatory participants in clinical trials.[1103] Monitors' obligations were described in details.[1104] In the structure of the IOCM Regulation, monitors were even given precedence over investigators.[1105] Similarly, the U.S. FDA requires that clinical trials testing the effectiveness of a drug be adequately monitored.[1106] Exceptions are tolerated under certain conditions.[1107]

Surprisingly, the OClin makes no direct mention of monitors.[1108] It does refer to the ICH E6 Guideline[1109] which has a detailed chapter on monitoring.[1110] However, this

---

1099 In addition to this summary, individual investigators are granted access to "relevant statistical tables, figures, and reports for the entire study." *Id.* at 23.

1100 SAMS (Collaboration), *supra* note 1075, at point I.5.

1101 *See* DuVal, *supra* note 1096, at 31-32.

1102 If there is no monitor, then the sponsor should perform most of the monitor's tasks. See in the United States, 21 C.F.R. § 312.50, § 312.53(d), § 312.56(a).

1103 Articles 9.2.c) and 10 of the (former) IOCM 1995 Regulation.

1104 Article 10.2 of the (former) IOCM 1995 Regulation; *see also* Article 2.4 of the accompanying Good Clinical Practices.

1105 Investigators' obligations are listed only after those of the monitors. *See* Article 11 of the (former) IOCM 1995 Regulation.

1106 *See* FDA (Effectiveness), *supra* note 529, at 20. In addition, IRBs can mandate adequate monitoring to ensure subjects' safety. 21 C.F.R. § 54.111(a)(6).

1107 "Factors that influence whether studies with limited or no monitoring may be relied on include the following:
1. The existence of a prospective plan to assure data quality.
2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.
3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).
4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively." FDA (Effectiveness), *supra* note 529, 20.

1108 In contrast, the former 1995 IOCM Regulation had a provision (Article 10) regarding monitors.

1109 *See* Article 4.1 OClin.

Guideline does *not* mandate monitors for all clinical trials. Instead, it leaves it up to the sponsor to "determine the appropriate extent and nature of monitoring … based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial."[1111] For instance, a small clinical trial (e.g., few subjects, short duration) done in a public hospital may not require a monitor, while a multicentric and international phase III drug study will always have one. Yet, for the ICH, monitoring should nonetheless be the rule.[1112] Only in exceptional cases can a clinical trial take place without a distinct entity being appointed to monitor it; in these cases, the responsibilities typically attributed to monitors must be assumed by the sponsor.

The silence of the OClin is regrettable because monitors assume an important function. Their role is essential because direct contacts between the sponsor and the investigator are discouraged (after approval of the protocol).[1113] The idea is to preserve the latter's independence by making pressure by the former more difficult. Indeed, one can guess that, if at the end of each day, the investigator was summoned by the sponsor to discuss the day's progress, the investigator would feel pressured into giving the agreeable – if not correct – answers. The monitor therefore acts as a go-between.[1114] She relays the comments of the investigator to the sponsor and vice versa. She makes sure that the trial advances as planned (without delays) and that the investigator strictly follows the protocol. If she uncovers mistakes or protocol deviations by the investigator or her team,[1115] she discusses them with the investigator to take corrective actions.[1116] She also reports them to the sponsor,[1117] which may find it necessary to put the investigator's participation in the clinical trial to an end.[1118]

In the Swiss VanTx affair, the Working Group identified serious flaws in the monitoring of the CRO's clinical trials. It warned that monitoring breakdowns may have serious consequences for both the safety of subjects and the reliability of data. It recommended improving this essential function in clinical studies. Yet, the legislator did not act up on this recommendation. As stated above, this is regrettable. Monitors, especially when they are independent from the CRO and from the sponsor, represent an important additional security for subjects. They are the ones most likely to uncover violations of the protocol by the investigator. Aside from the investigator and her team, they are the only ones to be present on the research site. Although monitors typically answer only to the sponsor, it would have been desirable to make them accountable also to the authorities. For example, if monitors detect serious flaws that neither the investigator nor the sponsor remedy, the law does not invite them, nor *a fortiori* compel

---

1110 *See* chapter 5.18 (p.26-29) of ICH E6.

1111 Section 5.18.3 (p.26) of ICH E6.

1112 "[I]n exceptional circumstances, the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP." Section 5.13.8 (p.26) of ICH E6 Guideline.

1113 *See* section 5.18.4(a) (p.27) of ICH E6.

1114 Under the former intercantonal regulatory system, see Article 2.4 of the Good Clinical Practices accompanying the IOCM 1995 Regulation.

1115 *See* section 5.18.4(d)&(h) (p.27) of ICH E6.

1116 *See* section 5.18.4(q) (p.28) of ICH E6.

1117 *See* section 5.18.5(c) (p.28) of ICH E6.

1118 *See* section 5.20.2 (p.29) of ICH E6.

them, to report these to the authorities.[1119] Such a reporting requirement would have been a welcome addition to the Swiss regulatory system.[1120]

5.4.2. Role of the monitor

In practice, the monitor's responsibilities can be quite extensive. They must be set in writing by the sponsor.[1121] Before trial initiation, the monitor checks whether the investigator understands the protocol and is prepared to comply with it. She makes sure that the test facilities are suitable and that the medical staff is duly aware of the sponsor's main requirements.[1122] When enrollment of subjects begins, the monitor checks the informed consent documents.[1123] She verifies that only eligible subjects are enrolled.[1124] She keeps track of the subject accrual rate.[1125] However, the monitor rarely speaks with subjects to obtain further confirmation that they understand the objectives and risks of the trial.

Throughout the trial, the monitor regularly meets with the investigator.[1126] She examines the raw/source data collected and checks whether they are correctly reported in the case report forms* ("CRFs").[1127] She pays close attention to reports of adverse events.[1128]

> The information she receives is sometimes referred to as "the essential documents":
>
> [They] individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP [good clinical practice] and with all applicable regulatory requirements. Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator's institution and sponsor sites in a timely

---

1119 *But see* VanTx Report, *supra* note 148, at 25.

1120 It was in vain that the VanTx Working Group recommended that the sponsor be obliged to notify the authority of negative reports by study monitors. *See id.* at 26.

1121 *See* section 5.18.5 (p.28) of ICH E6.

1122 *See* section 5.18.4(b) (p.27) of ICH E6.

1123 *See* section 5.18.4(e) (p.27) of ICH E6.

1124 *See* section 5.18.4(i) (p.27) of ICH E6. However, monitors are in general not in direct contact with research subjects.

1125 *See* section 5.18.4(j) (p.27) of ICH E6.

1126 Visits at clinical site should take place every four to six weeks for a "normal risk" phase III trial. "Perhaps the greatest determinant of appropriate monitoring frequency is rate of enrollment." Sites that enroll many subjects over a short period of time should be monitored more tightly during this period. Also, if previous visits detected violations of protocols, then the rhythm of future visits should be stepped up. *See* Douglas R. Mackintosh et al., *Clinical Monitoring, Answers to Questions about Good Clinical Practice*, APPLIED CLINICAL TRIALS 27, at 28 (July 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=80047.

1127 *See* section 5.18.4(l)&(m) (p.28) of ICH E6.

1128 *See* sections 5.18.4(m)(iii) and 5.18.4(o) (p.28) of ICH E6. "Serious adverse events (SAEs), also called Serious Adverse Drug Reactions (Serious ADRs), are defined as "any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect." Section 1.50 (p.7) of ICH E6. *See also* Annex 1 of E.U. Guidance (Adverse Reaction), *supra* note 270, at 12. For the U.S. definition of "serious adverse drug experience," see 21 C.F.R. 312.32(a).

> manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of the data collected.[1129]

The mission of a monitor is somewhat similar to that of a bank's external auditor. She may proceed with sample corroboration or check all report forms for certain features. She may also assist the investigator with the writing of the intermediary or final report. On-site inspections take place at average intervals of 4 to 6 weeks. Each visit will yield a written report.[1130] The report should notably mention any deficiency found and corrective action recommended.[1131] If the deficiencies are serious, the monitor may have to recommend the interruption of the trial.

One source indicates that monitoring costs can amount to 30% of the total cost of a clinical study.[1132] Yet, a U.S. study found that monitoring of trials by sponsors is often deficient.[1133] Sponsors sometimes fail to act upon reports by monitors.[1134] For example, they pursue studies that should be stopped, they do not replace the investigator, they fail to notify the drug agencies of violations. There are stories of individual monitors being replaced because their reports irritated either or both the investigator and the sponsor.

5.4.3. Appointment of monitors

The qualifications of the monitor vary, since her mission can extend from simple technical tasks up to a real teamwork in association with the sponsor and the investigator.[1135] Monitors are often former nurses with experience of clinical trials. Their mission should be described in a written document drawn up by the sponsor.[1136] The latter may also offer tutoring to the monitor or instruct her to follow training courses.

Monitors are generally not independent from the sponsor. On the contrary, they tend to be affiliated with the latter or with the appointed CRO. Sometimes, investigators or their institutions (e.g., a large academic hospital) appoint their own monitors. In such a case, appropriate cooperation between the two teams of monitors (that of the

---

1129 *See* section 8.1 (p.50) of ICH E6.

1130 FDA, Guidance for Industry for Monitoring of Clinical Investigations, (Jan. 1988), at 5, at http://www.fda.gov/cder/guidance/old006fn.pdf [hereinafter FDA (Monitoring)].

1131 *Id.* at 5.

1132 Institute of Medicine ("IOM"), Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making, Workshop Report, 1999, at p.7, at http://www.nap.edu/readingroom/books/data_quality/adq.pdf [hereinafter IOM (Assuring)].

1133 "According to CDRH's bioresearch monitoring inspections of sponsors conducted in FY 1998, over 50 percent of sponsors failed to ensure the proper monitoring of their clinical investigators. … [In 1998, CDER also] found that serious misconduct was not reported by sponsors and that the majority of the objectionable problems should have been detected by adequate monitoring." OIG (FDA Oversight), *supra* note 95, at 10.

1134 *See, e.g.,* VanTx Report, *supra* note 148, at 16 and 25.

1135 *See* section 5.18.2(b) (p.26) of ICH E6. In the United States, see FDA (Monitoring), *supra* note 1130, at 1.

1136 *See* FDA (Monitoring), *supra* note 1130, at 2.

sponsor and that of the institution) must be ensured.[1137] Violations or failures detected by either team must be reported to the sponsor, and, if necessary, to the ethics committee and the drug agency.

The number of appointed monitors depends mainly on the number of study sites and investigators.[1138] When monitors are legal persons, a single monitor with branch offices can control multicentric trials. When the monitor is an individual, appointing more than one may be necessary, especially if the number of enrolled subjects is important.

5.5. Auditors

In addition to supervision by the sponsor's appointed monitors (see subsection above) and Data and Safety Monitoring Board ("DSMB") (see subsection 5.8. below), the sponsor can designate auditors.[1139] The objectives of an audit are somewhat similar to that of monitoring activities.[1140] The auditors must verify that the investigator and her team are complying "with the protocol, the standard operating procedures ("SOPs"), GCP and the applicable regulatory requirements."[1141] However, contrary to the monitor's regular visits to the trial sites, audits are conducted on a more *isolated* basis. Moreover, auditors must be independent "independence from the clinical trials/systems,"[1142] while this is not a requirement for monitors. Unfortunately, the ICH E6 Guideline does not define what is meant by "independence from clinical trials/systems."

The ICH Guideline does not impose auditors for all clinical trials. As in the case of monitors, the sponsor must determine whether auditors are necessary.[1143] Complex, large and long trials are obviously more likely to require audits. However, the OClin contains no reference to auditors.

1137 In the VanTx affair, the two teams of monitors did not collaborate properly. *See* VanTx Report, *supra* note 148, at 16.

1138 According to the FDA Guidelines, other relevant factors are the type of product being tested, the complexity of the study and the nature of the studied disease. *See* FDA (Monitoring), *supra* note 1130, at 4.

1139 Of course, other clinical trial participants (e.g., the ethics committee, the investigator herself) can theoretically order an audit too.

1140 *See* section 5.19.2(a) (p.29) of ICH E6.
Under the previous intercantonal system, the sponsor was obliged to conduct an internal audit. *See* Article 2.1 and the glossary (under audit) of the GCPs accompanying the (former) IOCM 1995 Regulation.

1141 Section 5.19.1 (p.29) of ICH E6; compare with section 5.18.1(c) (p.26) for monitors. Moreover, the two other stated objectives of monitoring (at section 5.18.1(a)&(b)) fall within 5.18.1(c).
See also EFGCP Audit Working Party, GCP and the Clinical Laboratory, at section 2, page 2, at http://www.efgcp.org/webitems/GCP_and_clinical_laboratory.pdf.

1142 Compare sections 5.19.2(a) (p.29) and 5.18.2 (p.26) of ICH E6.

1143 Compare sections 5.19.3(b) (p.29 and 5.18.3 (p.26) of ICH E6.

5.6. Contract research organizations

5.6.1. A growing presence

Until the 1990s, pharmaceutical companies assumed themselves the responsibility of sponsoring and running their clinical trials.[1144] Early clinical trials were often conducted at the firms' own facilities by their own investigators. Studies conducted *extramuros* were entrusted to academic centers.

As clinical trials have grown larger and more complex (involving multiple jurisdictions and heavier regulatory requirements), pharmaceutical firms have looked for ways to minimize their costs and administrative burden.[1145] Starting in the 1990s,[1146] the industry began to outsource the management of its clinical trials.[1147] Correspondingly, specialized firms realized that managing clinical studies on behalf of pharmaceutical companies could be a profitable line of business. These firms, called contract research organizations (CROs[1148]), are dedicated to all or specific aspects of clinical trials, taking over the corresponding responsibilities of the pharmaceutical sponsor.[1149] Many CROs have grown to be large corporations[1150] able to provide a broad range of services and skills that most public hospitals cannot supply.[1151]

1144 Kristen A. Lamb, *Bridging the Gap between Drug Discovery and Market Introduction: The Rise of Contract Research Organizations,* Food and Drug Law (Feb. 2, 1998), at http://leda.law.harvard.edu/leda/data/203/klamb.html.
See also VanTx Report, *supra* note 148, at 10.

1145 *See* Lamb, *supra* note 1144, at 12 ("By outsourcing to CROs [contract research organizations], pharmaceutical and biotech companies can turn fixed internal costs into lower external variable costs and optimize internal staffing while gaining near-instant access to product development expertise.").
See also EFGCP, The EFGCP News, (Autumn 2000), at 6, http://www.efgcp.org/webitems/doc/newsletters/2000_Autumn.pdf ("CROs have grown out of GCP. By turning GCP into a service, CROs have given it an economic role that is now rated on the stock exchange – GCP is publicly traded!").

1146 This trend may be slowing down. *See, e.g.,* Susan Warner, *Pipeline Anxiety: Scientists Pumped into New Roles*, 17.10 THE SCIENTIST (May 19, 2003), http://www.the-scientist.com/yr2003/may/prof1_030519.html (describing how Pfizer has decided to move its early clinical research back in-house).

1147 "[T]he contract research industry has evolved largely as an extension of big pharma's internal R&D infrastructure." Michael Bowden & Steve Mackenzie-Lawrie, *Looking to the next generation of CROs*, SCRIP MAGAZINE, (Mar. 2002), at http://www.healthdec.com/downloads/Next%20Generation_Bowden.pdf.

1148 In the past, CROs have been called Human Experimentation Corporations (HECs).

1149 Section 1.20 (p.3) and 5.2.1 (p.20) of ICH E6.

1150 Among the most important U.S. CROs:
- Quintiles Transnational, website at http://www.quintiles.com;
- Covance Inc., website at http://www.covance.com;
- PPD Inc.: website at http://www.ppdi.com;
- Parexel, website at http://www.parexel.com/;
- Averion, website at http://www.averioninc.com/;
- Kendle research: www.kendle.com.

See also Lamb, *supra* note 1144, at 15 (stating that "the top five CROs account for half of the outsourced market").

1151 According to Bodenheimer: "CROs, which employ physician-scientists, pharmacists, biostatisticians, and managers, offer manufacturers a menu of services. Large drug companies often create their own study designs and contract with CROs to develop a network of sites, implement the trial protocol at those sites, and send report forms to the sponsoring company, which performs the data analysis. Smaller pharmaceutical firms may hire a CRO to manage the entire trial, including study design, data analysis and preparation of FDA applications and journal articles." *Supra* note 693.

Between 1993 and 1997, use of CROs by pharmaceutical companies has jumped from 28% to 60% of all clinical studies.[1152] As mentioned above (see subsection 5.2.3.), the share of U.S. academic centers has decreased to 40%.[1153] In 2000, CROs participated in 52,000 U.S. drug trials (65% of all trials).[1154]

In the United States, where CROs are quite common,[1155] they are in a position to exert pressure on academic institutions since they are often endowed with the power to select investigators. Competition between CROs and academic medical centers is intensifying.[1156] Sponsors can profit from this competition to impose harsher contract terms on academic investigators.[1157]

5.6.2. Permissible delegation

In the United States, CROs can assume *all* of the sponsor's responsibilities.[1158] In Switzerland, the sponsor cannot transfer all its responsibilities.[1159] In particular, the sponsor remains financially liable toward subjects who suffer harm in the course of the trial.[1160] The CRO may bear its own liability, but the sponsor is accountable for the CRO's actions. Moreover, the sponsor probably retains the obligations to supervise the trial, as there could be a conflict of interest if the CRO acts as the only monitor.[1161]

The delegation of obligations by the sponsor to the CRO must be based on a written agreement.[1162] Responsibilities that are not so transferred remain with the sponsor.[1163] The agreement is communicated to the ethics committee[1164] and to the drug

---

Smaller CROs have also been successful. *See* Bowden & Mackenzie-Lawrie, *supra* note 1147.

1152 *See also* PriceWaterhouseCoopers, Pharma 2005, *Silicon Rally: The Race to E-R&D*, (1999), at 4, at http://www.pwc.com/gx/eng/about/ind/pharma/silicon_rally.pdf ("The percentage of clinical projects involving CROs has risen still more rapidly; it is now 60%, up from 30% just six years ago.").

1153 This figure is for 2000. *See* Davidoff et al., *supra* note 603, at 825.

1154 Astralis Group, Patient Recruitment, A chronic disorder for the pharmaceutical industry, at 2, at http://www.astralisgroup.com/patientrecruitment.pdf.

1155 In the United States, "[t]o expedite trials, industry is turning from academic medical centers to a growing for-profit marketplace whose key players are CROs and SMOs [site management organizations; as defined below]. In 1991, 80 percent of industry money for clinical trials went to academic medical centers; by 1998, the figure had dropped precipitously to 40 percent." Bodenheimer, *supra* note 693.

1156 See also in Switzerland, Kleist (Abhängigkeit), *supra* note 800, at 2348.

1157 *See* Davidoff et al., *supra* note 603, at 825.

1158 In the United States, see 21 C.F.R. § 312.3(b) and § 312.52. When all responsibilities have been transferred from the sponsor to the CRO, references to the former, for example in regulations, are meant to apply to the latter. *See, e.g.,* FDA (DMC), *supra* note 920, at 1.

1159 Pursuant to Article 14.2 OClin, if the sponsor or the investigator transfers certain tasks to a CRO, this transfer should be recorded in a contract, notified to Swissmedic. This expression "certain tasks" (also present in the previous IOCM regulations) was relied upon by the VanTx Working Group to conclude that only certain tasks, and not all of them, can be transferred. *See* VanTx Report, *supra* note 148, at 15 and also at 25. This interpretation makes sense, taking also into account the language of Articles 5.b and 7 OClin.
The VanTx Working Group admits an exception to this rule when a CRO decides on its own to launch a clinical trial and only sells the ensuing results to a pharmaceutical firm once the study is completed.

1160 Section 5.2.1. of ICH E6 Good Clinical Practice, at 24.

1161 *See* VanTx Report, *supra* note 148, at 15.

1162 *See* section 5.2.2 (p.20) of ICH E6.

1163 *See* section 5.2.3 (p.20) of ICH E6.

agency.[1165] Swissmedic checks that the agreement clearly assigns responsibilities to each party so as to avoid situations where neither the sponsor nor the CROs consider a reporting duty to be theirs. Such breakdowns in communication are not uncommon.[1166] Swissmedic does not materially assess the contents of the agreement, except when the latter is clearly incomplete or otherwise inadequate.[1167]

5.6.3. Activities commonly delegated

In practice, CROs often prepare the study protocol, monitor the study and evaluate the investigator's reports. When the investigator has not been selected in advance by the sponsor, CROs may subcontract the trial's conduct to investigators of their own choice, including sometimes *in-house* investigators:[1168]

> CROs are typically involved in the design of clinical study protocols and case reports forms, and gathering and managing clinical data by monitoring and auditing clinical studies. They may also provide statistical support for the sponsor by performing such functions as analyzing study data, developing databases, writing reports, preparing regulatory documents for filing, and representing the sponsor to federal agencies. Some CROs provide full study monitoring support, and some provide additional support for the sponsor's own monitors.[1169]

However, CROs' contribution is sometimes viewed by the pharmaceutical industry as "a necessary evil,"[1170] services provided by CROs not being always satisfactory.

1164 *See* Article 10.2.n OClin. The VanTx Working Group insisted that such a requirement be introduced in the legislation. *See* VanTx Report, *supra* note 148, at 24.
See also FDA Form 1571, at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1571.pdf.

1165 Articles 9.2.k, 10.2.n and 14.2 OClin.
See in the United States, 21 C.F.R. § 312.23(a)(1)(viii).

1166 *See* VanTx Report, *supra* note 148, at 16.

1167 *See* Interview with Vital-Durand, *supra* note 484.

1168 *See* Michael Bowden, *Publish … but don't be damned*, SCRIP MAGAZINE, (Dec. 2001), at http://www.healthdec.com/downloads/scrip_publish.pdf [hereinafter Bowden (Publish)].

1169 Madeleine M. Jester, *Potential Risk Exposures for IRBs, CROs, SMOs, and CSOs*, (posted Apr. 1999), at http://www.cnahealthpro.com/amt/potenrisks.html.

1170 "Problems common within the sponsor-CRO relationship have included the rent-a-body mentality; lack of breadth and depth of experience within the CRO; unsophisticated choice and management of contacts by the sponsor and real or perceived failure to deliver by the CRO." Michael Bowden, *More than 'Rent a Body'*, 3D (Spring 2000), at http://www.healthdec.com/downloads/3D_rent_a_body.pdf.

5.7. Site Management Organizations

Another new actor on the clinical scene is the site management organization ("SMO").[1171] Presently, SMOs are not subject to any specific regulation.[1172] Depending on the functions they undertake, rules pertaining to investigators, sponsors, or CROs may be applicable to SMOs.[1173]

The main task of a SMO is to coordinate clinical activities among its network of research sites. To secure this network, a SMO may enter into collaborative agreements with research institutions and investigators. Alternatively, it can buy research sites and hire its own researchers.[1174] Ideally the SMO guarantees research sites of a high and standardized quality. SMOs are hired by sponsors or CROs that want access to this site network.[1175] Thus, the sponsor does not have to handpick its investigators. The expected benefit is a gain in time, cost and quality.[1176]

Investigators chosen to be part of the SMO's network must show their ability to recruit subjects within deadlines. The existence of the network is viewed as a leverage instrument to facilitate the recruitment of subjects.[1177] The SMO may also run advertisements to assist the investigators in their recruitment efforts. Standardized procedures are also introduced to improve data collection practices.

Once the trial has started, management and monitoring of data are generally left to the CRO,[1178] though there are companies that fulfill both the functions of an SMO and of a CRO.

1171 Among the largest SMOs are Radiant (http://www.radiantresearch.com), Comprehensive Neuroscience (http://www.cnsclinicaltrials.com/), nTouch Research (http://www.ntouchresearch.com) and AmericasDoctor (http://www.americasdoctor.com/).

1172 *See* Stan W. Woollen, *Why a SMO is not a CRO, or is it?* FDA (Oct. 2001), at http://www.fda.gov/oc/gcp/slideshows/smo2001/smotext.html.

1173 *Id.*

1174 For example, "Radiant Research employs nearly 1,000 research professionals throughout our 50+ wholly-owned clinical research facilities." Radiant Research, About Us, at http://www.radiantresearch.com/about_us.asp.

1175 *See* Woollen, *supra* note 1172.

1176 See, e.g., Hans-Georg Eichler, An SMO in a public setting – added value or added expense, Part 2: The role of the SMO, DRUGDEV123, (July 13, 2000).

1177 *See* Bowden (Publish), *supra* note 1168.

1178 *See* Jester, *supra* note 1169.

5.8. Data Safety Monitoring Boards

A possible addition to the research team is the Data and Safety Monitoring Board ("DSMB").[1179] In commercial clinical trials, DSMBs are appointed by the sponsor.[1180] However, large academic centers providing investigator services may have their own internal DSMBs.[1181]

5.8.1. Necessity of a DSMB

DSMBs are strongly recommended for large clinical trials of public health significance (e.g., a phase III cancer trial).[1182] Particularly long, complex, risky or ethically problematic trials call for DSMB monitoring,[1183] to ensure that subjects' risk exposure stays within appropriate bounds.[1184] For example, when the trial studies survival rate with a new drug, the DSMB helps by regularly monitoring the number and cause of subjects' deaths,[1185] a task that the investigator may not be able to carry.[1186]

There is no blanket requirement to have a DSMB for all clinical trials. In fact, Swiss law does not even mention DSMBs. Although the American FDA supports DSMBs, it does not make them mandatory.[1187] The U.S. regulation comports one exception, pertaining to emergency clinical trials for which subjects do not give prior informed con-

---

1179 In the European Union, DSMBs are referred to as data monitoring committees ("DMC"). *See* E.U. Guidance (Adverse Reaction), *supra* note 270, at 9. Elsewhere they are also called independent data monitoring committees ("IDMCs"). *See e.g.,* section 1.25 (p.4) of ICH E6 and section 4.5 (p.20) of ICH E9.
According to a study by Schulman, sponsors rarely require investigators and their affiliated academic institutions to set up data safety monitoring boards. *See* Schulman et al., *supra* note 907, at 1335-1341.

1180 *See* section 5.5.2 (p.21) of ICH E6.

1181 *See* NCI, Data and Safety Monitoring Guidelines, *supra* note 2. Historically, DSMBs were first implemented in large trials sponsored by the U.S. National Institutes of Health (NIH). *See* FDA (DMC), *supra* note 920, at 2.

1182 *See* ICH E9. *See* David L. DeMets et al., *The agonizing negative trend in monitoring of clinical trials*, 354 LANCET 1983 (Dec. 4, 1999). *See* National Institute of Neurological Disorders and Stroke (NINDS), NINDS Guidelines for Data and Safety Monitoring in Clinical Trials, (reviewed July 1, 2001) at http://www.ninds.nih.gov/funding/research/clinical_research/data_safety_monitoring.htm [hereinafter NINDS (Monitoring)] (recommending a DSMB for "trials which may modify the current standards of treatment or public health policy, result in the licensing of a therapeutic agent or device, or extend approved indications to new groups of patients.").

1183 For example, trials enrolling vulnerable populations, such as children or incapacitated subjects, generally have DSMBs. *See* FDA (DMC), *supra* note 920, at 3.
Placebo-controlled trials may also require a DSMB to make sure that the risks incurred by the placebo group are at all times reasonable. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 8 (commentary) and at Guideline 11 (commentary).

1184 *See, e.g.,* BRODY, *supra* note 447, at 31.

1185 *See* FDA (DMC), *supra* note 920, at 3 (stating that such committees should be established whenever the primary or secondary endpoint is mortality or major morbidity).

1186 Because investigators must normally remain blind throughout the trial (i.e., not know which of two or more treatments subjects are receiving), they cannot determine whether there are more deaths in the group taking the investigational drug as compared to the control group.

1187 In the United States, see FDA (DMC), *supra* note 920, at 2 and 3 and at 18-20; OIG, HHS, Institutional Review Boards: Their Role in Reviewing Approved Research (June 1998), at 10, at http://oig.hhs.gov/oei/reports/oei-01-97-00190.pdf [hereinafter OIG (Reviewing)].
In the European Union, see E.U. Guidance (Adverse Reaction), *supra* note 270, at 9.

sent (see also subsection 8.4.2.2. below). In this case, there must be a DSMB and it has to be fully independent.[1188]

5.8.2. Appointment of a DSMB

Though selected by the sponsor, a DSMB should be *independent* from all parties involved in the clinical trial.[1189] Obviously, it should not have any financial interest in the outcome of the clinical study.[1190]. It must not be involved in the design or the execution of the trial.[1191] It must also be independent from the sponsor since it may have to issue recommendations adverse to the sponsor's interests (e.g., early termination of a trial when the sponsor wants to continue it or continuation of a trial when the sponsor wants to end it). The DSMB must also be independent from the investigator, since it supervises in part the latter's activities.[1192]

Members of the DSMB must be chosen primarily for their uncontested scientific *expertise*.[1193] Their expertise should be relevant to the medical and ethical problems that the clinical study entails. Furthermore, its members must have expertise in bioethics and in statistics. DSMBs sometimes enroll patient representatives or disease activists.[1194] Many of the considerations pertinent to the appointment of ethics committees (see below subsection 7.1.1.) are also valid for DSMB members.[1195]

The protocol describes the tasks to be performed by the DSMB.[1196] The latter should also adopt its own written standard operating procedures (SOPs) to describe further its operation.[1197] SOPs state, for instance, how often the DSMB meets.[1198] They indicate

---

1188 According to the FDA, this means "that the committee [DSMB] should be composed solely of individuals who have no financial interest in the outcome of the study and who have not been involved in the design or conduct of the study." FDA (Emergency Guidance), *supra* note 261, at 15.

1189 Whether or not IDMCs may have ties to the sponsor is contentious: "The consensus conference involved 46 people from industry and 36 from academic institutions. Over three-quarters of company representatives did not agree that sponsors should be excluded from committees governing the operations of a trial, such as the trial board, data monitoring committee, coordination center and data quality center, in order to minimize bias. In contrast, over three-quarter of the academic researchers agreed with introducing such measures as a means of minimizing bias." Haiweb, *supra* note 970. *See also* PhRMA (Principles on Clinical Trials), *supra* note 902, at 15 ("Employees of the sponsor may not serve as members of the DSMB but may otherwise assist the DSMB in its evaluation of clinical trial data."). *See also* NINDS (Monitoring), *supra* note 1182.

1190 *See* PhRMA (Principles on Clinical Trials), *supra* note 902, at 15 ("A voting member of a DSMB should not have significant financial interests or other conflicts of interest that would preclude objective determinations."); FDA, Final Rules on the Protection of Human Subjects, Informed Consent and Waiver of Informed Consent in Certain Emergency Research, 61 Fed. Reg. 51,497, at 51,518 (Oct. 2, 1996) [hereinafter FDA (Emergency Research)].

1191 *Id.* at 51,518.

1192 *See* FDA (DMC), *supra* note 920, at 6.

1193 *See id.* at 5-7. *See also* Arthur S. Slutsky & James V. Lavery, *Data Safety and Monitoring Boards*, 350 NEW ENG. J. MED. 1143 (Mar. 11, 2004), at http://content.nejm.org/cgi/reprint/350/11/1143.pdf.

1194 *See* BAZELL, *supra* note 673, at 31.

1195 *See* FDA (DMC), *supra* note 920, at 6.

1196 *See, e.g.,* section 4.5 (p.20) of ICH E9.

1197 *See* section 5.5.2 (p.21) of ICH E6 and section 4.6 (p.21) of ICH E9.

1198 *See* FDA (DMC), *supra* note 920, at 8.

who, apart from DSMB members, attends meetings.[1199] They describe the statistical methods used to assess interim reports of clinical data. In the United States, the FDA receives a copy of the SOPs.[1200] All meetings should be properly documented and corresponding records kept.[1201] In the United States, the FDA receives copy of these records along with the final study report.[1202] The DSMB should issue its advice to the sponsor in writing, stating clearly its underlying rationale.[1203]

5.8.3. Role of a DSMB

The role of a DSMB falls in between that of a monitor and an ethics committee. Compared to monitors, the DSMB devotes greater attention to subjects' safety, and less to "data cleanliness."[1204] For example, a DSMB will not routinely check case report forms* (CRFs),[1205] a task devolved to monitors.[1206] DSMB members are also not present on the study site. The DSMB is concerned foremost with adverse event reports, its focus being primarily on safety issues.[1207] It also assesses the clinical trial's progress and evaluate efficacy data.

Compared to the ethics committee, the DSMB focuses more on the *ongoing review* of efficacy and safety data, and not so much on the initial consent stage (see subsection 7.1.2.5. below). However, it often has to grapple with ethical issues similar to those that concern ethics committees. For example, it may recommend that the informed consent process be repeated to incorporate a new assessment of risks.[1208]

A key difference with all other participants resides in the fact that the DSMB is the only participant that is not blinded (on the notion of blinding, see subsection 6.3.3.5. below).[1209] The DSMB needs to know the treatment allocation so as to check whether one group of research subjects (also called a study "arm"*) is responding better than the other.[1210]

An very important function of the DSMB is to recommend to the sponsor to *stop or modify a trial* if it has concerns about the well-being of research subjects.[1211] For instance,

---

1199 Often, the investigator and the sponsor participate in the first part (the "open" part) of the meeting. Then, when unblinded data are reviewed, the session is closed and only the DSMB members can attend it. *See id.* at 8-9.

1200 *See id.* at 8.

1201 *See id.* at 17.

1202 *See id.* at 17.

1203 *See id.* at 16.

1204 *See however id.* at 14.

1205 See further on case report forms, subsection 6.2.3. below; see also the glossary at the end.

1206 See, under the former intercantonal system, Article 2.4.e) of the Good Clinical Practices accompanying the IOCM 1995 Regulation.

1207 *See* section 5.5.2 (p.21) of ICH E6.

1208 *See* FDA (DMC), *supra* note 920, at 13.

1209 *See id.* at 7.
See also NINDS (Monitoring), *supra* note 1182.

1210 *See* DeMets et al., *supra* note 1182.

1211 Section 5.5.2 of ICH E6 Guidance on Good Clinical Practice, at 25. *See* FDA (DMC), *supra* note 920, at 16 ("Other recommendations that might be made [by the DSMB] include … study continuation with major or

if preliminary data show that subjects are doing much better in one arm of the trial (whether the investigational or the control arm[1212]), the DSMB may propose early termination of the trial so that all subjects can be given the treatment found most efficacious.[1213] The DSMB should be consulted whenever the sponsor plans to terminate a trial before its normal completion date.[1214] It is on the basis of documents and information received from the investigator that the DSMB decides whether the trial meets all necessary conditions for its continuation or for its termination.[1215]

The decision to halt a trial is a momentous one.[1216] A trial stopped too early when reliable results have not yet been generated may condemn, possibly forever, a promising treatment. A trial stopped too late puts the health of subjects at risk.[1217] Moreover, the longer a beneficial treatment remains in clinical trials, the longer the public will have to wait to have access to it. Hence, AIDS activists in the 1990s lobbied for an early termination of the first HIV trials so that the drug (here, AZT) could rapidly obtain its marketing authorization.[1218] In an indecisive situation, the DSMB may have to multiply interim reviews (also referred to as "futility analysis"[1219]) to achieve the "right" timing.

The DSMB may also advise the sponsor on other *ethical issues*.[1220] Unfortunately, the DSMB is not made to work in cooperation with the ethics committee. Although both are concerned with subjects' safety, they operate side by side. Communications between the two are limited.[1221] While the DSMB should communicate important findings to the ethics committee, this is not always the case.[1222]

Where no DSMB has been appointed, its main tasks should be carried out by the ethics committee. For instance, the REC ought to review interim data to make sure that the subjects' safety is not at risk. But the REC is kept ignorant of subjects' treatment allocation (i.e., whether a given subject is administered the investigational new drug or

---

minor modifications, or temporary suspension of enrollment and/or study intervention until some uncertainty is resolved."). The DSMB's recommendation to end a trial is generally only advisory and not mandatory. *See* FDA (DMC), *supra* note 920, at 23.

1212 For more information on the control arm of a clinical trial, see subsection 6.3.3. below.

1213 *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 326. See also paragraph 17 of the Helsinki Declaration requiring that clinical trials be stopped "if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results."

1214 *See* DeMets et al., *supra* note 1182.

1215 A clinical trial should be stopped if it "(a) has answered the primary study question, (b) will not be able to reach a firm conclusion, (c) is not being conducted according to high scientific or ethical standards, or (d) poses an unreasonable or unnecessary risk to study participants." NINDS (Monitoring), *supra* note 1182. *See also* FDA (Emergency Research), *supra* note 1190, 51,517.

1216 *See* Slutsky & Lavery, *supra* note 1193, at 1143-44.

1217 *See* DeMets et al., *supra* note 1182.

1218 *See* Editorial, *On stopping a trial before its time*, 342 LANCET 1311 (Nov. 27, 1993).

1219 *See, e.g.,* Philip B. Gorelick et al., *Aspirin and Ticlopidine for Prevention of Recurrent Stroke in Black Patients*, 289 JAMA 2947, at 2949 and 2953 (June 11, 2003), at http://jama.ama-assn.org/cgi/reprint/289/22/2947.pdf.

1220 However, it should not be confused with the ethics committee (REC). See generally on the role of RECs, subsection 7.1. below.

1221 *See* OIG (Reform), *supra* note 877, at 3.

1222 *See* OIG (Status), *supra* note 987, at 2 and 13 (reporting that this recommendation has been partly implemented). *See* OIG (Reviewing), *supra* note 1187, at ii and 10 (criticizing the lack of communication between DSMBs and ethics committees).

the control product);[1223] this necessarily constrains the accuracy of their risk review. In addition, RECs are often confronted with such a heavy workload that they are unable to take over the DSMB's task. They rather need the DSMBs to discharge them.[1224] As an example, the DSMB can do a preliminary analysis of adverse events and pass on its assessment to the REC.[1225]

[1223] *See* FDA (DMC), *supra* note 920, at 4.

[1224] *See* OIG (Reform), *supra* note 877, at 13.

[1225] *Id.*

6. The types and characteristics of drug clinical trials

This long section is divided into three main subsections. The first subsection goes over the four main phases of drug clinical development (phase I through IV). After a brief introduction on the gold standard of randomized controlled trials, the second subsection describes the key documents that underlie the conduct of clinical trials. These include the protocol, the investigator's brochure, and the case report forms. The third subsection analyzes the different methods to obtain reliable results, by minimizing sources of bias. As the name indicates, "randomized controlled clinical trials" incorporate (at least) two anti-bias methods: the inclusion of a *control group* that receives a control treatment (as opposed to the investigational product being tested) and random allocation of subjects to one of the two groups. This section 6 essentially presents scientific or medical information; only few statutory provisions are applicable.

6.1. The different kinds of clinical trials

When the sponsor believes to have acquired sufficient safety and efficacy information from laboratory tests and animal experimentation, it launches its first clinical trial.[1226] Drug clinical trials are typically staged in successive phases.[1227] The first three phases take place *before* the drug is approved, while the fourth phase occurs *afterwards*.[1228] This division in phases is supposed to reflect a chronological evolution; thus, phase III follows phase II which comes after phase I.[1229]

Each phase is meant to build upon the previous one. Each phase generates additional information used to decide whether it is worth (from an economic and scientific standpoint) launching the next phase of study.[1230] For example, a phase II study may cause the compound to be definitely abandoned, because side effects are deemed excessive. The additional data also allow to improve the design of the next battery of tests.[1231] For instance, phase II results may show that the compound is more efficacious if taken

---

1226 Nowadays, software programs can assist the sponsor in the design of a trial and its protocol.

1227 One of the common exceptions are clinical trials required to support a simplified marketing authorization for generics.

1228 On phase IV clinical trials, see subsection 6.1.4. below.

1229 Arabic numbers (Phase 1, 2, 3) sometimes replace roman numbers.

1230 Finance tells use that trial phases can be viewed as real options: the sponsor is paying to learn more about the risks and expected gains of a project. Knowledge acquired during a phase is used to determine the net present value of a project. Financial tools allow to put a value on the real option (i.e., the option to pay for a study that will produce additional information).

1231 *See* FDA Guidance for Industry, General Considerations for the Clinical Evaluation of Drugs, at 2 (Feb. 1997), www.fda.gov/cder/guidance/old034fn.pdf [hereinafter FDA (General Clinical Considerations)].
Drug companies have been criticized for not taking all advantages of former clinical trials to develop their next phase of testing: "However, many companies do not even use information they have gleaned from earlier trials on the same drug, let alone from trials on kindred drugs. In an effort to keep development time as short as possible, they start further studies before completing their analyses of the results from earlier tests. So decisions to proceed in a clinical development programme are often based on conjecture rather than hard-core information. Making decisions based on conjecture inevitably increases the number of trials that are needed. ... This is a very expensive way of doing things." PricewaterhouseCoopers, *supra* note 1152, at 6.

according to a given dosage schedule; this characteristic will be incorporated in the design of the following phase III study.

However, one should bear in mind that this division into different phases is partly artificial, as we will see in subsection 6.1.5. below.[1232]

6.1.1. Phase I

6.1.1.1. Conditions of phase I trials

Phase I (also called "human pharmacology"[1233]) begins after *nonclinical* studies ("NLS") have shown that the compound is reasonably safe (e.g., no major hepatoxicity in animals).[1234] Nonclinical studies include laboratory and animal investigations. It is important to detect potential toxicity as early as possible so as to end clinical development before too much money has been invested.[1235] The FDA has regretted that the current methods to achieve this goal are still inadequate.[1236]

NLS have also revealed at which dose the compound has no observed adverse effect level ("NOAEL").[1237] This initial safe starting dose for animals is the starting point for computing the maximum recommended starting dose (MRSD) for humans in a phase I clinical trial.[1238] This dose, or even a smaller one, is administered to healthy volunteers to learn its effects.[1239] This phase presents some similarities with animal studies,

---

1232 "[T]here is no sharp delineation between the phases. Rather, they represent a progression of clinical research that broadens as it goes …." Kessler (Regulation), *supra* note 447, at 281-86. Nonetheless, the FDA asks sponsors to identify the stage of their study in their IND application. *See* Form 1571, *supra* note 1164.

1233 *See* ICH E8, *supra* note 533, at 3.1.3.1 (p.6).

1234 Clinical trials may begin even though *not all* preclinical (animal) studies have been completed and evaluated. Often long-term animal studies are conducted in parallel with clinical development. *See, e.g.,* Motion of Public Citizen Health Research Group in Court of Appeal case versus FDA, Schering and Hoechst Marion Roussel, at section A (July 20, 1998), at http://www.citizen.org/print_article.cfm?ID=978.

1235 *See* FDA (Critical Path), *supra* note 708, at 16.

1236 *Id.* at 16-20.

1237 The FDA defines the NOAEL as "the highest dose level that does not produce a significant increase in adverse effects." Thus, at the NOAEL, certain adverse effects are observed. "Although the nature and extent of adverse effects can vary greatly with different type of therapeutics and it is anticipated that in many instances experts will disagree on the characterization of effects as being adverse or not, the use of NOAEL as a benchmark for dose-setting in healthy volunteers should be acceptable to all responsible investigators." *See* FDA, Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, Guidance for Industry, at 5, and also at 4, (July 2005), at http://www.fda.gov/cder/guidance/5541fnl.pdf [hereinafter FDA (Starting Dose)]. See also the critical comments filed by Human Genome Sciences Inc. on April 15, 2004, (docket No. 02D-0492), at http://www.fda.gov/ohrms/dockets/dailys/03/Apr03/040103/80064266.doc.

1238 The most appropriate (animal) NOEL is converted to an equivalent dose for human (called HED for human equivalent dose), based on a body surface area coefficient. Then, the HED is increased by multiplying it by a safety factor (usually 10%) so as to minimize risks for Phase I human subjects. Other factors may suggest added precautions and the use of a greater safety coefficient. *See* FDA (Starting Dose), *supra* note 1237, at 4.
Compare with *Barrett*, 660 F. Supp. 1291 (where the U.S. government inappropriately tested a mescaline hybrid on mice and then supplied this compound for administration on an unconsenting human subject who died following the injection of an excessive dose; this experiment was part of a chemical warfare project; see also subsection 2.3.1.3. above).

1239 For an example of a phase I protocol, see the template proposed by the NCI at http://ctep.cancer.gov/forms/ph2_sing_temp3.doc.

as its purpose is chiefly to set the *safe dosage level*.[1240] Phase I trials are sometimes referred to as pilot studies.

6.1.1.2. Objectives of a phase I trial

Phase I is also called *dose escalation* (or dose rising) study, because of the progressive increase of the initial dosage (i.e., titration) in successive groups (cohorts) of subjects. The objective is to find out at which dose the compound is entirely safe (i.e., it has no side effect) and at which dose it starts to have adverse effects (e.g., vomiting).[1241] This information helps define the *therapeutic index*, that is the difference between an effective dose and a dangerous dose.[1242] Drugs with a small therapeutic index are more dangerous, because even minute mistakes in dosage can have catastrophic consequences.

To be sure that reported adverse effects are due to the dosage, progressively bigger doses of the tested drug are administered to volunteers. Phase I trials are not always randomized and blinded, although these precautions lead to more reliable data.[1243] Thus, they allow to distinguish adverse effects that are due to the compound, from those that might have been caused by some other reason (e.g., the alimentary regimen followed by volunteers).

The duration of the study depends in part on the expected period of use by patients. But even though the drug may have to be taken for a lifetime (e.g., antidiabetics), a phase I study lasts only a few weeks.

Besides analyzing dose-related effects (i.e., dose-response), investigators also want to determine how the compound works inside the body: how fast it is absorbed, metabolized and excreted. In that respect, once again, this phase bears resemblance with nonclinical animal studies, given that pharmacokinetic effects are among the topics of interest. As is true for animal studies, specimens (e.g., blood, urine) are regularly taken.[1244]

A third objective is to assess *local tolerance* to the compound. For instance, if the drug is formulated as a cream, the product is applied to the skin of the volunteer to see whether an irritation occurs. If the drug is to be injected, then tolerance at the site of injection is studied. At this stage, the sponsor may not be certain of what the final route(s) of administration for its product will be; hence, it may have to do several different tolerance tests.

1240 *See, e.g.,* Gilead, FDA Advisory Committee Briefing Document, Adefovir Dipivoxil for the Treatment of Chronic Hepatitis B, at 18, (NDA 21-449) (July 5, 2002), at http://www.fda.gov/ohrms/dockets/ac/02/briefing/3885B1_01_Gilead.pdf (explaining how a 10 mg therapeutic dose was selected over a 30mg dose).

1241 *See* E4 Guideline on Dose-Response Information to Support Drug Registration, at 4-6, adopted at step 4 (Mar. 10, 1994), at http://www.ich.org/MediaServer.jser?@_ID=480&@_MODE=GLB [hereinafter ICH E4]. This is referred as the maximum tolerated dose ("MTD"). *See also generally* VASELLA, *supra* note 127, at 69, 71 and 78.

1242 For example, if the effective dose is 1 mg/kg and the dangerous dose is 10 mg/kg, the therapeutic index would be 10. A related notion is that of therapeutic window.

1243 Pharmacokinetic trials often have no control groups.

1244 The subject's serum drug levels is tested, for example, every hour during one day.

6.1.1.3. Therapeutic and nontherapeutic trials

Phase I trials traditionally belong to a category of studies referred to as *nontherapeutic* (the opposite being a therapeutic trial). The basic definition is that therapeutic trials intend to confer individual therapeutic benefits to subjects. On the contrary, nontherapeutic trials are not meant to improve the subject's condition. It is only in phase I trials on healthy volunteers that a therapeutic benefit can be excluded with certainty.

This distinction (between therapeutic and nontherapeutic trials) used to be very important because the legal rules applying to each type of trial differed. For instance, some countries had prohibited nontherapeutic trials.[1245] Ethical guidelines had tighter informed consent requirements for nontherapeutic trials. [1246] In contrast, therapeutic trials were treated too much like (innovative) individualized medical care.[1247]

In part because this distinction triggered the application of different rules, it was severely criticized by Sprumont and others.[1248] Sprumont found it dangerously misleading for subjects, who would place undue hope on the world "therapeutic."[1249] Indeed, the distinction between the two types of studies is hard to draw.

First, it may be very difficult to determine whether the anticipated benefits are sufficiently assured. Especially for early phase trials, the investigators may hope to establish some sort of benefits, but there is no guarantee that these will indeed occur.[1250] Even when benefits are relatively certain (e.g., a phase III trial), it may be impossible to know for sure whether they will extend to *all* patients. For example, when the improvement is known to occur only in one patient out of five, can it be said that the trial is therapeutic for all subjects? The same problem arises in connection with the use of placebo; it is somewhat artificial to assert that subjects on the placebo are deriving an individual therapeutic benefit.[1251]

1245 This was for a long time the case of France. The situation changed in the 1990s. *See* Article 290-4 to 290-7 of the French "*Code de la santé publique*" [Code on Public Health].

1246 *See however* the Helsinki Declaration which operates a distinction between the two types of research, since its chapter C (paragraphs 28 to 32) applies when "medical research [is] combined with medical care."

1247 On the distinction between research and ordinary medical care, see subsection 3.4. above.

1248 *See* SPRUMONT, *supra* note 16, at 33-37. This condemnation of the therapeutic/nontherapeutic distinction is one of the central tenets of Sprumont's thesis and carries several corollaries. See for example, *id.* at 46. *See also* Spriggs, *supra* note 240, at 177-78.
See also Robert J. Levine, *The Need to Revise the Declaration of Helsinki*, 341 NEW. ENG. J. MED. 531 (Aug. 12, 1999) [hereinafter Levine (Helsinki)].

1249 *See also* BEAUCHAMP & CHILDRESS, *supra* note 16, at 320.

1250 *See* Federal Council's Message, at FF 1999 3151, at 3229.
In the United States, two criteria should be taken into account: "the possibility of benefit to the subject must be fairly immediate [and t]he expectation of success should be well-founded scientifically." NBAC, Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Volume I, Report and Recommendations, at chapter IV, (Dec. 1998), at http://www.georgetown.edu/research/nrcbl/nbac/capacity/TOC.htm [hereinafter NBAC (Mental)]. Hence, a trial that would only result in the acquisition of preliminary information to develop a new drug in the next phase of study would not entail direct benefits.

1251 *See, e.g.,* Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé ("CCNE"), Avis n° 79, Transposition en droit français de la directive européenne relative aux essais cliniques de médicaments: un nouveau cadre éthique pour la recherche sur l'homme, at 4 (Sept. 18, 2003), at http://www.ccne-ethique.fr/francais/pdf/avis079.pdf [hereinafter CCNE N°79].

A second difficulty is that, while some aspects of a trial may hold the prospect of direct individual benefits, this may not be true for other key aspects of the trial.[1252] For example, a trial of a promising cancer treatment may call for certain medical procedures that are risky, painful and whose purposes are not to benefit subjects, but only to ascertain the treatment's efficacy. In such a case, it may be misleading to qualify the *entire* trial as therapeutic. On the contrary, it might be necessary to assess the various aspects of the trial separately.

A third problem is that patients often wrongly assume that even a phase I trial will bring them some benefits. This tends to happen when phase I trials enroll sick patients, instead of healthy volunteers.[1253] Although the admitted purpose of a phase I trial is not to demonstrate efficacy,[1254] subjects often agree to participate because they have faith in the new drug.

A 1983 study by the U.S. General Accounting Office ("GAO") found that many phase I clinical trials for cancer drugs were designed with "therapeutic intent," that is with the intent to potentially confer some therapeutic benefits to – at least some of – the enrolled subjects.[1255] The same study found, however, that this therapeutic promise was rarely truly fulfilled: only between 1 and 3% of enrolled patients did exhibit significant improvements.[1256] This dichotomy raises ethical issues since subjects may be enrolling in these clinical trials with the mistaken expectation that their conditions will improve – a belief referred to as the "therapeutic misconception."[1257]

Although a study of informed consent forms for U.S. NIH-sponsored phase I trials found that sponsors were not articulating promises of therapeutic benefits,[1258] this silence is probably not enough to quell patients' desperate hopes.[1259] In fact, a survey of research subjects found that the majority of them take part in research in order to find

---

1252 *See* Levine (Helsinki), *supra* note 1248, at 531 (evoking the "fallacy of the package deal").

1253 *See* Mariner, *supra* note 59, at 292; Annas & Grodin, *supra* note 63, at 308.

1254 According to FDA regulations, phase I trials should be designed "if possible, to gain early evidence on effectiveness." 21 C.F.R. § 312.21(a).

1255 GAO, Statement of Edward A. Densmore, before the Senate Committee on Labor and Human Resources, Clinical Testing of Anticancer Drugs, 1983, at p. 3, at http://161.203.16.4/d40t12/121728.pdf [hereinafter GAO (Anticancer)].

1256 For cancer clinical trials, "[m]eta-analyses place the average response rate for phase 1 oncology trials at less than 6 percent and the rate of death from toxic effects at approximately 0.5 percent." *See* Sam Horng et al., *Descriptions of Benefits and Risks in Consent Forms for Phase 1 Oncology Trials*, 347 NEW. ENG. J. MED. 2134-2140 (2002), at http://content.nejm.org/cgi/content/full/347/26/2134.

1257 *See also* Manish Agrawal & Ezekiel J. Emanuel, *Ethics of Phase 1 Oncology Studies, Reexamining the Arguments and Data*, 290 JAMA 1075-1082 (Aug. 27, 2003), at http://jama.ama-assn.org/cgi/reprint/290/8/1075.pdf.

1258 "Of all consent forms [studied, that is 272 of them], 268 (99 percent) contained an explicit statement indicating that the study was research. In 231 of these forms (86 percent), this statement was considered by the coders to be "prominent," in that it appeared in the first paragraph, was easy to identify, and was repeated at least once. Of all forms, 249 (92 percent) indicated that safety testing was the goal of the research, and 17 (6 percent) stated explicitly that it was not the purpose or the expectation of the trial to be therapeutic." Horng et al., *supra* note 1256.

1259 *See also* CCNE, Les essais de phase I en cancérologie, Avis N° 73 [Phase I cancer trials, advice N°73], at 1 (Sept. 26, 2002), at http://www.ccne-ethique.fr/francais/pdf/avis073.pdf [hereinafter CCNE N°73].

relief for their own medical conditions.[1260] They are not deterred by the ostensibly nontherapeutic purpose of the trial.

Today however, this distinction has lost much of its importance. Under Swiss law, there is only one indirect reference to this notion at Article 54 LPTh.[1261] The rules are now essentially the same for both types of trials.[1262] The European 2001/20/EC Directive has taken the same course.[1263]

6.1.1.4. Subjects recruited for a phase I trial

A phase I study enrolls between 20 and 100 subjects.[1264] They are usually *healthy male volunteers*.[1265] *Male* volunteers are traditionally preferred because, at the phase I stage, the safety profile for women and their fetus has often not been ascertained by the appropriate batch of reproductive animal studies.[1266] In the past, phase I clinical trials enrolled the medical students of the investigator or the employees of the pharmaceutical sponsor;[1267] their motivation was to get a good grade or a laudatory recommendation letter.[1268]

The *risks* phase I volunteers face are at the same time lower and higher than for other phases. Often these volunteers have to stay near to, or in, the hospital or the specialized clinic where the testing takes place; they are closely and daily monitored for every side effect possible;[1269] at the beginning, they are administered the compound at a low dose and only during a short time period. On the other hand, this is the first time

---

1260 *See* CenterWatch (Word from), *supra* note 681, at 4. Only 40% did not have this reason in mind, the other objectives being to advance science (23%), to earn money (11%) or to receive better medical care (6%). *Id.* More generally, a survey of subjects participating in phase I to III clinical trials found that "45% of patients cited personal benefit [as their reason for enrolling in a trial], 30% of patients cited physician influence, and 21% of patients cited a desire to benefit others." *See* ECRI (Guide), *supra* note 869, at 53.

1261 *See* Article 55.2 LPTh on nontherapeutic clinical trials on minors, incompetent and incapacitated subjects. See subsection 8.4. below.

1262 See for Switzerland, the Federal Council's Message accompanying the LPTh, at FF 1999 3151, at 3228-29.

1263 According to Article 3.2.(a) of the Directive, a "clinical trial may be undertaken only if, in particular, the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject *and other present and future patients*." (emphasis added).
Other European countries however have maintained this distinction for the time being. For example, France still insists on this distinction. *See* Article L.209-1 of the Code of Public Health (Code de la santé publique). *See also* CCNE N°79, *supra* note 1251, at 2.

1264 *See* 21 C.F.R. § 312.21(a). However if all volunteers enrolled in all phase I studies performed for the same drug were added up, the figures would be much higher. CMR International has calculated for a new active substance an average of 20 Phase I clinical trials enrolling more than 400 patients; CRM (Describing Dossiers), *supra* note 687.

1265 *See* 21 C.F.R. § 312.21(a)(1). That the subjects are referred to as *healthy volunteers* does not absolutely exclude that they suffer from some disease or medical condition. However, the purpose is to enroll subjects who are as healthy as possible.

1266 Women are increasingly given the choice of participating in phase I studies, provided they use contraceptive methods. Generally on the enrollment of women in clinical trials, see subsection 8.5.2. below.

1267 *See* OIG (Recruiting), *supra* note 815, at 19; FDA (General Clinical Considerations), *supra* note 1231, at 8. *See also* LEDERER, *supra* note 54, at 119-20; VanTx report, *supra* note 148, at 18. The University of California at San Diego treats students asked to participate in research as a vulnerable (protected) population. *See* UCSD-SOPP, *supra* note 485, at 57.

1268 *See, e.g.,* VanTx report, *supra* note 148, at 18.

1269 In clinical trial terminology, side effects are referred to as "adverse events." See also the glossary at the end.

humans are administered the compound: If prior animals studies did not detect an existing harmful effect, these healthy volunteers will be the ones bearing the consequences.

Conducting the study on healthy volunteers *simplifies the analysis* for the researcher. Scientists can concentrate on the adverse effects caused by the compound; they will not have the additional burden of distinguishing adverse effect due to the patient's disease, weak state (e.g., a malfunctioning liver) or concomitant medications. A related reason not to start with patients is that even a low dose might still be fatal or dangerous to their debilitated organism; taking such a risk would be unethical.

The recruitment of healthy volunteers in phase I trials raises *ethical difficulties*. By definition, these volunteers do not stand to derive any personal benefit from the study, aside from the payment they may receive and the general health check-up they may be given (on payments, see subsection 8.6.4.1. below). Contrary to sick patients, healthy volunteers do not participate in the trial in order to receive medical care. Yet, they do face medical risks, for example if unexpected adverse events are discovered. This is a situation where the subject's interest is subordinated, though with his express consent, to the progress of science. Although this is rarely acknowledged as such, phase I trials with healthy volunteers constitute an exception to the general bioethical principle that insists on the primacy of the individual interest over those of the collectivity. For these reasons, certain countries had banned clinical trials on healthy volunteers. [1270] France was, until 1988, a case in point.[1271] Today, French clinical trials on healthy volunteers have to take place in specially designated facilities. Healthy subjects are listed in a national register.[1272]

The rule about using healthy volunteers allows for *exceptions*.[1273] Compounds to treat serious diseases are often known to be toxic,[1274] too toxic to test on healthy volunteers having nothing to gain out of it. Alternatively, these compounds can be less toxic to the extent they are administered to patients with the disease. Thus, trials targeting diseases such as cancer or AIDS are generally conducted on subjects with the disease.

6.1.2. Phase II clinical trials

Phase I has given the sponsor and the investigator initial information about the product's safety and side effects at various dosage. Starting with the dose that was found safe in healthy volunteers during the phase I trial[1275] (or even sometimes a slightly

---

1270 *See* J.-M. ROUZIOUX, LES ESSAIS DE NOUVEAUX MÉDICAMENTS CHEZ L'HOMME at 52, 113-25 (Masson 1978) (citing also the case of Spain and Portugal).

1271 *See* Pierre Bechtel, *Les règles légales imposées à la recherche clinique sur l'humain en France*, 39(1) CAHIERS MÉDICO-SOCIAUX 75 (1995). *See also* CCNE N°2, *supra* note 57, at 9-10; CCNE N°73, *supra* note 1259, at 6.

1272 *See* Bechtel, *supra* note 1271, at 79.

1273 But not necessarily, see for instance ICH E8, *supra* note 533, at section 3.1.3.1. (c). *See also* VASELLA, *supra* note 127, at 69-71 (explaining the process through which the first research subjects were selected for the Phase I trial of Gleevec).

1274 *See* FDA (Starting Dose), *supra* note 1237, at 2.

1275 *See, e.g.*, Edgardo Rivera et al., *Phase II Study of Pegylated Liposomal Doxorubicin in Combination With Gemcitabine in Patients With Metastatic Breast Cancer*, 21(17) JOURNAL OF CLINICAL ONCOLOGY 3249-3254 (Sept. 1, 2003).

lower dose[1276]), the compound is now administered for the first time in human subjects suffering from the relevant disease or condition.[1277] The objective is to get the first inputs as to the drug's efficacy.[1278] This is why this second phase is also called therapeutic exploratory:[1279] It explores the possible therapeutic benefits of the compound.

The number of subjects with the disease or condition that participate in this phase varies between 50 and 400.[1280] As for phase I, phase II patients are closely monitored. They may be hospitalized if the seriousness of their conditions requires it or if the duration of the study permits it. They are to undergo physical examination at least once a week, but often more frequently. Their vital signs, fluids and tissues are regularly checked, with specimens taken to provide as much information as possible on how the drug operates. The sponsor wants to know not only if its drug works, but also how. This knowledge is important to improve the compound or to reduce its side effects, possibly in future line extension of the product.

As was the case for phase I trials, phase II trials generally involve dose escalation to find the dosage that appears to work best, while limiting side effects.[1281] Adapting and finding the right dose is of great importance for subsequent phase III trials, as it is the only dose that will be administered to phase III patients. Adapting the dosage during phase III is nearly impossible which is why mistakes committed during phase II can be very damaging.

Subjects who participate in phase II trials are often selected on the basis of criteria chosen so as to increase the probabilities of a positive outcome. At this point, this is a normal choice, it would be regrettable if an efficacious compound was mistakenly abandoned. An illustration: AIDS treatments typically show greater efficacy on treatment-naïve subjects; if a drug were tested on a group comprised mostly of patients having run through several other medicines, the drug might show no efficacy even though it would have shown extraordinary results had it been tested on patients for whom this was the first treatment. Choosing a homogenous patient population by having stringent inclusion and exclusion criteria also facilitates interpretation of the results.[1282]

Phase II may also serve to identify the most appropriate patient population (target population) or the most appropriate therapeutic indication. General classes of diseases may have subdivision with subparts constituting different medical conditions. For ex-

---

1276 According to the ICH, "[h]istorically, drugs have often been initially marketed at what were later recognized as excessive doses …, sometimes with adverse consequences …. This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effects is seen, but practical study designs do not exist to allow for precise determination of these doses." ICH E4, at 1.

1277 For an example of a Phase II protocol, see the template proposed by the NCI at http://ctep.cancer.gov/forms/ph2_sing_temp3.doc.

1278 *See* 21 C.F.R. § 312.21(b).

1279 *See* ICH E8, at 3.1.3.2. (p.7)

1280 *See* 21 C.F.R. § 312.21(b). For example, Elan's and Wyeth Pharmaceuticals' Phase II clinical trial enrolled 375 subjects to study the efficacy of a possible vaccine for Alzheimer's disease; Douglas Steinberg, *Companies Halt First Alzheimer Vaccine Trial*, 16[7] THE SCIENTIST 22, (Apr. 1, 2002), at http://www.the-scientist.com/yr2002/apr/steinberg_p22_020401.html.

1281 ICH E8, section 3.1.3.2.

1282 The opposite rule should apply during a phase III trial: the subject population should be as diverse as possible. See further subsection 6.1.3.3. below.

ample, gastrointestinal disorders give rise to multiple subsets of conditions (e.g., gastroenteritis, reflux, esophagus), each one considered as a different therapeutic indication.

6.1.3. Phase III clinical trials

6.1.3.1. Objectives

Phase III trials are also called *therapeutic confirmatory* studies.[1283] As this expression suggests, the objective of such a trial is to confirm the initial showing of efficacy.[1284] While phase II had suggested positive outcomes for a few dozens or hundreds of patients, phase III verifies this result on a larger pool of subjects.[1285] The design of the phase III trial should follow up on that of the phase II trial (e.g., same combination of drugs used), given that the phase II results are the ones supporting the phase III trial. If the design of the two trials is too dissimilar, the sponsor may lack sufficient information to justify exposing a large pool of subjects to the risks of the phase III trials.

Although there are exceptions, the FDA has traditionally required not one but two well-controlled large clinical studies before approving drugs (see subsection 4.1.1.2. above).[1286] For some diseases, it takes *several* phase III trials to show *just one or two* positive outcomes. This is for example the case when the disease is very sensitive to the placebo effect (e.g., depression) (see on this notion, subsection 6.3.3. below). On the contrary, when the disease is life-threatening and there is no alternative treatment, even a single phase II/III clinical trial showing only slightly positive results may be reason enough to file immediately a marketing application.

6.1.3.2. Importance of phase III trials

Phase III studies are the most important of all phases. They determine whether the drug will finally be approved.

In the United States, the importance of phase III trials warrants a meeting between the sponsor and the FDA. Both want to make sure that the concept of the trial as it has been devised in its protocol is valid so that its results will be an appropriate basis to decide on the future marketing application.

1283 *See* ICH E8, at 3.1.3.3. (p.7).

1284 *See* 21 C.F.R. § 312.21(c).
The ICH distinguishes between trials designed to assess the safety and/or efficacy of a given drug and those that focus on comparative safety/efficacy of two treatments. *See* chapter 1.4 (p.5) of ICH E10. *See also* paragraph 6 Helsinki Declaration ("The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of aetiology and pathogenesis of disease.").

1285 According to CenterWatch, seven out of ten subjects are enrolled in phase III trials. *See* CenterWatch (Word from), *supra* note 681, at 2.

1286 *See, e.g.*, Kessler (Regulation), *supra* note 447, at 283. "The obvious purpose of a second study is to see if the results claimed in one study are reproducible and confirmed by another study." T-Up Inc. v. Consumer Protection Division, 801 A.2d 173, at 186 (C.App.Mar. 2002).

It is not rare to have a marketing application rejected because the phase III trials did not yield sufficient information for the agency to make up its mind. For the sponsor, such negative decisions are a huge setback, not least because this may drastically impact its market valuation.

Phase III trials may also fail even if they are well designed. In fact, between 50% and 75% of these studies end up failing. Either the drug is not as efficacious as expected or it has too many or too serious side effects. Serious drug adverse reactions generally have to do with hepatoxicity (e.g., liver injury).[1287]

6.1.3.3. Organization of phase III trials

Phase III trials are complex, expensive and time-consuming to run.

The number of research subjects enrolled in phase III depends on the disease investigated. If the disease affects only a small patient population, the size of the phase III trial will necessarily be small. Conversely, diseases that are widespread in the population will lead to bigger phase III trials. Chronic diseases, in particular, call for testing on a larger set of subjects.[1288] Very large clinical trials (sometimes called mega-trials) may include over 10,000 subjects, and last for several years.[1289] According to U.S. average data, an approved drug calls for testing on 4,400 subjects.[1290] Usually, the larger the pool of subjects, the better the odds of statistically proving efficacy.[1291]

Given the large number of subjects required, the organization of a phase III trial is particularly challenging. Patients do not originate from one same region and will therefore not all be treated by the same team of doctors. On the contrary, phase III trials are usually multicentric with many hospitals and clinics participating as investigators.[1292] Increasingly, primary physicians in private medical practices are involved in clinical trials; this allows the patient to continue seeing his usual doctor while participating in the trial (see also subsection 8.3.3.6. below).[1293] Multicentric trials also present the advantage of reducing bias or errors that could more easily occur if all the studies were per-

---

1287 Very often, hepatoxicity is difficult to anticipate because not strictly dose-related. *See generally* CDER, PhRMA, AASLD, Clinical White Paper, Conference 2000, at 1, (Nov. 2000), at http://www.fda.gov/cder/livertox/clinical.pdf.

1288 For example, the ICH recommends as a minimum "a database of about 1500 patients" for trials of antihypertensive drugs. Chapter 4 of the Draft ICH Principles for Clinical Evaluation of New Antihypertensive Drugs, E12A, signed as a principle document on March 2, 2000, from http://www.ich.org/cache/compo/475-272-1.html#E12A [hereinafter ICH E12A].

1289 *See* Press Release, Bristol-Myers Squibb, Clopidogrel Studied in one of the Largest Clinical Trial Programs, (Apr, 1, 2003), at http://investor.bmscom/ReleaseDetail.cfm?ReleaseID=161512.

1290 Centerwatch Sample, Sample, Patient Recruitment and Enrollment, Critical to Success, at 137, at http://www.centerwatch.com/bookstore/samples/grwinv02_ch10.pdf [hereinafter Centerwatch (Patient)]. According to OIG, "[a]n average of 4,237 subjects were used in New Drug Applications from 1994 to 1995, compared with an average of 1.321 subjects from 1981 to 1984." OIG (Recruiting), *supra* note 815, at 12.

1291 *See* Antman, *supra* note 3, at 763.

1292 Conducting a multicentric trial may be the only way to have enough subjects participate. *See* ICH E9, at section 3.2, (p.12). For example, the CURE trial of clopidogrel for acute coronary syndromes took place in 482 centers in 28 different countries. *See* Salim Yusuf et al., *Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials*, 266 JAMA 495 (July 3, 1991).

1293 *See* Franklin G. Miller & Donald L. Rosenstein, *The Therapeutic Orientation to Clinical Trials*, Sounding Board, 348 NEW. ENG. J. MED. 1383-1386 (2003), at http://content.nejm.org/cgi/content/full/348/14/1383.

formed in only one research site. Hence, drug agencies mistrust marketing applications whose data originate from a single source.[1294] Many phase III trials are also international with research sites located in different countries.[1295]

Besides involving many more patients than phase II, phase III lasts also much longer. A single clinical trial can take up to six or nine months, especially if the drug is intended for prolonged use. In its E1 Guideline, the ICH recommends that a drug be tested for one year if it is intended for use during 6 months.[1296] Moreover, the data gathered is typically so large (several hundreds kilograms of paper) that a lot of time is required for analyzing the data.

Phase III clinical trials always incorporate some control so as to compare the effect of the investigational drug with that of the control. As we will see in greater details in subsection 6.3.3., the product used as a control can either be a placebo or an active comparator* drug. The number of subjects who receive the investigational treatment need not be equal to the number of those who receive the placebo.[1297] On the contrary, in practice, the size of the control arm is often smaller than the size of the active arm. This is attractive to potential volunteers who logically have little if any interest in receiving a placebo.[1298]

6.1.4. Phase IV clinical trials

Under Swiss law, phase IV clinical trials are subject to the same regulations as earlier phase trials, even though at this stage the drug has already received its marketing authorization. In contrast, in the United States, certain phase IV trials are partially exempt from clinical trial regulations.[1299] This exemption targets low-risk studies exploited neither for advertising purposes nor to change the marketing authorization's specifications. Subjects' informed consent and ethical committee's approval is nonetheless still obligatory.[1300]

1294 *See, e.g.,* Press Release, Serono, Serono Announces Results of Fda Advisory Committee on Serostim® For Use in Patients with Short Bowel Syndrome, (June 25, 2003), at http://www.serono.com/media/stories2003/20030626_en.jsp?major=4&minor=1.

1295 "By 1997, 25% of Phase III protocols were conducted in multiple jurisdictions." Lamb, *supra* note 1144, at 11.

1296 To detect adverse events, the ICH recommends a pool of 300 to 600 subjects exposed for 6 months, with 100 subjects exposed for 12 months (at the dosage corresponding to that of the future final product). However, the total number of subjects enrolled in the trial should be in the 1500 range. Sections 5 and 6 (p.2) of the ICH E1 Guideline on the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-life-threatening Conditions, (Oct. 27, 1997), (step 4 of the ICH process), from http://www.ich.org/cache/compo/475-272-1.html#E1.
According to Jan Leschly, former CEO of SmithKline Beecham, "it takes about 1200 days to complete a Phase III trial." Ernst & Young, *supra* note 708, at 3.

1297 The ICH calls this practice "unbalanced randomization." It observes that such a study design helps to gather more information about the safety profile of the investigational compound. Chapter 2.1.5.2.5 (p.18) of ICH E10 Guideline.

1298 *See id.*

1299 *See* 21 C.F.R. 312.2(b)(1).

1300 *See* 21 C.F.R. 312.2(b)(1)(iv).

In Switzerland, phase IV studies must stay strictly within the ambit of the approved notice of use.[1301] Drug studies done to support an *entirely new* therapeutic indication (e.g., a breast cancer drug used this time against AIDS) cannot be done as phase IV[1302]. The whole procedure starting with either preclinical or phase I clinical studies must be started again.[1303]

6.1.4.1. Phase IV trials requested by the drug agency

We need to distinguish two types of phase IV clinical studies: those requested by the drug agency and those launched "spontaneously" by the sponsor. The first category is the subject of this subsection, while the phase IV studies of the second category are reviewed in subsection 6.1.4.2. below.

6.1.4.1.1. Reasons for phase IV studies

As soon as a sponsor has sufficient data to support a marketing application, it will file an application with the drug agencies of each country/region where it plans to market its product. It is in the interests of both the sponsor and the patients that this application be submitted as early as possible.[1304]

However, the corollary of early submissions is that some information may be missing or incomplete. To complete missing or weak data, drug agencies require complementary studies.

Hence, such studies are commonly requested for drugs approved on an *accelerated basis*. Because of their life-saving potential,[1305] these drugs may not even have gone through a phase III trial. Second, requests for phase IV studies are frequent for applications approved based on *surrogate* endpoints (see subsection 6.3.6.3. below). Third, drugs intended for prolonged use are often subjected to phase IV requirement, because even a long phase III trial may not be sufficient to ascertain all long-term effects of the drug.[1306]

1301 The drug being tested in phase IV trial must be identical to the one that received marketing approval (e.g., same strength, some galenic form). *See* IOCM Compassionate Explanations, *supra* note 471, at chapter B.1.2, at 171.

1302 The testing of a new therapeutic indications for an already approved drug should be conducted as a phase II or a phase III trial.

1303 Under the previous intercantonal system, see the glossary (under Phase IV trial) of the GCPs accompanying the (former) IOCM 1995 Regulation; *also* IOCM Compassionate Explanations, *supra* note 471, at chapter B.1.2, at 171.

1304 U.S. law even pushes for submission rapidly after sufficient data has been obtained; 21 C.F.R. § 312.7(c).

1305 See in the United States, 21 C.F.R. § 312.85.

1306 For example, in the case of mifepristone, the abortion-causing pill, the U.S. sponsor had to acquiesce in six post-marketing studies: "1) to monitor the adequacy of the distribution and credentialing system, 2) to assess long-term effects of multiple uses of the drug, 3) to follow the outcome of women who had surgical abortion following failed chemical abortions, 4) to ascertain how often women complete the whole regimen and find out what happened to women who did not, 5) to study the safety and efficacy in women under 18 or over 35 who smoke, and 6) to find out what happened to children born when the method 'fails.'" Randall K. O'Bannon, Complaint Filed With FDA Against RU486, at http://www.nrlc.org/news/2002/NRL09/ru.html.

In these three situations, the drug agency will make its marketing approval contingent on the sponsor's agreement to undertake one or several post-marketing studies.[1307] These studies are called phase IV clinical trials, post-marketing or post-approval studies. Phase IV trials are also referred to as phase IV *commitments*, because the sponsor usually negotiates the content of its obligations with the drug agency. If the sponsor and the agency cannot agree – which is rare in practice –, the agency will reject the sponsor's application.

The number of requested phase IV studies has regularly increased.[1308] In the United States, for the 1985-1986 period, they were required for 45% of all drugs approved by FDA.[1309] Between 1991 and 2001, on a total of 1,090 new drug applications ("NDAs") approved by the FDA, there were 2,328 postmarketing commitments.[1310]

6.1.4.1.2. Characteristics of phase IV studies

Phase IV studies may be about safety data (e.g., cardiovascular side effects), adverse drug reactions[1311] (e.g., determining the prevalence of a rare side effect[1312]), drug-drug interactions, efficacy on a given population (e.g., efficacy on patients aged over 75), efficacy on a specific form of the disease (e.g., efficacy on patients whose cancer is at an advanced stage).[1313] A drug agency is not limited as to the type of phase IV studies it can demand. It may ask for such studies in order to reduce risks that were not considered as being major enough to justify rejection of the application; it may also wish to improve the drug's ease of use by broadening the eligible patient population or by evaluating the drug's interactions with other medications.[1314] Thus, phase IV studies may lead to changes to the physician's label or to the patient's notice of use;[1315] it may even, though more rarely, result in changes to the approved therapeutic indications.

Often the design of phase IV trials is more *relaxed* compared to that of a phase III trial. Subjects and investigators in a phase IV trials are often not blinded, as this would pose too many problems. Patients can acquire the drug directly on the market and

---

1307 *See* in the United States, 21 U.S.C. § 356(b)(3), 21 C.F.R. 314.530, 314.81(b)(2)(viii & iv), and 601.43; FDA (Postmarketing Rule), *supra* note 1090, at 64,607. *See also* M.D. Greenberg, *supra* note 129, at 322-23 (discussing phase IV commitments in the context of Subpart E accelerated approval).

1308 Ronald S. Waife, *Rigor Vivus*, APPLIED CLINICAL TRIALS, (May 2003), at 35, at http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/222003/58177/article.pdf.

1309 In 1983, this percentage was only 17 percent. Office of Technology Assessment (OTA), Pharmaceutical R&D: Costs, Risks and Rewards, at 150-51, (OTA-H-522), (Feb. 1993), at http://www.wws.princeton.edu/cgi-bin/byteserv.prl/~ota/disk1/1993/9336/9336.PDF [hereinafter OTA (Pharmaceutical R&D)].

1310 *See* OIG (FDA Review), *supra* note 20, at 19.

1311 See, for definition, section 1.1 (p.2) of ICH E6.

1312 "[U]ncommon adverse events, such as those occurring at a frequency of less than 1 per 100 patients, cannot be identified in phases I-III." Thomas C. Jones, *Call for a new approach to the process of clinical trials and drug registration*, 322 BMJ 920 (Apr. 14, 2001), at http://bmj.com/cgi/reprint/322/7291/920.

1313 There may also be *preclinical* postmarketing studies (e.g., toxicology study). Similarly, postmarketing studies may entail manufacturing or chemistry control (e.g., a drug stability study).

1314 According to ICH, Phase IV studies may help "optimizing the drug's use." ICH E8, at section 3.1.3.4.

1315 Under Swiss terminology, the label intended for the patient is called the "*notice d'emballage*," "*Packungsbeilage*," and "*foglietto illustrativo*." Under E.U. terminology, it is called the Patient Information Leaflet ("PIL"). In the United States, labels intended for patients are not always mandatory; they are called Patient Package Insert ("PPI").

therefore have scant incentive to participate in a blinded study where they could receive only a placebo. Similarly, the physicians in private practice (who are hired as investigators to conduct phase IV studies) would not want to endanger their patients by submitting them to a blinded study.

Additionally, the large number of investigators-physicians and subjects-patients makes it hard to extend the same control as over phase III trials.[1316] Subjects may not go through the same number of tests or medical check-ups. Standards for the filling of case report forms (CRFs) by investigators may be loosened.

However, from a business perspective, investing in costly phase IV studies without retaining the same high scientific standards of "classic" clinical trials may not make sense, since a well-conducted phase IV trial may represent a first stepping stone for the extension of the drug's approved therapeutic indication.[1317] If the sponsor conducted this phase IV trial in a way that did not comply with the requirements imposed by drug agencies to phase I to III trials, the sponsor may have to replicate it in order to incorporate it in its future marketing application.[1318]

6.1.4.1.3. Compliance with phase IV commitments

The U.S. system of phase IV commitments based on voluntary compliance has significant *drawbacks*. Once the sponsor has obtained its prized marketing approval, it may not be too intent on honoring its commitments.[1319]

The REC deems that it cannot outright reject a study that entails no risks for patient-subject; it prefers to decline jurisdiction.

Public Citizen, an influential consumer organization in the United States, found that a large percentage of U.S. phase IV promises were not fulfilled.

> From 1990 through 1994, a total of 88 new molecular entities (NMEs) were approved which had at least one phase IV commitment. Only 13 percent (11 of the 88) were classified by the FDA as complete as of December 1999. This means that for at least five and as long as 10 years after drug approval, all of the studies for 87 percent of these drugs had not been completed. For the 107 NMEs with phase IV commitments approved between January 1995 and the end of 1999, not one drug has been classified by the agency as having completed commitments as of December 23, 1999. …
>
> The Medical Officers stated in our survey that 28 drugs had been approved in the previous three years only because phase IV studies were required.[1320]

1316 *See however* OTA (Pharmaceutical R&D), *supra* note 1309, at 150-51.

1317 *See* Waife, *supra* note 1308, at 36.

1318 "Sponsors cannot predict when they may want to use postmarketing data for a label extension, secondary indication, or competitive claims. When the opportunity strikes, data units in postmarketing organizations have to scramble to apply rigor retrospectively – something notoriously difficult to do. … The cost of rigor in postmarketing trials cannot compare to the cost of rerunning a trial under stricter standards or of trying to clean a trial retrospectively." *Id.*

1319 Mike Mitka, *Accelerated Approval Scrutinized: Confirmatory Phase 4 Studies on New Drugs Languish*, 289 JAMA 3227-3229 (2003), at http://jama.ama-assn.org/cgi/reprint/289/24/3227.pdf.

1320 Public Citizen's letter to FDA dated April 13, 2000, www.citizen.org/hrg/PUBLICATIONS/1520.htm. *See also* OIG (FDA Review), *supra* note 20, at 19.

Drug agencies can only counter this dishonest conduct by threatening to withdraw the drug's marketing authorization. However, it is difficult to use this threat, especially if the drug treats serious diseases.[1321] Pharmaceutical sponsors take advantage of this reluctance and ignore their previous commitments. Additionally, conducting rigorous phase IV clinical trials once the drug is available on the market is far from easy: patients see little reason to enroll in a trial when they can readily access the drug of their choice through their usual doctor.[1322]

The FDA has taken measures to induce better compliance from pharmaceutical firms.[1323] Firms have to provide yearly reports on the progression of their phase IV trials.[1324] The FDA has set up a web page listing all phase IV commitments.[1325] The FDA makes publicly available all information regarding phase IV commitments, except when it is considered a trade secret or would impinge on someone's privacy.[1326] The FDA also requests that phase IV studies be published.[1327] A prior and broader version of the disclosure requirements was opposed by the industry, and later abandoned by the FDA.[1328]

6.1.4.2. Phase IV trials decided by pharmaceutical companies

6.1.4.2.1. Objectives

Sponsors frequently decide to organize phase IV clinical trials for an approved drug, even though the drug agency has not requested it. In this case, sponsors' objectives are often more selfish: The aim is to "seed the market"[1329] and to capture larger market shares. The sponsor remunerates several, preferably preeminent, physicians (acting as

---

1321 Public Citizen surveyed medical officers from the FDA: "[Their] comments on the issue of relying on post-marketing studies for approval of new drugs included the following: 'Good idea but not way to enforce Phase IV studies. If sponsors don't do them correctly what recourse does FDA have? It's tough to pull a drug.' … 'My office director told me that he was going to overrule me because the sponsor (Wyeth-Ayerst) would just go over our heads to Capitol Hill. He felt it was best to approve the drug for an indication not studied and have the sponsors of a Phase IV post-marketing trial in support of the indication. I reminded him that this sponsor had failed to honor other Phase IV studies. He went ahead and approved the drug.'" Public Citizen, Study of the drug industry's performance in finishing required postmarketing research (Phase IV) studies. (HRG Publication #1520), (Apr. 13, 2000), at http://www.citizen.org/publications/release.cfm?ID=6721#report.
See also ASCO/FDA, *supra* note 572, at 8.

1322 *See generally* ASCO/FDA, *supra* note 572, at 8.

1323 *See, e.g.,* OIG (FDA Review), *supra* note 20, at 34.

1324 *See* FDA (Postmarketing Rule), *supra* note 1090.

1325 *See* CDER, FDA, Postmarketing Study Commitments, at http://www.fda.gov/cder/pmc/.

1326 Confidential commercial information that is not a trade secret can be disclosed. FDA, Draft Guidance, Reports on the Status of Postmarketing studies, (Apr. 2001), at chapter VI, at http://www.fda.gov/cber/gdlns/post040401.htm.

1327 *See, e.g.,* letter of FDA to AstraZeneca (conditionally approving the application for the drug Iressa), at http://www.fda.gov/cder/foi/appletter/2003/21399ltr.pdf. The distribution of Iressa has been severely restricted in 2005. *See* FDA, Gefitinib (marketed as Iressa) Information at http/www.fda.gov/cder/drug/infopage/gefitinib/default.htm.

1328 The former version would have made "the study protocol, … reports of unexpected suspected adverse drug reactions, and study results" available to the public. See FDA (Postmarketing Rule), *supra* note 1090, at 64,611.

1329 Eric Rose, *Pharmaceutical Marketing in the United States, A Critical Analysis*, Research paper, Washington University (1997), at http://faculty.washington.edu/momus/pharm.htm.

investigators) to administer the (now approved) drug to a large number of patients.[1330] It is hoped that these physicians will become familiar with the drug and get into the habit of prescribing it. Their patients may also get used to it so that they continue to demand it from their doctors.[1331] Participating investigators may also be invited to sign as co-authors of the published report summarizing the result of the trial;[1332] later, they give presentations and conferences to describe the study and – the sponsor hopes – to praise the drug to other health care providers. In this sense, phase IV studies are powerful marketing tools.[1333] This is illustrated by the fact that Phase IV studies may absorb up to 25% of drug companies' R&D funds.[1334]

Pharmaceutical companies may also conduct clinical trials to benefit from the U.S. *safe harbor* provisions for off-label advertising: Under certain conditions, companies may circulate information about off-label use of their products if that information is derived from their clinical trials.[1335]

6.1.4.2.2. Characteristics

As mentioned earlier, phase IV studies tend to be conducted less rationally and competently than phase III trials.[1336] Sponsor-initiated phase IV trials can be significantly worse, because the drug agency exercises very little control over them. The sponsor has no obligation to submit the result to the agency. Thus, if the trial yields adverse information, the sponsor may choose to keep it secret.[1337]

The shortcomings of these phase IV trials also spawn *ethical* concerns. Is it fair to let subjects enroll in a study done not to expand knowledge, but to convince physicians to prescribe the sponsor's drug instead of a competing product, which may well be more effective or cheaper?

The Geneva outpatient ethics committee has had to grapple with these ethical issues.[1338] Many – if not most – protocols it receives are for promotional phase IV studies.

1330 Those prestigious doctors are sometimes referred to as thought or opinion leaders.

1331 "This [Phase IV trials] is marketing thinly disguised as research and is greatly helped by – and probably not possible without – a system of undisclosed payments." Rao & Sant Cassia, *supra* note 960, at 36.

1332 However, according to ICMJE, "collection of data … alone, does not justify authorship." ICMJE, *supra* note 945, at II.A.1.

1333 *See* ARNO & FEIDEN, *supra* note 125, at 156 (describing a sham phase IV study of pentamidine by Lyphomed).

1334 *See* Ogg, *supra* note 664 (pointing out that the increase in clinical research investment has been "largely driven by an increase in post-marketing clinical activities"); Melody Petersen, *What's Black and White and Sells Medicine*, N.Y. TIMES, Aug. 27, 2000, at http://www.nytimes.com/library/financial/sunday/082700biz-pfizer.html.

1335 *See* § 401 of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), at http://www.fda.gov/cdrh/modact97.pdf (p.61-67). The section 401 was "modified" by the decision in Washington Legal Found. v. Henney, 56 F. Supp. 2d 81 (D.D.C. 1999). *See also* O'Reilly & Dalal, *supra* note 429, at 297.

1336 *See* Waife, *supra* note 1308, at 35.

1337 *See generally* Bruno Truniger et al., *Ethikkommissionen zwischen Anspruch und Wirklichkeit*, 82(45) BULLETIN DES MÉDECINS SUISSES 2398, at 2402 (2001), at http://www.saez.ch/pdf/2001/2001-45/2001-45-1114.PDF; Sarah Boseley, *GSK 'held back' data on drug for children*, THE GUARDIAN, Feb. 3, 2004, at http://society.guardian.co.uk/mentalhealth/story/0,8150,1137715,00.html.

1338 Interview with Stefano Ciaroni, President of the ethics committee for outpatient/private physicians (the "outpatient REC"), in Geneva, (Aug. 20, 2003).

The scientific validity of these studies leaves much to be desired. These studies will not answer any real and open medical question – often because the answer is already well known. Hence, this ethics committee finds itself in a difficult situation. When the study really seems "bogus," it refuses to even consider the application, telling the investigator that the study is outside the REC's scope of review. The REC deems that it cannot outright reject a study that entails no risks for patient-subject; it prefers to decline jurisdiction. When the study is not entirely absurd, and provided that subjects are not put at risk, the REC gives a favorable opinion, even though it may not like the underlying motivations (see also subsection 7.1.3.3. below).

6.1.4.3. Pharmacovigilance

Once a drug is authorized and placed on the market, its sponsor has to set up a pharmacovigilance program.[1339]

6.1.4.3.1. Purpose of pharmacovigilance

Pharmacovigilance programs aim at gathering additional information about the safety and efficacy of the drug. They mainly focus on *serious or unexpected adverse events**. Pharmacovigilance data can result in an endorsement of the benefit-risk assessment reached by the drug agency or in its reversal.

Pharmacovigilance is a broad concept which can take a variety of forms. Phase IV commitments fall within this concept, as well as non-interventional trials (see above subsection 3.4.6.1.). However, the focus of this subsection is on "routine" pharmacovigilance through reports from third parties. Such pharmacovigilance information is derived from individual observations made by health care practitioners prescribing the drug to their patients.[1340] There are no protocols, no enrollment of subjects, no control. Rather, it is based on the reporting of multiple observations made in ordinary health care settings.

Pharmacovigilance is essential because even large size clinical trials (e.g., phase III or IV) cannot enroll enough subjects to detect *all* adverse effects. Imagine that a drug is used by 4 million people throughout the world and that a serious side effect (e.g., stroke) affects 1 patient in every 2,000; in real life, that would mean 2'000 patients whose conditions will deteriorate. But during clinical trials, the sponsor had little chance to discern this adverse reaction, since on a large trial of 4,000 subjects, only two will experience this side effect.[1341] These two occurrences may easily go unnoticed, for example, because the investigator was unable to distinguish strokes caused by the drug from those due to other causes (e.g., the subject's preexisting cardiac conditions). Furthermore, patients taking the drug once it is approved differ from the subjects who took it

---

1339 *See* Articles 58.3 and 59 LPTh; Articles 35 to 39 OMéd.

1340 Health care providers to (e.g., physicians, hospitals) send their reports to the drug manufacturer, to the drug agency, or to both. In the United States, patients can report an adverse effect directly to the drug agency (see below).

1341 *See, e.g.,* GAO, Adverse Drug Events, Substantial Problem but Magnitude Uncertain, at 6, (Feb. 1, 2000), (Testimony before the Senate Committee on Health), (GAO/T-HEHS-00-53), at http://www.gao.gov/new.items/he00053t.pdf.

before approval; they are not as closely monitored as subjects (e.g., lower compliance with the drug's notice of use); they may be taking other drugs (i.e., drug-drug interaction problems); they may be in poorer health as compared to subjects (e.g., older patients suffering from concomitant diseases).[1342]

Consequently, postmarketing pharmacovigilance regularly reveals facts (whether positive or negative) that were ignored at the time the drug was approved. When it unveils side effects that were previously unknown or that are more serious than initially thought, the drug's label is changed accordingly. Health care practitioners receive "Dear Doctor/Dear Healthcare Professional" letters to warn them of the new risk assessment.[1343] When the adverse reaction is too severe as compared to the drug's benefit, the drug may be withdrawn from the market (see subsection 4.1.1. above).[1344]

Despite this crucial role of pharmacovigilance, the industry has been accused of minimizing reports of adverse reactions.[1345] Once the drug is on the market, negative pharmacovigilance statements are evidently going to affect its sales. Consequently, the financial community systematically "punishes" the manufacturer by pushing its stock price down. Naturally, to avoid this, the manufacturer can be tempted to downplay physicians' and patients' negative reports. The manufacturer incurs little risk because drug agencies rarely succeed in exposing such a fraud. Drug agencies experience difficulties in assessing pharmacovigilance reports and balancing them with the industry's responses.[1346] Assessing pharmacovigilance reports is difficult, among other reasons, because the reports rarely contain enough information to attribute with certainty an adverse event to a given drug. The manufacturer generally contends that the event was provoked by another cause (e.g., a concomitant medical condition of the patient) and the drug agency lacks the data that would permit to disprove this contention.

6.1.4.3.2. Periodic safety update reports

Pharmacovigilance is most important during the first few years after the drug reaches the market, because at that point in time, physicians have little experience with the drug. During these first few years, marketing authorization holders ("MAH") are therefore asked to submit yearly reports summarizing the newly acquired knowledge per-

---

1342 *See id.*

1343 *See, e.g.,* Novartis, Important Drug Warning Letter (Feb. 22, 2002) http://www.fda.gov/medwatch/SAFETY/2002/Clozaril_deardoc.pdf; Aventis, Important Prescribing Information (Oct. 2003) (regarding Arava), at http://www.fda.gov/medwatch/SAFETY/2003/arava_deardoc.pdf.

1344 In the United States, only a couple of drugs are withdrawn each year. "[B]etween FY [fiscal year] 1983 and FY 1992, the rate of safety-based withdrawals for NMEs [new molecular entities], based on the year of receipt, was 2.5 percent, and between FY 1993 and FY 2002, it was 2.8 percent…" OIG (FDA Review), *supra* note 20, at 2.

1345 *See* DONATINI, *supra* note 127 (recounting, throughout his book, several occurrences where information about adverse reactions was deliberately – and sometimes fraudulently – concealed by the industry). See also the U.S. cases of Stanton v. Astra Pharmaceutical Products, Inc., 718 F. 2d 553 (3d Cir. 1983) (where Astra had decided not to file its adverse reaction reports with the FDA); Rolland v. SmithKline Beckman, 1990 U.S. Dist. Lexis 6252 (D.C.E.Penn. 1990) (where SmithKline delayed reporting of serious adverse reactions reports).

1346 *See, e.g.*, DAVID HEALY, LET THEM EAT PROZAC (New York Univ. Press 2004).

taining to the drug.[1347] These reports are often called "PSURs," for periodic safety update reports. PSURs present a comprehensive analysis of new safety information acquired by the MAH during a given lapse of time following placement on the market. PSURs include serious adverse events reports, but go far beyond them to encompass, for example, literature review and post-marketing clinical trial data.[1348] PSURs must also contain evidence of lack of efficacy, especially when the drug targets a serious disease.[1349] The MAH should explain therein the number of patients who have been administered the drug (i.e., patient exposure).[1350] PSURs also describe the status of the drug – approved for marketing or submitted for authorization, authorization denied or restricted – throughout the world.[1351] Their purpose is to determine whether the evidence on the basis of which the marketing authorization was delivered is still valid or, on the contrary, warrants a change of the product information, particularly the physician's and the patient's notices of use.[1352]

In Switzerland, the obligation to file PSURs lasts five years following marketing approval.[1353] According to Swissmedic's guidance, these reports have to be filed every six months during the first two years following issuance of the marketing authorization for a new drug; during the three remaining years, the reports must be provided annually.[1354] For changes in the marketing authorization of an already approved drug, including a new therapeutic indication, the periodicity is decided by Swissmedic.

In the United States, the MAH must file a PSUR every six months during the first two years following marketing approval, then every year for the next three years, and finally every five years.[1355] The ICH recommends setting the interval between PSURs at six months.[1356] It proposes to use a single starting point – the International Birth Date ("IBD"), that is the date of the first marketing authorization delivered in an ICH region – to begin calculating the periodicity of PSURs.

1347 To facilitate uniform reporting throughout the three ICH regions, the ICH has adopted a common terminology, called MedDRA (Medical Dictionary for Regulatory Activities Terminology). *See* ICH, MedDRA, Introduction, at http://www.ich.org/Main.jser?@_ID=514.

1348 *See* ICH, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, E2C, Step 4 of the approval process, at section 1.4.6, at p.5 (Nov. 6, 1996), at http://www.ich.org/MediaServer.jser?@_ID=477&@_MODE=GLB [hereinafter ICH E2C Guideline].

1349 *Id.* at chapter 1.4.2, at p.3 and at chapter 2.8.1, at p.14.

1350 *Id.* at chapter 2.5, at p.10.

1351 *Id.* at chapter 1.2, at p.2 and at chapter 2.2, at p.9.

1352 *Id.* at chapter 1.4.5, at p.4.

1353 Article 34 OMéd.

1354 *See* Swissmedic, Journal 8/2002, at 529, (Aug. 2002), at http://www.swissmedic.ch/files/pdf/08_2002.pdf. This rule applies to drugs or drug changes approved after January 1, 2002. Moreover, the relevant date to calculate the interval between PSURs is the international birthdate according to ICH E2C Guidance (see *supra* note 1395). See also for further information, Swissmedic, Journal 6/2003, at 511 (June 2003), at http://www.swissmedic.ch/files/pdf/06_2003.pdf.

1355 In the United States, see 21 C.F.R. § 314.80(c)(2) (making *quarterly* periodic adverse drug experience reports mandatory for three years).

1356 *See* ICH E2C Guideline, at chapter 1.4.4, at p.4.

6.1.4.3.3. Adverse reactions reports

Marketing authorization holders ("MAH") must also file adverse reaction reports whenever a serious or unexpected adverse reaction is observed.[1357] In Switzerland, physicians are *required* to file adverse drug reaction reports.[1358] Patients are allowed to make such reports, but are encouraged to do it through their doctors.[1359]

In the United States, both physicians' and patients' reporting are optional.[1360] An advantage of the U.S. system resides in the fact that pharmacovigilance reports are available for consultation.[1361] These reports are indeed perused by watchdog groups, which can use them to request the withdrawal of the drug of concern.[1362]

6.1.5. Flexibilities in the phase division

As noted at the beginning of subsection 6.1., the division according to phases is partly artificial.[1363]

First, a phase often encompasses more than one study; for instance, a phase II may entail several tests on different subgroups of patients. For any given drug, it is rare that a *single* phase I, phase II and phase III trial is enough to obtain marketing approval. On the contrary, there are several clinical trials for each phase, in particular for early phases.

Second, there are often overlaps between clinical trials of various phases.[1364] Certain tests belonging to a given phase can take place simultaneously with the next phase.

1357 Articles 35 and 36 OMéd (once the drug has been approved). During clinical trials, see Articles 22 and 23 OClin and subsection 9.1.2. below.
In the United States, see 21 C.F.R. § 314.80 (after issuance of a marketing authorization).

1358 *See* Article 37 OMéd. Swissmedic asks that both *serious* and unexpected (new or insufficiently labeled) adverse reactions be reported. *See* Swissmedic, Que faut-il annoncer et dans quels délais? [What must be reported and when?], at http://www.swissmedic.ch/html/content/Was%20und%20wann-f.html.
See also decision of the Swiss federal appeal commission for therapeutic products, JAAC 67.59, at point 2.3.2. (Nov. 6, 2002), at http://www.vpb.admin.ch/franz/doc/67/67.59.html (denying the manufacturer the right to be told the identity of reporting physicians).

1359 *See* Swissmedic, Qui est soumis à l'obligation d'annoncer ? [Who is subject to the duty to report?], at http://www.swissmedic.ch/html/content/Wer%20meldet-f.html.

1360 *See* FDA, MedWatch Reporting by Consumers, at http://www.fda.gov/medwatch/report/consumer/consumer.htm; FDA, Voluntary Reporting by Health Professionals, at http://www.fda.gov/medwatch/report/hcp.htm; FDA, MedWatch, Form 3500 for voluntary reporting of adverse events and product problems, at http://www.fda.gov/medwatch/safety/3500.pdf. *See also* Susan J. Landers, *Doctors key to triggering FDA's warning signals*, AMN News (Nov. 17, 2003), at http://www.ama-assn.org/amednews/2003/11/17/hlsb1117.htm (indicating that, in 2002, about 25,000 voluntary reports had been filed by health care practitioners and patients).

1361 *See* MedWatch, FDA Adverse Event Reporting System, at http://www.fda.gov/medwatch/index.html.

1362 *See, e.g.,* Letter of Public Citizen to the Commissioner of the FDA, (Sept. 3, 2003), (requesting the withdrawal of Abbott's diet drug Meridia on the basis of safety concerns), at http://www.citizen.org/publications/print_release.cfm?ID=7273; Letter of Public Citizen to the Commissioner of the FDA, (Mar. 4, 2004), (requesting the withdrawal of AstraZeneca's Crestor due to safety concerns), at http://www.citizen.org/publications/release.cfm?ID=7305.
The approximate percentage of safety-related withdrawals is 3%. *See* Kaitin, *supra* note 717, at 2.

1363 *See* ICH E8, at section 3.1.3.

For example, certain pharmacology tests typically classified as phase I (e.g., drug-drug or drug-food interaction) can take place while phase III trials are already underway.[1365]

Third, some nonclinical tests are conducted during all three phases, albeit with refinements brought from each of the successive phases. For instance, manufacturing controls (which do not involve human subject participation) are necessary at each of the three phases, although the type and severity of controls vary and evolve. Certain in vitro or animal tests may be performed in parallel with clinical tests, for example to investigate further adverse reactions.[1366]

Four, a sponsor may choose to skip or merge certain phases. This occurs when the drug is intended for a life-threatening condition for which no treatment is yet available. To accelerate the regulatory approval process and possibly to save the lives of people dying, drug agencies consent to the drug being put on the market with only preliminary evidence of its efficacy and safety.[1367] In 1986 Burroughs Wellcome's AZT was tested in phase II on 282 treatment-naïve subjects infected with AIDS.[1368] After six months of study, the trial was halted as subjects on AZT were found to fare much better than those on placebo.[1369] Shortly afterwards, the FDA approved the drug without requesting a phase III trial.[1370] In 1988, the FDA adopted new regulations that codified this accelerated approach to clinical trials. Under Sub-Part E,[1371] life-saving drugs could be approved without data from a formal phase III trial. In 1991, the FDA approved Bristol-Myers' ddI, an anti-AIDS drug, mostly on the basis of phase I studies and post-marketing commitments.[1372]

Five, some clinical trials are so difficult to classify according to this system that they are called phase I/II or phase II/III.[1373] Distinctions are sometimes made depending on whether the study is pivotal or not. Pivotal studies are those deemed decisive in order to gain marketing approval. Non-pivotal studies are frequently done for marketing purposes; it would be preferable and less misleading not to include them in the phase I to III classification. The FDA rejects the term "pivotal" as misleading since it wrongly implies that the study was important or that it had highly positive results.

Six, there can be significant differences within clinical trials belonging to the same phase depending, for example, on the number of subjects recruited. A small trial in which subjects continue to be "treated" by their primary doctor acting as investigator

---

1364 *See* 21 C.F.R. § 312.21. *See* Bernd Rosenkranz, *Biomarkers and Surrogate Endpoints in Clinical Drug Development*, APPLIED CLINICAL TRIALS 32 (July 2003), at http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/312003/64896/article.pdf.

1365 *See* ICH E8, at section 3.1.3 and at 3.1.3.1. *See* FDA (General Clinical Considerations), *supra* note 1231, at 6.

1366 *See* ICH S7A, at 7; ICH M3, for example at 5.

1367 See in the United States, 21 C.F.R. § 312.84.

1368 *See, e.g.,* BRODY, *supra* note 447, at 170.

1369 The results were startling: "19 of the 137 patients on placebo had died, compared with just 1 of the 145 patients taking AZT." *See* ARNO & FEIDEN, *supra* note 125, at 43.

1370 The drug was approved in March 1987, only a few months after Burroughs Wellcome had finalized its application. *Id.* at 43-44, and also at 45-46 (recounting the FDA advisory committee's discussion of the AZT clinical data). *See also* Kessler (Regulation), *supra* note 447, at 287; M. D. Greenberg, *supra* note 129, at 312.

1371 *See* 21 C.F.R. § 312.84. *See* ARNO & FEIDEN, *supra* note 125, at 108.

1372 *See* ARNO & FEIDEN, *supra* note 125, at 220-23.

1373 *See e.g.,* Evelyn B. Toigo et al., *supra* note 687. *See also* CCNE N°73, *supra* note 1259, at 4.

can be utterly different from a large study taking place in an academic research center and managed by CROs or specialized physicians-investigators. Trials belonging to the first category will very much resemble "ordinary medical care." Good Clinical Practices, such as the ICH E6, rather target trials of the second category. Similarly, this thesis focuses chiefly on large and "professional" clinical trials.

Despite its limitations, the phase division has advantages. It serves as a good indicator of the risks and the degree of uncertainty. Thus, financial analysts attach great weight to the passage of these phases. When a pharmaceutical company successfully achieves a phase II trial for one of its promising compounds, the chances that this compound will make it to the market increase and the company's valuation rises. On the contrary, if a young biotech company announces disappointing results for a phase III trial, this can trigger a massive drop in market valuation.

This phase division is also reflected in the guidelines of drug agencies. For example, in the United States, a drug sponsor will typically meet with the FDA to discuss study design before beginning a phase III trial.[1374] For practical reasons, many ICH guidelines relate to a given phase of clinical trials even though ICH has criticized this partition. ICH has suggested replacing the phase denomination by an alternative designation based on the study purpose; it advocates the following terminology: human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use.[1375]

[1374] "At specific times, during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies …." 21 C.F.R. § 312.47(b).

[1375] *See* section 3.1.3 of ICH E8.

6.2. The key documents of a clinical trial

6.2.1. The protocol

The protocol is *the* central document that governs a clinical trial.[1376] The norm is one protocol per clinical study[1377] and per tested compound.[1378] The protocol should cover all important aspects of the trial, from a medical, practical, ethical, and statistical point of view.[1379] It can be depicted as a set of precise instructions for the investigator. Read-

[1376] See, for a definition, section 1.44 (p.6) of ICH E6 and Article 2(h) of E.U. Directive 2001/20/EC. *See also* paragraph 13 Helsinki Declaration.

[1377] One protocol generally governs a trial conducted at several different centers or locations: "A multicenter study is a single study under a common protocol, involving several centers (e.g., clinics, practices, hospitals) where the data collected are intended to be analyzed as a whole (as opposed to post-hoc decision to combine data or results from separate studies)." ICH E3 Guideline on the Structure and Content of Clinical Study Reports, (Step 4 of the ICH Process), (Nov. 30, 1995), at chapter 11.4.2.4. (p.17), from http://www.ich.org/cache/compo/475-272-1.html#E3 [hereinafter ICH E3].
The advantages of multicenter studies are manifold: "Multicenter trials are carried out for two main reasons. First, a multicenter trial is an accepted way of evaluating a new medication more efficiently; under some circumstances, it may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable timeframe. Multicenter trials of this nature may, in principle, be carried out at any stage of clinical development. They may have several centers with a large number of subjects per center or, in the case of a rare disease, they may have a large number of centers with very few subjects per center. Second, a trial may be designed as a multicenter (and multi-investigator) trial primarily to provide a better basis for the subsequent generalization of its findings. This arises from the possibility of recruiting the subjects from a wider population of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. FDA, Guideline on Statistical Principles for Clinical Trials, in Fed. Reg., Friday, May 9, 1997, at 25717.

[1378] Generally, different molecules tested will be the subject of separate protocols. Similarly, different formulation of an active substance will normally be studied by distinct protocols. *See generally* FDA, Center for Drug Evaluation and Research, Screening INDs, Manual of Policies and Procedures, at 1 (MAPP 6030.4), (May 9, 2001), at http://www.fda.gov/cder/mapp/6030-4.pdf.

[1379] The length of a protocol varies; the average range is between 20 and 40 pages without the appendixes. The typical chapters of a protocol are the following. There is first a short abstract or synopsis. The background section gives information about prior preclinical (laboratory and animal) and/or clinical studies. This background usually offers justification for the pending next step of clinical testing. Another section of the protocol describes the trial's objectives. There are often several objectives, divided into primary and secondary objectives. A chapter clarifies the design of the trial. It includes a description of the study population and the corresponding inclusion/exclusion criteria. If the subjects are allowed to take concomitant medications, the protocol should say which and how to take them into account. A chapter focuses on the experimental pharmaceutical, detailing its content, storage, labeling and how it should be administered to the subjects. An important chapter explain the study procedures and their assessment. For example, it states the method of randomization and blinding. It lists the number and timing of each subject's visit or investigator's intervention. Generally, subjects' visits take place every two to four weeks so as to monitor the effects of the drug by taking serum samples. It enumerates the measurements and the data to be collected. These data are often divided into safety/tolerability and efficacy. For a better understanding of the procedures, protocols typically provide a flowchart depicting the timing of the study's key steps. A chapter says at which conditions the clinical trial must be stopped, whether in part (for certain subjects) or in its entirety (see also subsection 5.8. above on the data and safety monitoring board (DSMB)). A chapter contains the procedure to be observed for reporting adverse events, serious or minor. A key chapter describes how the results of the trial are to be evaluated and lists the statistical methods to be used. The type of evaluation is derived from the study objectives, i.e., the outcome considered and the endpoints studied. The investigator's duties are itemized in one chapter; they embrace the mandatory standards with respect to subjects' protection (i.e., prior approval by ethical review board, subject's informed consent). The same goes for the monitor's duties. Other issues dealt with in the protocol are: confidentiality, record retention, publication, reimbursement, insurance, and time table. A protocol normally ends with a list of scientific articles that can be used as references with regard to the experimental product or the conduct of the trial. It also encloses various schedules or appendixes, including the informed consent forms. *See* 21 C.F.R.§ 312.23(a)(6)(iii)(*a*), (*c*), (*f*). *See* CDER, PhRMA, AASLD, *supra* note 1334, at 4. *See* WHO, Operational Guidelines for Ethics Committees that Review Biomedical Research (2000), at point 5.3.3 (p.7-8), at

ing the protocol, the investigator should know exactly what to do, when and how; she should know what to report and how. The protocol should be as simple and straightforward as possible so as to limit the risks of errors.[1380] In multicentric trials, videotaped instructions for the benefit of the investigator are increasingly common to ensure uniformity in the conduct of these trials.[1381] The investigator may assume that what is not in the protocol is left to her own discretion.

Besides being a set of instructions for the investigator, the protocol also incorporates systematic strategies to minimize bias (see further subsection 6.3. below). The protocol must clearly state the statistical methods used to guarantee and assess the reliability of the clinical trial results. These methods will be an indication of whether the study outcome can be generalized or is due to chance.[1382] Proper use of these methods become increasingly important with each successive development phase.[1383]

6.2.1.1. Contents of a protocol

Protocols are about 20-page long documents.[1384] The more complex the clinical trial, the more detailed the protocol should be. Hence, phase I protocols can be less exhaustive than phase III protocols.[1385] Conversely, the simpler the protocol, the better the chances that it will be thoroughly followed. Exceedingly complex or demanding protocols give rise to compliance problems.[1386]

Protocols are habitually written in English, which has emerged as the universal language of clinical medicine.[1387] Clinical trials are given a name[1388] and one or several numbers.

---

http://www.who.int/tdr/publications/publications/pdf/ethics.pdf [hereinafter WHO (Operational Guidelines)]; COREC's statement on Governance arrangements for NHS Research Committees, at point 10.6.c (p.30), (July 2001) at http://www.doh.gov.uk/research/documents/gafrec.pdf [hereinafter COREC]. The COREC statement is based on the WHO's Guidelines. For an example of flowchart, see the Dryvax pediatric smallpox protocol (DMID 01-650 protocol), at 23 (Sept. 27, 2002), at http://www.hhs.gov/ohrp/dpanel/tdryvax.pdf.

1380 *See* IOM (Assuring), *supra* note 1132, at 13. *See* ICH E9, at section 2.1.2, p.4 (recommending that a confirmatory trial only address "a limited number of questions.").

1381 *Id.* at 15.

1382 *See* ICH E9, at section 1.2, p.2 (requesting that the trial statistician be submitted the protocol for prior approval); EMEA, Biostatistical methodology in clinical trials, Note for Guidance, at 135, (last revised in May 1993), at http://dg3.eudra.org/F2/eudralex/vol-3/pdfs-en/3cc7aen.pdf [EMEA (Biostatistical Methodology)].

1383 *See* ICH E9, at section 1.2, p.2 and at section 2.1.2., p.4.

1384 Templates for drug clinical protocols can be found, for example, from http://www.med.upenn.edu/ohr/protocol/templates.html. Examples of entire protocols are available, for example, at http://ctep.cancer.gov/guidlines/templates.html, and at http://www.hhs.gov/ohrp/dpanel/tdryvax.pdf (Dryvax pediatric smallpox clinical trial). *See also* CIOMS 2002 Guidelines, *supra* note 105, at Appendix 1.

1385 *See* 21 C.F.R. § 312.23(a)(6)(1).

1386 For example, if the protocol sets the subjects' visits at too close intervals (e.g., subjects must go the hospital three times a week), the subjects may refuse to obey the instructions and, as a result, the investigator will not be able to collect the necessary data and fill the appropriate forms. *See generally* EFGCP Audit Working Party, Protocol Compliance, at section 4, page 5, at http://www.efgcp.org/webitems/protocol_compliance.pdf [hereinafter EFGCP (Protocol)].

1387 *See also* Article 3.22 of the (former) Good Clinical Practices accompanying the IOCM 1995 Regulation (accepting Case Report Forms (CRFs) in English).

The number serves to identify the protocol and the trial. A first number is given by the sponsor. A second number is ascribed by drug agencies.[1389] Finally, to facilitate the worldwide identification of clinical trials, the British Medical Research Council ("MRC") and Current Controlled Trials have set up an interesting system of using a unique identifier, the ISRCTN number.[1390] Upon application by the sponsor, a single eight-digit number is given to each and every randomized clinical trial. This number thus identifies a unique trial. It should be mentioned in all relevant correspondence, administrative action, and publications.[1391] This proposal reins in duplicative publications whereby the same trial results are in fact published in different journals as if these results arose from different trials.[1392] The unique identifier allows to track and isolate a particular trial in the different databases where it may be registered several times.

Protocols usually comprise one sentence confirming that the trial will be conducted according to ethical principles, generally referring to the Helsinki Declaration[1393] or, in the United States, the Belmont Report.[1394]

6.2.1.2. Preparation of the protocol

The protocol is the product of the sponsor's methodical ideas on how best to reach its goals, that is to gauge the safety and efficacy of its experimental compound. Because drug agencies only accept reliable information, the sponsor must make sure that infor-

---

See generally Matthias Egger et al., *Language bias in randomized controlled trials published in English and German*, 350 LANCET 326-329, at 328 (Aug. 2, 1997) (finding that authors are more likely to publish significant results in English-language journals).

1388 The protocol and its corresponding clinical trial are given a title. Nowadays, the main title often consists in a catchy abbreviation of the full title (e.g., CURE, ENABLE, MIRACLE, WIZARD). The "branding" of clinical studies is a fairly recent phenomenon, thought to reflect various trends such as collaboration between academic researchers and pharmaceutical companies. A recent review identified more than 2000 named trials as of 1998." Michael Berkwits, *CAPTURE! SHOCK! EXCITE! Clinical Trial Acronyms and the "Branding" of Clinical Research*, 133 ANN. INTERN. MED. 755-762 (Nov. 7, 2000), at http://www.annals.org/cgi/reprint/133/9/755.pdf. Choosing a catchy name may help create public interest in the study whether at the recruitment stage or when its results are published. However, this practice was also criticized as potentially misleading for potential enrollees. *See also* James P. Orlowski & James A. Christensen, *The Potentially Coercive Nature of Some Clinical Research Trial Acronyms*, 121 CHEST 2023-2028 (June 2002) (evaluating named studies for possible subliminal enticement).

1389 *See* Swissmedic form, *Formulaire de notification pour les essais cliniques de médicaments* [Notification form for drug clinical trials], at 4 (updated in April 2005), at http://www.swissmedic.ch/files/formulare/B3.1.121-f.pdf.

1390 Guidance Notes for the Use of the International Standard Randomised Controlled Trial Number (ISRCTN) System, at http://www.controlled-trials.com/isrctn/sample_documentation.asp.

1391 *See, e.g.,* E.U. Guidance (Database), supra note 270, at 4 (requiring the entry of the ISRCTN number, if there is one, on the European EUDRACT database).

1392 Several medical journals already require that the ISRCTN number be indicated in the publication of study results. *See also* ICMJE*, supra* note 945, at III.D.2. ("Duplicate publication of original research is particularly problematic, since it can result in inadvertent double counting or inappropriate weighting of the results of a single study, which distorts the available evidence."). Also on duplicative publication, see Erik von Elm et al., *Different Patterns of Duplicate Publication*, 291 JAMA 974 (Feb. 25, 2004), at http://jama.ama-assn.org/cgi/reprint/291/8/974.pdf ("[T]o produce an article that overlaps substantially with an already published article without adequate, cross-referencing is misconduct."); MRC, *supra* note 938, at 13.

1393 *See* paragraph 14 Helsinki Declaration.

1394 See subsection 2.3.2. above.

mation is collected according to methods that reduce the potential for bias to the maximum (see further subsection 6.3.3. below).[1395]

Pharmaceutical companies that intend to apply for marketing approval must *promptly* think about how to conduct their research in general, and their clinical trials in particular. Botching this stage may have critical consequences. An example: Syntex started widely distributing its investigational compound to AIDS patients on a compassionate basis.[1396] The reports it got back from doctors and patients were excellent: The drug was very effective against CMV (cytomegalovirus) retinitis. However, this good new was also bad news. Because both the medical and patient community were convinced that the drug was effective, nobody wanted to recommend, let alone participate in, the clinical trials.[1397] And so Syntex had practically no data to submit to the FDA. Even though the FDA agreed that the drug was safe and efficacious, it could not approve it because its traditional rules required the sponsor to submit a full marketing application with the appropriate clinical trial data. It was an impossibly absurd situation for Syntex, for the FDA, for the doctors and for the patients. It showed how drug development can stumble on startling obstacles. Eventually, the FDA approved the drug bypassing its own regulations.

The sponsor may get assistance in the drafting of the protocol and retain the assistance of experts.[1398] The investigator should provide her own input, since she must agree to the protocol's contents. CROs and SMOs may give their own advice in their respective field of expertise.

6.2.1.3. Drug agencies' role in the design of clinical trials

In the United States, the FDA publishes guidance on how to design a good clinical trial protocol. The guidance may be specific to a given disease.[1399] Still in the United States, sponsors can discuss their plans for clinical studies with FDA officers (see also subsection 4.1.1.2.3. above).[1400] This discussion ensures that the negotiated protocol will satisfy the agency's requirements once completed and submitted in support of a marketing application. This opportunity to discuss the design of clinical trials is much appreciated by sponsors.[1401] It is almost mandatory before phase III clinical trials start.[1402] For drugs

---

1395 Bias can be defined as "the systematic tendency of any factors associated with the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value." *See* ICH E9, at section 1.2, p.2. *See also* 21 C.F.R. § 312.23(a)(6)(iii)(*d*). See for more details subsection 6.3. below.

1396 *See* ARNO & FEIDEN, *supra* note 125, at 159-68.

1397 See also subsection 6.3.5.1. below on equipoise.

1398 *See* section 5.4.1 (p.21) of ICH E6.

1399 For example, the FDA has issued a draft guidance regarding clinical trials of allergic rhinitis products. *See* CDER, FDA, Allergic Rhinitis: Clinical Development Programs for Drug Products, Draft Guidance, (Apr. 2000), at http://www.fda.gov/cder/guidance/2718dft.pdf.

1400 *See, e.g.*, 21 C.F.R. § 312.47. *See also* FDA (Critical Path) *supra* note 708, at iii.

1401 "In [fiscal year] 2001, CDER [the drug approval division of the FDA] conducted 1,021 formal meetings with sponsors. … According to 94 percent of FDA respondents and 96 percent of sponsors responding to our surveys, interaction between sponsors and reviewers during this stage contributed to an effective NDA review process." OIG (FDA Review), *supra* note 20, at 7.

1402 "The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and

targeting life-threatening diseases, the meeting between the sponsor and the FDA takes place even sooner, usually after phase I trials.[1403] In some cases, the FDA may even look at preliminary study reports to make sure that the drug development effort is on the right track.[1404]

In contrast, outside the United States, such interactions are much less common. This inability to have constructive discussions on the study design is regularly criticized by the industry.[1405] However, the European Union has been contemplating – though for some time already – the development of dialogue opportunities between sponsors and the EMEA.[1406] On the contrary, the Swiss Agency is of the opinion that such dialogue would waste precious resources.

6.2.1.4. Changes to the protocol

The protocol resembles a contract. It must be signed by the investigator.[1407] The investigator's institution and the sponsor may also have to sign it. Approved changes to the protocol must also be incorporated in writing and signed by the sponsor and the investigator.[1408]

Normally however, the protocol initially accepted (by the sponsor, the investigator and the drug agencies) is *not to be modified* throughout the course of the clinical trial.[1409] There are exceptions, in particular to protect subjects.[1410] Yet changes are rare and unfavorably looked upon. Drug agencies are suspicious of studies for which the protocol was changed midway.[1411] They fear that the change was implemented *a posteriori* to mask a faulty study design or accidental violations of the initial protocol.[1412]

---

effectiveness and to identify any additional information necessary to support a marketing application for the uses under investigation." 21 C.F.R. § 312.47(1).

1403 Since these drugs are often approved based only on phase II trial(s), (that is without a phase III trial), the meeting between the sponsor and the FDA must necessarily take place earlier. *See* 21 C.F.R. § 312.82(b). For these important drugs, the FDA may also help the sponsor design its preclinical and clinical studies during a pre-IND meeting. *See* 21 C.F.R. § 312.82(a).

1404 *See* ARNO & FEIDEN, *supra* note 125, at 221.

1405 In the European Union, see Cameron McKenna & Andersen Consulting, Evaluation of the operation of Community procedures for the authorization of medicinal products, Evaluation carried out on behalf of the European Commission, at 82 and 265, (2000), at http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2000/nov/reportmk.pdf. *See also* EFGCP News (Autumn 2000), *supra* note 1145, at 3-4.

1406 *See, e.g.,* E.U. (Future), *supra* note 685, at 11. For orphan medicines, see Article 6 on "protocol assistance" of Regulation 141/2000/EC, *supra* note 44.

1407 *See* section 4.5.1 (p.14) ICH E6.

1408 *See* EFGCP (Protocol), *supra* note 1386, at section 4, page 4.

1409 See in the European Union, EMEA, Concept Paper on the Development of a Committee for Proprietary Medicinal Products (CPMP) Points to Consider on Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis Plan, (CPMP/EWP/2459/02), (July 25, 2002), at http://www.emea.eu.int/pdfs/human/ewp/245902en.pdf.

1410 For example, unexpected risks may require changes in the procedures that research subjects have to go through. In such cases, the protocol must be modified to reflect these changes.

1411 *See, e.g.,* EFGCP (Protocol), *supra* note 1386, at sections 1 and 4, pages 2 and 4.

1412 For a list of common protocol violations, see *id.* at section 5, pages 5-6.

The consequence is that protocols should be appropriate from the start. The sponsor may have to consider alternative study designs and contingency plans whenever obstacles can be foreshadowed.[1413]

6.2.2. The brochure

The brochure is a separate document that evolves during, and accompanies, each clinical trial of a specific drug. It summarizes what is currently known about the experimental product.[1414] When the first clinical trial begins, the brochure mainly contains data derived from in vitro and animal tests. Each clinical trial then results in a brochure update. Useful brochures are clear, impartial and easy to read, thus making compliance with the protocol easier. The brochure must also be consistent with the protocol, as some information is found in both documents.

The brochure also serves to educate the investigators as to the proper handling of the product. It explains how the drug must be stored and administered; investigators must also be told how unused products are to be dealt with (e.g., discarded or returned to the sponsor).

It is the sponsor's role to prepare the brochure and to keep it up-to-date. Brochures should be revised at least once a year.[1415] The investigator and the monitors should always have the most current text at their disposal. Likewise, the ethics committee must be provided with the most recent edition.[1416]

6.2.3. Case report forms ("CRFs")

Case report forms ("CRFs") are the primary instrument used to gather and present data in clinical trials. The sponsor supplies the investigator with CRFs to fill for each subject.[1417]

1413 See in the United States, 21 C.F.R.§ 312.23(a)(6)(ii).

1414 See section 1.36 (p.6) of ICH E6 and the very similar definition of the European Directive 2001/20/EC at its Article 2(g).
A typical complete brochure contains the following information: the name of the experimental drug (the brand name (if there is already one) or else its given "nick name," as well as the generic name), its active ingredients, its important excipients, its pharmacological class, its structure and molecular weight, its manufacturing steps. The non-clinical and clinical data about the pharmacology, pharmacokinetics and pharmacodynamics of the product are also described. Toxicology data, including known adverse events and overdose risks, are mentioned. The non-clinical and clinical sections lists the past reference studies and their conclusions. A brochure generally ends with explanatory tables and appendixes with scientific references. The brochure bears the sponsor's name, is dated, and mentions its edition number. Like the protocol, it typically bears a confidentiality statement. Like the protocol, it is generally in English. The average length is about 40 pages. *See* 21 C.F.R. § 312.23(a)(5).

1415 *See* sections 5.12.2 (p.24) and 5.12.2 (p.29) ICH E6. See in the United States, 21 C.F.R. § 312.55. Despite the fact that the sponsor is the party responsible for establishing the brochure, the document is generally referred to as the investigator's brochure or "IB."

1416 Pursuant to Article 9.2.c OClin, the ethics committee receives the brochure from the investigator. *See also* section 4.4.2 (p.13) ICH E6.

1417 See, for a definition, section 1.11 (p.3) of ICH E6.

6.2.3.1. Role of CRFs

CRFs list which information must be collected by the investigator and her team in order to be provided to the sponsor. For example, CRFs recap, for each subject visit, the series of tests and measurements that have been made. Commercial sponsors usually request very detailed CRFs to be filled out, while forms used in noncommercial trials tend to be less exhaustive.[1418]

As is true for the protocol, the sponsor must ponder the design of CRFs. Good CRFs facilitate the gathering of complete data. Conversely, badly designed CRFs make the life of investigators harder. For example, there should be enough room to write down all observed adverse effects.[1419] If there is too much paperwork to fill out for an adverse event, investigators may just "skip it."[1420]

CRFs should be filled out completely and legibly; they should be dated and signed. The investigator is generally assigned the responsibility to complete and sign the CRFs. In practice however, most of the observations and corresponding CRF entries are made by other members of the research team.[1421]

CRFs must not identify the *subjects* by name, but by a code identifier. This code preserves the confidentiality of subjects' records, given that CRFs circulate broadly among the different parties involved in the trial, including the investigator, the monitor and the sponsor.[1422]

Together with other documents concerning the subject (e.g., his informed consent form), CRFs form part of the case history.[1423] "CRFs are based on 'source data'," which constitute the complete file holding all subjects' medical information.[1424] These source data are held by the investigator, while the sponsor sees the CRFs. However, auditors may have to verify whether CRFs match the raw observations found in the source data.[1425]

1418 *See, e.g.,* FDA, Cancer Drug and Biological products, Clinical Data in Marketing Applications, Guidance for Industry, at 2 (Oct. 2001), at http://www.fda.gov/cber/gdlns/canclin.pdf [hereinafter FDA (Cancer Guidance)]. A long case report form can extend on a dozen pages, which have to be filled for *each* subject's visit.

1419 *See* DONATINI, *supra* note 127, at 157 and 230.

1420 Serious adverse events need generally to be reported separately by the investigator to the sponsor. *See A confetti of adverse event forms*, THE EFGCP NEWS, at 13, (Spring 2001).

1421 *See* EFGCP Audit Working Party, The Handling of Case Report Form (CRF) at an investigational site, at sections 1 and 2, pages 2 and 3, at http://www.efgcp.org/webitems/handling_of_CRF.pdf [hereinafter EFGCP (CRF)].

1422 The original CRFs are typically retained by the sponsor at the end of the trial. Conversely, the investigator normally retains the subject's medical history file.

1423 See, in the United States, 21 C.F.R. § 312.62(b).

1424 *See* EFGCP (CRF), *supra* note 1421, at section 2, page 2. CRFs are usually not source documents themselves, in the sense that initial observations (e.g., weight of the subject) are often not made directly on the CRF, but recorded first in the subject's medical file.

1425 On the distinction between raw data and CRFs, see *id.* at section 2, page 3.

6.2.3.2. Completing and changing CRFs

The FDA specifically requires that data be "attributable, original, accurate, contemporaneous and legible."[1426] In particular, the person having made the observation should fill out form at the time of the experiment, making sure to identify himself therein.

Any *subsequent change* brought to CRFs, for whatever the reason, should not obliterate the precedent entry, but should be added so as to preserve the precedent inscription. The person operating the change should state the underlying reasons for this. This rule is particularly important,[1427] since too many CRFs have been doctored either to hide errors committed by the investigator's team or to match the sponsor's expectations.[1428]

To facilitate entry of complete and correct data, sponsors and investigators are moving towards digital CRFs (e-CRFs).[1429] E-CRFs present several advantages, including automatic identification of the author and rejection of incorrect or incomplete entries.[1430]

6.3. The gold standard: chasing bias

"Modern" clinical trials aim at identifying and minimizing bias by following recognized scientific methods. As we saw before (subsection 4.1.1.2.3.), the gold standard is now the randomized controlled clinical trial ("RCT").[1431] This type of trial has led to the

---

1426 FDA, Guidance for Industry, Computerized Systems Used in Clinical Trials, (Apr. 1999), chapter I., at http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm [hereinafter FDA (Computerized)].
Other attributes of desirable data are correct, clear, objective, believable, accessible, secured, relevant, timely, complete, consistent. Wang describes desirable attributes as "intrinsic quality …, accessibility …, contextual quality …, and representational quality." National Institute of Statistical Sciences (NISS), Workshop Report on Data Quality, at 3, (Mar. 15, 2001), at http://www.niss.org/affiliates/dqworkshop/report/dq-report.pdf. *See also* EFGCP (CRF), *supra* note 1421, at section 5, at page 5.

1427 "CRFs are never completed to perfection and making errors or omissions is only human. Likewise, a clinical study is scientific experimentation: things can go wrong, patients can drop-out, machines can break down. What is not acceptable is the lack of explanation of omissions and errors." *See* EFGCP (CRF), *supra* note 1421, at section 3, at page 3 (original emphasis omitted).

1428 For a list of common compliance problems with CRFs, see *id.* at section 4, at page 4.

1429 2003 saw the first report of a purely Internet-based clinical trial. This trial was conducted first and foremost as a feasibility test. Internet clinical trials are likely to raise concerns (e.g., lack of human interaction in the informed consent process, lack of regular control of the subject's health, faults with the reporting of adverse events), but also present advantages (e.g., lower cost, greater convenience for subjects). Tim McAlindon et al., *Conducting clinical trials over the internet: feasibility study*, 327 BMJ 484-87 (2003), at http://bmj.com/cgi/reprint/327/7413/484.pdf.

1430 According to Roche "[i]t is estimated that 70 percent of all discrepancies in the data records of a clinical trial can be discovered and eliminated at the RDE [Remote Data Entry] stage. Since the correction of clinical data is one of the most cost-intensive steps in the development process, RDE could help to save millions." *e.g.,* Roche, How information technology is revolutionising clinical testing, at http://www.roche.com/pages/facets/18/infotechne.htm. On the other hand, e-CRFs rile researchers when glitches in their operations occur (e.g., system crashes before entries were saved).

1431 Some say the gold standard has acquired a cult status. In other words, its value is sometimes exaggerated, while other types of studies are excessively belittled.

advent of "evidence-based medicine" ("EBM"), hailed as possibly the most important revolution in the history of medicine.[1432]

The ICH defines "bias" as "the systematic tendency of any aspects of the design, conduct, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value."[1433] Sources of possible bias are numerous: up to 70 different types of bias have been identified.[1434] We will not examine them all here, but instead we will distinguish three main sources. An error may stem from the *study design*, the *investigator,* or the *subject*.

A clinical trial may be *designed* in such a way as to unduly advantage the sponsor's drug. This may occur, for example, when the selected control is an active drug administered at an unsuitably low or high dosage, when the study is halted at a point in time before the sponsor's drug is to lose ground against the control product, or when the recruited subject population does not match that of the "real world."

The bias is related to the *investigator* when she intentionally or unconsciously favors one of the products being tested in the trial. She may do so by reporting artificially inflated (positive) results for the subjects taking her preferred drug. She may also lavish her care on this group of subjects, while neglecting those taking the other product.

Third, bias may be due to the *subject*. For example, the subject may provide false or misleading information because he feels the need to please the research team; he may thus report greater medical achievements than really occurred.[1435]

Reducing bias is particularly important for phase III clinical trials because national drug agencies rely mainly on these studies to grant marketing approval. Bias in phase I trials is partly inevitable since practical considerations make it difficult to implement all anti-bias measures (e.g., introducing a placebo control).[1436] Hence, the methods described below are applicable primarily to phase III trials.

Even though bias can be minimized, it can never be eliminated entirely.[1437] Clinical trials are not run by machines on machines. Human errors, mostly unintentional, remain unavoidable.

1432 *See* Paolo Bruzzi, *Randomised Clinical Trials, unproven treatments, and the patients' perspective*, 320 BMJ (June 29, 2000), at http://bmj.com/cgi/eletters/320/7251/1686#8550.

1433 Chapter 1.2 (p.2) of ICH E10.

1434 *See* Robert Slinger, *How To Assess New Treatments*, 174(3) WEST JOURNAL OF MEDICINE 182-186 (2001). I have not found independent confirmation of this rather high number. *See also* James Lind Library, Avoiding Biased Comparisons, at http://www.jameslindlibrary.org/essays/bias/bias.html.

1435 Patients who have agreed and/or volunteered to participate in a clinical study may be more inclined to please their doctors by reporting improvements. Carol Hart, *The mysterious placebo effect*, MODERN DRUG DISCOVERY, 2(4), 30-40, (July/Aug. 1999), at http://pubs.acs.org/hotartcl/mdd/99/aug/mysterious.html; Slinger, *supra* note 1434.

1436 *See* ICH E9, at section 2.1.3, p.4.

1437 Worse, it seems that many studies suffer from bias, always in the same direction. "Lisa Bero and Drummond Rennie looked at how the design of a drug study can introduce bias. In a review of studies published between January 1966 and April 1994, they found that 'flaws in the study design almost always favor a new drug in comparison with competing products' and suggested that 'pharmaceutical industry funding influences drug study design and outcomes'." Haiweb, *supra* note 970.
Bias can be traced back to the sponsor: "A 1986 study reviewed 107 controlled clinical trials, each comparing a new to a 'traditional' (older) pharmaceutical (Davidson, 1986). The studies were classified as to whether the newer or the traditional drug were favored by the author's interpretation of the data, and as to whether

6.3.1. Importance of randomized controlled trials

Randomized controlled trials ("RCTs") represent one particular type of clinical trials. As the name indicates, RCTs incorporate two main features: control and randomization. These two attributes are analyzed in depth in subsections 6.3.3. and 6.3.4. below.

In the last twenty years, RCTs have become the central requirement of drug agencies' marketing approval process.[1438] Simply put, no better method to secure reliable data on human use has been identified.[1439] Yet, not all drug clinical trials satisfy this gold standard. Many studies combine different study designs (e.g., randomized withdrawal with placebo[1440]). This does not mean that drug agencies always reject studies which do not satisfy the gold standard. First, depending on the problem studied, it might be *impossible* to comply with the gold standard (e.g., trial for serious disease where placebo use is unethical)[1441]. The sponsor must then convince the drug agency that another approach is, considering the circumstances, sufficiently valuable.[1442] Sec-

---

the source of funding for the studies was drug companies which manufactured the newer drug (37 studies) or other sources (70 studies). The findings showed that drug company-supported studies were more likely, to a statistically significant degree, to favor the newer drugs than the studies supported by other sources." E. Rose, *supra* note 1329.

1438 This gold standard can further be expounded as a "randomized, placebo-controlled, double-blind*, multinational, multicentric clinical trial." *See also* chapter 2.14 (p.14) of ICH E10 Guideline. *But see* John Concato et al., *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 NEW. ENG. J. MED. 1887-1892 (2000) ("Contrary to prevailing beliefs, the "average results" from well-designed observational studies (with a cohort or case-control design) did not systematically overestimate the magnitude of the associations between exposure and outcome as compared with the results of randomized, controlled trials of the same topic. Rather, the summary results of randomized, controlled trials and observational studies were remarkably similar for each clinical tropic we examined." *Id.* at 1890).

1439 "To eliminate clinical trial procedures is to eliminate the scientific basis for medical decision making." DuBois, *supra* note 118, at 347.

1440 See chapter 2.15.2.4 (p.16-17) of ICH E10 Guideline.

1441 However, many scientists see no reason to exempt alternative remedies from the RCT method and the corresponding burden of proof. CAMs practitioners retort that the gold standard is ill-suited for their own medicines. This is logical considering that, for these products, trials with the best controls have also shown the least efficacy.
See Silvio Jenny, *Art médical et conceptions médicales*, *in* Médecines complémentaires, point de vue de la science, rapport du groupe d'experts du Programme national de recherche 34, 1992-1998, at 99, Fonds National Suisse de la Recherche Scientifique, édition Médecine et Hygiène.

1442 In the United States, "FDA regulations for drugs describe five kinds of study designs that can be used in carrying out the well-controlled investigations needed under law to provide the 'substantial evidence of effectiveness' needed to market a drug. They are: Placebo concurrent control, dose-response concurrent control, no-treatment concurrent control. Active treatment concurrent control, and historical control. … The study design used must, however, be adequate to the task of providing evidence that the drug or device will have the effect claimed." FDA (Emergency Research), *supra* note 1190, chapter II, B., at 51,509.
The ICH recognizes that trial design can vary and its guidelines about study design are not mandatory; they only represent a best current practice. "These Guidelines … are a starting point rather than an end point. They provide a basis from which an investigator can devise a strategy for testing according to available knowledge of the test material and the state of the art. For encouragement some alternative test designs have been mentioned in this document but there are others that can be sought or devised. … Fine details of study design and technical procedures have been omitted from the text. Such decisions rightly belong in the field of the investigator since a technique that may be suitable for one laboratory may not be suitable in another. The investigator needs to utilize staff and resource to do the best he or she can achieve and should know how to do this better than any outsider; human attributes of attitudes, ability, and consistency are more important than material facilities." ICH, S5A Guideline on Detection of Toxicity to Reproduction for Medicinal Products, June 1993, Note 1 (1.1) on scientific flexibility, p.3, at
http://www.ich.org/MediaServer.jser?@_ID=498&@_MODE=GLB.

ond, a sponsor may submit uncontrolled studies to *corroborate* results already established by a controlled clinical trial.[1443]

Conversely, the fact that a study meets the gold standard does not automatically imply that its findings will be exceptionally valuable in practice. There are important differences between clinical and real-world settings.[1444] Despite a perfect design, a study may be difficult to extrapolate to "real" patients. For example, the side effects of the drug can cause patients not to adhere to the treatment regimen, while this would not be of concern when the substance is administered directly by the investigator to subjects participating in a clinical trial.[1445] Moreover, a clinical trial only tells if a drug is efficacious for a group in general; within this group, the drug may be very efficacious for some individuals and not at all, or even harmful, for other persons. Thus, clinical trials' findings only provide results helpful for the "average patient," without necessarily disclosing what the latter's characteristics are.[1446].

Finally, one should never forget that scientific "truths" are often discarded over time. Science is not cast in iron but constantly evolves. Even good research performed according to strict scientific methods can be proved erroneous.[1447] Thus, many "truths" firmly believed in the past have later been disproved by well designed and well conducted clinical trials.[1448] These so-called "truths" were derived from observational, historical and patient studies – all of them suffering from multiple sources of bias. It may well be that current medical beliefs will be supplanted by even more accurate study methods (e.g., pharmacogenomics-based trials).

1443 Kessler (Regulation), *supra* note 447, at 283.

1444 *See e.g.*, Robert E. Becker, *Focusing Pharmaceutical Research on Patient Care*, 22(5) CLIN. DRUG INVEST. 267-278 (2002), at http://www.medscape.com/viewarticle/434081_print.

1445 It is often written that 30% to 50% of patients do not use medication as prescribed; Jeannette Y. Wick & Guido R. Zenni, *Informed Consent: What Every Pharmacist Should Know*, 41 JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, at 523 (July/Aug. 2001), at http://www.medscape.com/viewarticle/406721.

1446 Subjects who respond to a drug in a manner that is very different from that of the group's average are sometimes called "outliers." Yet the reasons for their particular response to the drug are not always examined during the clinical trial.

1447 According to a study by Thierry Poynard et al., only 60% of the findings of articles on cirrhosis and hepatitis published between 1945 and 1999 were still held to be true in 2000: "In 2000 …, 91 (19%) [of these articles' conclusions) were considered to be obsolete, and 98 (21%) were considered to be false. The half-life of truth was 45 years. … The survival of conclusions was not different when studies of high methodological quality were compared with those of low quality." *Truth Survival in Clinical Research: An Evidence-Based Requiem?*, 136 (12) ANN. INTERN. MED. 888-895 (June 18, 2002), at http://www.annals.org/issues/v136n12/abs/200206180-00010.html.

1448 "In a review of seventy-two studies of treatment published in selected American and British psychiatric journals between 1951 and 1956, uncontrolled studies reported that 83 percent of the treatment were successful and 17 percent were failures; by contrast (somewhat or variably) controlled studies reported that 75 percent of the treatments were failures and 25 percent were successes (Foulds 1958). Similarly, in a review of fifty-seven studies of treatment published during 1957, unacceptably controlled studies reported 91 percent of treatments as successes and only 9 percent as failures, whereas acceptably controlled studies reported 54 percent as successes and 46 percent as failures (Fox 1961)." THE SHAPIROS, *supra* note 4, at 96.

6.3.2. Historical aspects

Nowadays, all drug agencies of industrialized countries require that sponsors of new drugs applying for marketing approval submit the results of one, and often two, large well-controlled double-blind randomized trials. The FDA began to impose this requirement in the mid-seventies (see also subsection 4.1.1.2.3. above).[1449] It progressively became a widely accepted practice among researchers and physicians in the United States.[1450] While England, Sweden and Germany rallied to this requirement at about the same time,[1451] other countries were significantly slower in coming round.[1452]

Still, placebo controls and double-blinding in human trials are recent phenomena.[1453] The word "placebo" was not even pronounced in the medical literature until 1887.[1454] The first known double-blind study occurred in 1907 or 1908.[1455] Some form of control, but neither placebo nor blinding, slowly came into use in the 1920s and 1930s.[1456] Placebos had a bad reputation as they were viewed as an inadmissible tool of deceit among physicians.[1457] The term had a pejorative connotation.[1458] Although physicians did prescribe ineffective drugs or effective drugs at an ineffective (too low) dosage[1459] – in fact, placebos –, they were unwilling to either admit the fact or endorse it. Beginning in the mid-1930s, physician Harry Gold started systematically using placebo controls and double-blind in his own studies.[1460] In that, he was almost unique among

---

1449 "Once established … the FDA policies [on use of placebo controls and double-blind] strongly influenced how studies of drugs were done, with ripple effects influencing studies of psychotherapy, surgery, instruments, and all other therapies." THE SHAPIROS, *supra* note 4, at 172, and 173 and also at 75; C. Hart, *supra* note 1435.

1450 "Papers criticizing the use of the double blind gradually decreased in number and virtually disappeared after about 1980." THE SHAPIROS, *supra* note 4, at 173.

1451 *Id.* at 160. "The development of clinical trials in the United States initially focused on the double-blind method and the placebo effect, whereas in England the focus was on randomization, statistics, the use of an active placebo … and other clinical design characteristics." *Id.* at 159.

1452 "The use of controlled clinical trials occurred much later in France … [P]lacebos were rarely used in France before 1978. In fact, most French investigators were still suspicious about the practicality and ethics of using placebos." *Id.* at 159. *See also* CCNE N°2, *supra* note 57, at 8 (defending in 1984 the utility and practicability of clinical trials). *See also* CLAUDE BÉRAUD, PETITE ENCYCLOPÉDIE CRITIQUE DU MÉDICAMENT 28, (Les Editions de L'Atelier, Mutualité Française 2002).

1453 *See however* Office of Technology Assessment ("OTA"), The Impact of Randomized Clinical Trials on Health Policy and Medical Practice: Background Paper (OTA-BP-H-22), (Aug. 1983), at 5 (recounting the Biblical story of Daniel's first nutritional experiments incorporating a control group), at http://www.wws.princeton.edu/cgi-bin/byteserv.prl/~ota/disk3/1983/8310/8310.PDF [hereinafter OTA (Impact)].

1454 *See* THE SHAPIROS, *supra* note 4, at 32. However, according to David B. Morris, it was in 1811 that the word "placebo" appeared in a dictionary with its present medical meaning. *See Placebo, Pain, and Belief: A biocultural Model*, *in* THE PLACEBO EFFECT 187 (Harvard University Press 1997).

1455 *See* THE SHAPIROS, *supra* note 4, at 137 (describing a study of alcohol by Rivers). Other isolated studies followed in the 1910s. *Id.* at 138-139. Earlier studies were not blind, such as the 1747 experiment of scurvy by Lind or Jenner's 1798 study of smallpox vaccination. *Id.* at 125 and 126. See however the possibly single-blind study by Haygarth in 1801. *Id.* at 126-27.

1456 *See id.* at 140.

1457 *See id.* at 140-41. *See also Placebo: Conversations at the Disciplinary Borders*, *in* THE PLACEBO EFFECT 208, 234-235 (Harvard University Press 1997).

1458 *See* THE SHAPIROS, *supra* note 4, at 32.

1459 *See id.* at 107.

1460 Gold's famous study of xanthines was published in 1937. *See id.* at 147-49 and 2.

clinical researchers.[1461] Until the 1940s, there were only very few such studies although the interest among scientists was growing.[1462] Still only a quarter of U.S. clinical trials published in the 1950s had controls.[1463] The general acceptance of controlled clinical trials grew during the 1960s,[1464] although not all sources of bias were always properly accounted for. Still in the mid-1970s, only 5% of articles published in general medical journals reported randomized clinical trials.[1465] Today, the placebo effect has become "mainstream," but still fascinates researchers.[1466]

Many physicians opposed clinical trials, perceiving them as a threat to their specialized knowledge derived from their day-to-day medical practice.[1467] Randomized placebo-controlled clinical trials are best conducted in hospitals or similar medical institutions, thus pushing the doctors in private practice to the sideline. Clinical trials also turned the limelight towards researchers, some of whom were not even physicians. For instance, statisticians, chemists and biologists' roles became central. Physicians may also have feared that their long tradition of medical care would be challenged and eventually discarded by the results of clinical trials – which proved to be the case. Many therapies that physicians had deemed excellent were revealed to be ineffective and occasionally harmful. In the United States, the FDA reacted by deciding that a long established history of use (i.e., general acceptance) was not enough to support the approval of drugs and that the positive reports of physicians in favor of a drug amounted to no more than anecdotes or testimonials.[1468] Physicians' parts in assessing therapies were indeed replaced by clinical trials.

6.3.3. Controls

This subsection focuses on the use of controls, in particular placebos, to assess the *true efficacy* of the test product (i.e., the investigational drug being tested). First, it examines the purposes underlying the use of controls. Then, it compares two different kinds of controls: the (inactive) placebo and the active comparator drug. This subsection also explains how the placebo must be "hidden," by using blinding techniques. This subsec-

---

1461 *See id.* at 148.

1462 *Id.* at 146 and also at 74F. *See* Zelda Di Blasi et al., *Informing participants of allocation to placebo at trial closure: postal survey*, 325 BMJ 1329 (Dec. 7, 2002), at http://bmj.com/cgi/reprint/325/7376/1329 (mentioning the introduction in 1948 of randomized placebo-controlled trials by the British Medical Research Council). *See also* Mariner, *supra* note 59, at 288.

1463 *See* THE SHAPIROS, *supra* note 4, at 34, 75, 149.

1464 *See* Mariner, *supra* note 59, at 288.

1465 This compares to zero in 1946. *See* OTA (Impact), *supra* note 1453, at 6.

1466 "In the past 10 years, the National Library of Medicine has annually listed an average of 3972 scholarly papers with the keywords "placebo," "placebos," or "placebo effect," with a low of 3362 papers in 1992 and a high of 4814 in 2000." Daniel E. Moerman & Wayne B. Jonas, *Deconstructing the Placebo Effect and Finding the Meaning Response*, 136 ANN. INTERN. MED. 471 (Mar. 19, 2002), at http://www.annals.org/cgi/reprint/136/6/471.pdf (proposing to replace the concept of "placebo effect" by that of "meaning response.").

1467 *See* OTA (Impact), *supra* note 1453, at 10-11.

1468 See the description by Goodrich of how clinical studies were conducted before the 1962 Act, FDA (Interview Goodrich I), *supra* note 52.

tion ends with the controversy over the use of placebo, both in developed and developing countries.

6.3.3.1. Purpose of controls

The natural evolution of most diseases cannot be accurately foretold.[1469] Some patients recover fast, others slowly; some recover without taking any drugs, others take drugs which may or may not help them. There are little reliable statistics to forecast exactly how a disease will progress. In a clinical trial, if a drug is given to ten subjects and cures eight, can this recovery be attributed solely to the drug? Could it be that these eight patients would have recovered anyway, perhaps because they are young and strong?

To check this supposition, various *control methods* can be applied.[1470] For example, once the medical disorder is diagnosed, ten subjects receive the drug only after ten days of no treatment. If the ten subjects remained sick during the first ten days and eight of them recovered between day 12 and day 15, it appears likely that the drug had some influence. However, some could argue that patients with this disease always recover after 10 days of disease (e.g., the flu).

Another method would be to have some patients receive no treatment at all. For example, out of the ten patients, five receive the drug and five are left home and receive no treatment. If after 15 days, four out of the five receiving the treatment are cured, while the five patients receiving no treatment are still sick, it can be supposed that the drug is to be thanked.[1471] However, this method is subject to bias, because the patients receiving treatment may have improved, not because of the active ingredient in the drug, but for another reason. Here the placebo effect steps in. The word "placebo" can be traced back to the Latin expression "I will please."[1472] Shapiro and Shapiro have defined it as:

> any therapy (or that component of any therapy) that is intentionally or knowingly used for its nonspecific, psychological, or psychophysiological, therapeutic effect, or that is used for a presumed specific therapeutic effect on a patient, symptom, or illness but is without specific activity for the condition being treated.[1473]

1469 *See* also Howard L. Fields, *Placebo: Conversations at the Disciplinary Borders*, *in* THE PLACEBO EFFECT 208, 216-17 (Harvard University Press 1997); Irving Kirsch, *Specifying Nonspecifics: Psychological Mechanisms of Placebo Effects*, *in* THE PLACEBO EFFECT 166, 167 (Harvard University Press 1997).

1470 "In most situations … a concurrent control group is needed because it is not possible to predict outcome with adequate accuracy or certainty." Chapter 1.2 (p.2) of ICH E10.

1471 Of course, results drawn from only 5 subjects are not sufficient to generalize this outcome for the whole patient population. The issue of sample size is analyzed further in subsection 6.3.10.1. below.

1472 According to Carol Hart, "[t]he word placebo ('I will please' in Latin) entered the English language by way of a peculiar mistranslation of the 116th Psalm that read, 'I will please the Lord' rather than 'I will walk before the Lord'. In medieval Catholic liturgy, this verse opened the Vespers for the Dead: because professional mourners were sometimes hired to sing vespers, 'to sing placebos' came to be a derogatory phrase describing a servile flatterer. By the early 19th century, 'placebo' had come to mean a medicine given 'more to please than to benefit the patient'." *Supra* note 1435, at 30-40. See for more detailed explanations, THE SHAPIROS, *supra* note 4, at 28-30.

1473 THE SHAPIROS, *supra* note 4, at 41. See also the definitions in Federal Trade Commission v. Pantron I Corp, 33 F.3d 1088, at 1090 (9th Cir. 1994); United States v. An Article … Acu-Dot, 483 F. Supp. 1311, at 1313 (D.C.Ohio 1980). These two other "definitions" of the placebo are also good:

According to this definition, a placebo can be an inert substance believed to have no inherent therapeutic effect, an active substance used at a dosage too low to have any specific intrinsic effect, or a substance (inert or active) erroneously believed to have a therapeutic effect.[1474]

In today's clinical trials, placebo are used knowingly to evaluate and cull the placebo effect (on this notion, see the next subsection). The investigator gives the real remedy to some subjects and to others a fake one. If the two groups (also called "arms") perform as well, this means that the real remedy is no better than the placebo.[1475] A study using a placebo is said to be placebo-controlled.[1476] Researchers need to use such a study design because there are no reliable statistics to predict the size of the placebo effect. Hence, they are forced to create their own statistics through clinical trials. To really determine how strong the placebo effect is, a third group receiving absolutely no treatment would have to be added.[1477] This is rarely done because the purpose of a clinical trial is to determine how effective the treatment is (by subtracting the placebo effect[1478]), and not how effective the placebo is.[1479] When the only control is the placebo, it is not possible to determine which proportion of the patients would spontaneously recover.

– "Everybody knows what a placebo is, until you ask him."
– "Placebo is perhaps simply about being human."

Both from: Placebo and Nocebo: effects and phenomena in general practice, an interim statement after a meeting of placebo specialists, 1997, at http://www.symposion.com/MediChart/englisch/index.html.

1474 "In other words, a placebo therapy may be used with or without knowledge that it is a placebo." *See* THE SHAPIROS, *supra* note 4, at 80

1475 Placebo-controlled trials provide "internal evidence of assay sensitivity," assay sensitivity referring to "the ability [of a clinical trial] to distinguish effective treatment from a less effective or ineffective treatment." Chapters 2.1.6.1 (p.18) and 1.5 (p.7) of ICH E10 Guideline "The difference in outcome between the active treatment and placebo groups is the measure of treatment effect under the conditions of the trial." Chapter 2.1.1 (p.13) of ICH E10 Guideline.

1476 See chapter 2.1.1 (p.13) of ICH E10 Guideline.

1477 This study design, also referred to as "no treatment concurrent control," does not allow double-blinding (see subsection 6.3.3.5. below) because the investigator and her team will have to know which subjects are receiving a treatment and which are not. See chapter 1.3.2 (p.4) of ICH E10 Guideline. The ICH allows this study design "when it is difficult or impossible to double-blind," for example because the investigational product is so toxic that both the investigators and the subjects could easily determine who is not receiving the placebo. The ICH also requires that the parameters studied in these types of trials (i.e., the endpoints) be objective. *Id.*

1478 If the subjects in the treatment group see their symptoms improve by 70%, while symptoms for subjects in the placebo group ameliorate by 40%, the drug's effect can be said to be 30%.

1479 For Irving Kirsch and Guy Sapirstein, "More placebo have been administered to research participants than any single experimental drug. Thus, one would expect sufficient data to have accumulated for the acquisition of substantial knowledge of the parameters of placebo effects. However, although almost everyone controls for the placebo effects, almost no one evaluates them." *Listening to Prozac but Hearing Placebo: A Meta-Analysis of Antidepressant Medication*, PREVENTION & TREATMENT, Volume 1, 1998, www.journals.apa.org/prevention/volume1/pre0010002a.html. Note that this article was deemed controversial, but the editors still found it merit.

6.3.3.2. The placebo effect

People who believe to have received medical treatment see their condition improve even if the intervention was a fake (e.g., the product administered was a "dummy" pill).[1480] This is the placebo effect. The amelioration is not only subjectively felt by patient (e.g., less pain),[1481] but can be measured objectively (e.g., blood pressure). The placebo effect must be distinguished from other factors that influence – or seem to influence – patients' medical conditions and therapeutic outcome, such as "natural fluctuations in symptoms …, spontaneous remission, and biased subjective reports."[1482]

The extent of patients' positive placebo response depends on a variety of different factors. In particular, patients react to multiple influences arising out of *medical settings*. These influences can be grouped in three categories: "pharmacologic (e.g., a tablet), physical (e.g., a manipulation, surgery), or psychological (e.g., a conversation, the handing out of a prescription)."[1483] In clinical trials, these three types of influence tend to combine for the greatest efficacy of treatment.[1484]

Other related symbolic factors may help create the appropriate healing atmosphere (e.g., the smell of the doctor's office, the number of medical diploma on the wall).[1485] Thus, the strength of the placebo effect is affected by *who administers what* product. The placebo effect is stronger if the product is administered by a physician than by a nurse.[1486]

The *aspect of the drug* also shape the placebo response. Injectable medicines have a stronger placebo effect than products applied on the skin or taken orally.[1487] A big pill has a larger effect than a small pill, except if the pill is extremely small.[1488] Red and blue tablets are said to have different effects.[1489] Branded inert products work better than unbranded ones.[1490] The placebo effect can be particularly strong for surgical operations.[1491]

1480 See generally the amusing book by PATRICK LEMOINE, LE MYSTÈRE DU PLACEBO 61 (Editions Odile Jacob 1996). *See however*, Asbjørn Hrobjartsson & Peter C. Gøtzsche, *Is the Placebo Powerless?*, 344 NEW. ENG. J. MED. 1594-1602 (2001). The placebo effect can be replicated in animals too, by using conditioning. *See* Anne Herrington, *Introduction*, *in* THE PLACEBO EFFECT 1, 5-6 (Harvard University Press 1997).

1481 According to Carol Hart, "[S]ubjectively assessed disorders such as migraine headache, back pain, postsurgical pain, rheumatoid arthritis, angina, and depression may respond very well to a placebo. Some objective signs also can respond significantly to placebos, including blood pressure, skin temperature, cholesterol level, and heart rate, and some skin conditions, such as warts and contact dermatitis, are reported to be affected by placebos." *Supra* note 1435. *See also* THE SHAPIROS, *supra* note 4, at 79.

1482 F. G. Miller et al., *supra* note 299, at 603.

1483 *See* Hrobjartsson & Gøtzsche, *supra* note 1480, at 1594.

1484 *See* Margaret Talbot, *The Placebo Prescription*, N.Y. TIMES, Jan. 9, 2000, at 34.

1485 *See* LEMOINE, *supra* note 1480, at 62; Howard L. Fields and Donald D. Price, *Toward a Neurobiology of Placebo Analgesia*, *in* THE PLACEBO EFFECT 37, 102 (Harvard University Press 1997).

1486 *See* LEMOINE, *supra* note 1480, at 61.

1487 *See* Howard Spiro, *Clinical Reflections on the Placebo Phenomenon*, *in* THE PLACEBO EFFECT 37, 48 (Harvard University Press 1997) [hereinafter Spiro (Reflections)].

1488 *See* D. B. Morris, *supra* note 1454, at 189.

1489 "Red tablets [act] as stimulants while the blue ones [act] as depressants." Moerman & Jonas, *supra* note 1466, at 472. *See also* LEMOINE, *supra* note 1480, at 53-54.

1490 *See* Moerman & Jonas, *supra* note 1466, at 472.

1491 In 1994, in the United States, 10 subjects were randomized to either real or "sham" knee surgery. It was found that the placebo group performed better. In other studies, sham surgery was performed on patients

Some *medical conditions* react more strongly to placebos than others (e.g., pain,[1492] hypertension, depression,[1493] irritable bowel syndrome,[1494] and even baldness[1495]).[1496] Overall, the effect of the placebo is very significant: For some medical conditions, it almost matches the performance of approved drugs.[1497] *People* are not all comparably susceptible to the placebo effect.[1498] It has been suggested that the country of origin may affect the strength of the placebo effect.[1499]

---

suffering from angina and from Alzheimer's disease. Both groups had similar response rates (except for young Alzheimer patients), thus demonstrating that the medical intervention was not truly beneficial. *See* M. Talbot, *supra* note 1484, at 34. *See also Placebo Surgery Gains Wider Acceptance*, Medscape, Mar. 23, 2001, at http://www.medscape.com/viewarticle/411258_print (also mentioning that insurance companies have started to argue that new experimental surgical operations should routinely be tested against placebo); J. Bruce Moseley, *A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee*, 347 NEW. ENG. J. MED. 81-88 (2002), at http://content.nejm.org/cgi/content/full/347/2/81?ijkey=dbd416d3fe38fde91bc9826893e7404fd6c2eb99 (presenting the results of the knee surgery clinical trial); David T. Felson and Joseph Buckwalter, *Debridement and Lavage for Osteoarthritis of the Knee*, 347 NEW. ENG. J. MED. 132-33 (2002), at http://content.nejm.org/cgi/reprint/347/2/132.pdf (discussing knee surgery); Thomas B. Freeman et al., *Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson's Disease*, 341 NEW. ENG. J. MED. 988-992 (1999), at http://content.nejm.org/cgi/content/full/341/13/988 (listing all surgeries initially believed to be effective but later abandoned as worthless); Curt R. Freed et al., *Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease*, 344 NEW. ENG. J. MED. 310-319 (2001), at http://content.nejm.org/cgi/content/full/344/10/710 (describing the Alzheimer study and its results); THE SHAPIROS, *supra* note 4, at 81-82. *See also* Moerman & Jonas, *supra* note 1466, at 473 ("Surgery is particularly meaningful: Surgeons are among the elite of medical practitioners; the shedding of blood is inevitably meaningful in and of itself.").

1492 *See* Spiro (Reflections), *supra* note 1487, at 37.

1493 *See, e.g.*, European Commission, Medicinal Products for the Treatment of Depression, Note for Guidance, at 1.2.1, and 4.1.1, (1990), at http://pharmacos.eudra.org/F2/eudralex/vol-3/pdfs-en/3cc22aen.pdf; Kirsch & Sapirstein, *supra* note 1479 (This article is considered controversial); Irving Kirsch et al., *The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration*, 5:23 PREVENTION & TREATMENT (July 15, 2002), at http://www.journals.apa.org/prevention/volume5/pre0050023a.html; Russell Joffe et al., *Antidepressant Treatment of Depression: A Metaanalysis*, 41 CAN J PSYCHIATRY 613–616 (1996), at http://www.cpa-apc.org/French_Site/Publications/Archives/PDF/1996/Dec/joffe.pdf; THE SHAPIROS, *supra* note 4, at 93 ("placebo effectiveness in depression is also high, ranging from 30 to 50 percent …. Placebos are 59 percent as effective as antidepressants …. 62 percent as effective as lithium."); Robert Temple & Susan S. Ellenberg, *Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments, Part 1: Ethical and Scientific Issues*, 133 ANN. INTERN. MED. 455-463 (Sept. 19, 2000), at http://www.annals.org/cgi/reprint/133/6/455.pdf [hereinafter Temple & Ellenberg (Part 1)] ("Overall, in recent experience at the U.S. Food and Drug Administration, about one third to one half of modern antidepressant trials do not distinguish a known effective drug from placebo…."); K. D. Wagner et al., *supra* note 973, at 1033-1041; CCNE, Avis sur l'utilisation de placebo dans les essais thérapeutiques d'antidépresseurs, at 2 (Rapport N°34) (Feb. 9, 1993), at http://www.ccne-ethique.fr/francais/pdf/avis034.pdf (admitting, under strict conditions, placebo-controlled studies of depression) [hereinafter CCNE N°34]; Jay M. Pomerantz, Antidepressants Used as Placebos: Is That Good Practice? 15(8) Drug Benefit Trends 32-33 (2003), at http://www.medscape.com/viewarticle/461430_print.

1494 *See* CPMP, Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome, (Mar. 19, 2003), at 3, at http://www.emea.eu.int/pdfs/human/ewp/078597en.pdf.

1495 *See Pantron I Corp*, 33 F.3d at 1098.

1496 *See, e.g.*, chapter 3.1 ICH E12A; chapter 1.5.1.1 (p.10) ICH E10.

1497 For example, in an analysis of 15 studies of over one thousand patients "treated with placebos for postoperative wound and anginal pain, the common cold, clinical and experimentally induced cough, headache, seasickness, anxiety, tension, and mood disturbance …[t]he average relief of symptoms was 35.2 percent, varying from 21 to 58 percent." THE SHAPIROS, *supra* note 4, at 78-79 (reporting similarly high rate of placebo response in other studies).

1498 However, the Shapiros report that studies attempting to link placebo responders to characteristics in the patients have so far been inconclusive. *Id.* at 39. *See also* LEMOINE, *supra* note 1480, at 71-72.

1499 Complementary and Alternative Medicine at the NIH, Winter 2001, Volume VIII, No 1.

Placebos do not only elicit improvements in the patient's conditions, they can also cause side effects.[1500] Hence, subjects being given a placebo regularly suffer from various medical disorders that resembles the side effects of a "real" drug (e.g., nausea).[1501] The term "*nocebo*" relay the fact that "dummy pills" can also worsen the patient's condition.

Finding a comprehensive explanation for the placebo effect has proven elusive. Various alternative or cumulative theories have been proposed to make sense of it:

> One is classic conditioning: People who have experienced relief in medical setting or from ingesting a pill are primed, like Pavlov's dogs, to do the same again.
>
> Another is the release of endorphins: several studies have suggested that placebo pain relievers, at least, work by stimulating the brain's own analgesics.
>
> Still a third is that taking a placebo, especially if it is administered in an atmosphere of hope, relieves stress, which tends to aggravate the symptoms of placebo-sensitive conditions like asthma and hypertension.[1502]

6.3.3.3. Active controls

Instead of a placebo, a clinical trial can compare the investigational drug with an *already approved drug*, whose efficacy for the studied condition has been duly established.[1503] Such a drug is referred to as an *active* comparator (or active control).

6.3.3.3.1. Scientific difficulties in connection with active controls

From a *scientific* perspective, active comparators are less convenient than placebo controls. The key problem is encapsulated in this question: If the experimental drug has the *same* effect as the active control, does this mean that both products are equally effective or that they are *equally ineffective*?[1504] The active comparator is supposed to have been proven effective, but sometimes the evidence provided is not very solid.

1500 *See* THE SHAPIROS, *supra* note 4, at 80 ("In our study of 1,006 patients who were given a one-hour placebo test, 57 percent of the subjects had one or more side effects.").

1501 These adverse events caused by the disease or by the placebo are sometimes called "background noise." *See* chapter 2.1.6.2 (p.18) ICH E10 Guideline. *See also* Robert A. Hahn, *The Nocebo Phenomenon: Scope and Foundations*, *in* THE PLACEBO EFFECT 56-76 (Harvard University Press 1997).

1502 Margaret Talbot, *Astonishing Medical Fact: Placebos Work*, NEW YORK TIMES MAGAZINE, Jan. 24, 2000, from http://www.chiro.org/research/DISCONTINUED/The_Placebo_Prescription.shtml.
See also United States v. An Article … Acu-Dot, 483 F. Supp. 1311, at 1314 (D.C.Ohio 1980); Moerman & Jonas, *supra* note 1466, at 471.

1503 "An active control (positive control) trial is one in which an investigational drug is compared with a known active drug." Chapter 2.4.1 (p.22) ICH E10; *see also* section 1.14 (p.3) ICH E6.

1504 *See* ICH E3, at chapter 9.2 (p.6). See also the introduction (p.1) to the ICH E1; THE SHAPIROS, *supra* note 4, at 188.
"When a well-controlled study relates an experimental agent to a control that is known to be effective, it yields meaningful results only if the remission rate associated with the experimental agent is at least as high as that of the control. If the experimental agent yields a remission rate that is less than that of the control, nothing is demonstrated as to the efficacy of the experimental agent, for it cannot be inferred from the study whether that lower remission rate is any higher than what would have been achieved by no treatment or a placebo." *See* Holland-Rantos Co. v. U.S. Department of Health, Education and Welfare, 587 F.2d 1173 (D.C. Cir. 1978).

In certain cases, this scientific problem can be addressed by using entirely objective endpoints (e.g., the tumor shrunk in one group, but not in the other). But, since both drugs incorporate a placebo effect, the decrease in tumor size may be attributable to the placebo effect and not to the active substance itself. A three-arm study design (comparison among the tested compound, a placebo and an active control drug) would solve this difficulty,[1505] but it significantly increases the trial's complexity and cost.[1506] The sponsor can also use information derived from previous studies to assess the size of the placebo effect and incorporate this estimate in the design of a two-arm clinical trial.[1507] However, past estimates of the placebo effect are rarely reliable.[1508] Therefore, to prove efficacy of a new drug in an active-controlled trial, the investigational compound must do *better* than the active comparator (a "superiority trial").[1509]

Clinical trials using active controls must be designed so as to give the active control arm a "fair chance." This is worth stating because there has been incidents where the active control treatment was deliberately administered in a way to produce lower efficacy (as compared to the investigational compound). Such a manipulation can be achieved, for example, by administering an inappropriate dose (i.e., too low or too high) of the active control (compared to what would normally be prescribed).[1510]

6.3.3.3.2. Sponsors' preferences for placebos

Commercial sponsors by and large dislike active controls.[1511]

First, if the sponsor launches a *placebo*-controlled trial, it can request and obtain marketing approval even if it demonstrated only a tiny improvement over the placebo. In other words, drug agencies normally do not require that the effect over the placebo be substantial. Nonetheless, once the authorization has been issued, the sponsor is free to advertise its product as being outstanding; in its marketing literature, the sponsor rarely confesses the placebo's rate of success. Likewise, the sponsor can also promote its drug as being far better than that of its competitors, even though it has no evidence to back its claim. Worse, the sponsor could even withhold non-public evidence suggesting that the rival product is in fact safer or more effective.

1505 *See, e.g.*, chapter 3.4 of ICH E12A; chapters 1.5.2 (p.12) and 2.15.1.1 (p.15) of ICH E10 Guideline.

1506 On the other hand, such a design may facilitate subject recruitment, since participants will have a greater chance of being assigned to a treatment group. *See* ICH E10 Guideline, at chapter 2.1.5.1.1 (p.15).

1507 *See, e.g.*, chapter 1.5.1.1 (p.9) of ICH E10 Guideline.

1508 The placebo effect depends on so many non-duplicable circumstances (e.g., the quality of the health care provided at a given hospital, the friendliness of its nurses, the number of painful procedures the subjects have to undergo) that it is difficult to reproduce the same measure of placebo effect.

1509 On the contrary, if the trial only verifies whether the tested drug is as efficacious as the control drug, the design is one of equivalence or non-inferiority. Equivalence trials are conducted for generic drugs which contain the same active ingredient as the active control.
Some new drug trials use a non-inferiority clinical trial design even though more reliable evidence of efficacy would be obtained using a superiority design. *See* ICH E9, at section 3.3.2, 15.

1510 *See* BÉRAUD, *supra* note 1452, at 29. *See* chapter 1.4.3 (p.6-7) of ICH E10 Guideline. "In some cases, to show superior efficacy or safety convincingly it will be necessary to study several doses of the control and perhaps several doses of the test treatment." *Id.* at p.6.

1511 *See, e.g.,* McKenna & Andersen, *supra* note 1405, at 32 and 267; Burls & Sandercock, *supra* note 789, at 1446.

On the reverse, if the sponsor initiates an *active*-controlled trial and "loses" it (i.e., the sponsor's drug is less effective than the comparator approved drug[1512]), this will severely damage the sponsor's commercial prospects.[1513] First, the drug agency may be reluctant to grant a marketing authorization, even if the new drug is still more effective than a placebo.[1514] Second, reimbursement authorities will use that information to refuse reimbursement or accept it only at a lower price; they will rightly ask "why reimburse a drug that is less effective at the same price?". Finally, physicians may be less likely to prescribe it. Thus, the sponsor is left with a drug no one wants. For the sponsor: a nightmare.[1515]

Placebo-trials tend also to be easier to conduct. For one, they require a smaller sample size so that fewer subjects need to be recruited.[1516] Similarly, placebo-controlled trials are completed faster.[1517] Additionally, the sponsor launching a clinical trial with an active comparator drug has to purchase this product from one its competitors. This product (e.g., antiretrovirals) is going to be significantly more expensive than a placebo, thereby increasing the sponsor's R&D costs.

Another difficulty related to active controls is that subjects who are already taking the control drug may fare worse when they are switched to the experimental drug, merely because they are not used to this new product. Subjects receiving the new experimental compound may need a while to get used to it; there might be new side effects they are not accustomed to. By contrast, the control group continuing with its usual treatment is accustomed to its therapy and thus "stable."

1512 A sponsor can either aim to prove *superior* efficacy in a comparative trial (i.e., the investigational compound is proved to be more effective than the active control) or equivalent efficacy in an equivalence trial (i.e., the investigational compound is shown to be as effective as the active control). Drug agencies prefer comparative trials but may nonetheless grant marketing approval on the basis of an equivalence trial. *See, e.g.,* EMEA (Biostatistical Methodology), *supra* note 1382, at 140.

1513 *See* Tunis et al., *supra* note 597, at 1629.

1514 "[T]rials that seek to prove that a new agent and an active control have similar efficacy are inherently less reliable than trials that seek to prove the superiority of the new agent to a comparator, whether inactive or active." EMEA/CPMP, Position Statement on the Use of Placebo in Clinical Trials with regard to the Revised Declaration of Helsinki, June 28, 2001, at http://www.emea.eu.int/pdfs/human/press/pos/1742401en.pdf. See also the updated EMEA document titled: EU Standard of Medicinal Product Registration: Clinical Evaluation of Risk/Benefit – The Role of Comparator Studies (EMEA/119319/04) (Oct.21, 2004), at http://www.emea.eu.int/pdfs/human/press/pos/11931904en.pdf.

1515 Sponsors therefore are inclined to cheat. "[A]ccording to a 1994 Archives of Internal Medicine study, in 54% of company-sponsored arthritis-drug trials the dose of the funding company's drug was higher than that of the comparison drug, increasing the likelihood that the funder's drug would appear more effective." Thomas Bodenheimer & Ronald Collins, *Telling the Truth: What Drug Companies Don't Want You to Know*, INTEGRITY IN SCIENCE, www.cspinet.org/integrity/tell_truth.html.

1516 The differential event rate for the outcome measured (e.g., the number of strokes) is higher when the trial is placebo-controlled than when it uses an active control. The consequence is straightforward: the larger the event rate, the smaller the necessary sample size.

1517 *See* William T. Carpenter et al., *The Declaration of Helsinki and Clinical Trials: A Focus on Placebo-Controlled Trials in Schizophrenia*, 160(2) AJP 365-362 (Feb. 2002), at http://ajp.psychiatryonline.org/cgi/content/full/160/2/356.

6.3.3.3.3. Obligation to conduct comparative trials

As mentioned before, a sponsor usually does *not* need to show *comparative efficacy* (with an approved drug) to get marketing approval. Drug agencies normally only require that efficacy be shown *over* a placebo.[1518] This general rule has a few exceptions.

First, drug agencies can refuse to authorize a new drug when there is already a similar product on the market which is viewed as having a *better safety profile* and comparable efficacy.[1519] This view may arise out of the comparison of two sets of placebo-controlled trials. In such a case, the sponsor has to undertake a comparative trial to rebut the inferior safety profile assigned to its drug.

Second, a sponsor may be obliged to enter a head-to-head "beauty contest" to overcome an orphan drug* exclusivity* bestowed upon a rival product. Drug agencies grant orphan drug exclusivities to the first drug being authorized for an orphan therapeutic indication, i.e., one that treats a disease from which only few patients suffer. For its duration (e.g., 7 years in the United States), the exclusivity blocks other drugs for the same therapeutic indication from being approved. However, under U.S. law, this exclusivity is cancelled in favor of a new drug which is deemed significantly safer or more effective. This occurred, for example, for Serono's Rebif.[1520] Serono successfully proved that its drug, Rebif, was better than Biogen's Avonex and thus obtained FDA approval and permission to enter the U.S. market.[1521]

Finally, as we will see in greater details in subsection 6.3.5.2. below, ethical constraints may force the sponsor to offer an active treatment to the control group of subjects. Nowadays, such an obligation is acknowledged whenever there exists a known effective treatment that would prevent serious injuries to the control group.

6.3.3.3.4. Advantages of comparative trials

Head-to-head comparative trials, when successful, provide the company with a superb marketing argument when promoting the drug to physicians. When doctors can choose among products for the same therapeutic indication, they are more likely to be swayed by flawless scientific data. Thus, while risky, such trials can have substantial payoffs.[1522]

[1518] In the European Union, see for example Whereas (28a) of the Proposal for a Regulation of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, (June 12, 2003), (2001/0252 (COD)), at http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2003/June/council10449en03.pdf. *See also* Whereas (34) of the final text, Regulation 726/2004.

[1519] See in Switzerland the September 13, 2002 decision of the Swiss appeal commission for pharmaceuticals, JAAC 67.31, *supra* note 562, at point 9.c and d. See, in the European Union, Final opinion of the Committee for Proprietary Medicinal Products on the refusal of a marketing authorisation for Rescupase, at 2, (Mar. 25, 1999) (CPMP/660/99), at http://www.emea.eu.int/pdfs/human/opinion/066099en.pdf.

[1520] Serono was among the first companies to overcome FDA marketing exclusivity. *See* Serono, Annual Report 2002, p.9, http://www.serono.com/ir/pdf/ar_2002_all.pdf.

[1521] The European Union has instituted a similar system of exclusivity. *See* Article 8.3.(c) of Regulation 141/2000/EC, *supra* note 44.

[1522] Thus, Astra-Zeneca and Bristol-Myers Squibb provided funds to support a study of olanzapine versus haloperidol given that they sell "products that compete with olanzapine." Robert Rosenheck et al., *Effectiveness*

Consumer groups are also petitioning for comparative trials.[1523] They rightfully point out that accumulating more "me-too drugs"*[1524] (of unknown comparative efficacy) is not in patients' best interest. Governments are just starting to heed their calls, although no drug agency is yet requiring comparative clinical trials.[1525] However, the industry retorts that relative effectiveness cannot be assessed until the relevant drugs have been on the market for a number of years. Moreover, it contends – probably rightly so – that me-too drugs contribute in bringing down the cost of drugs through inter-brand competition.[1526] Nonetheless, information about relative effectiveness remains hard to obtain and the industry is doing little to generate such information.[1527]

6.3.3.4. Washout periods

Because sick subjects enrolled in a clinical trial have been taking drugs to treat their medical conditions, a washout period may be introduced at the beginning of the trial. During this period, subjects are given no drug (at least no drug whose effects could interfere with the results of the trial), in order to progressively wash out the effects of previously taken medications.[1528] The length of this period depends on how long it typically takes for the effects of earlier medications to disappear.[1529] Often, a rule of thumb is applied to determine this period since not all subjects were taking the same medications before the trial's initiation.

The washout period also allows the investigator to record subjects' baseline characteristics, without this assessment being biased by treatments previously prescribed to the subjects.[1530] For instance, the severity of the symptoms cannot be measured in a fair manner if subjects are taking different medicines which could, to varying degrees, mask these symptoms.

---

and Cost of Olanzapine and Haloperidol in the Treatment of Schizophrenia: A Randomized Controlled Trial, 290 JAMA 2693, at 2701 (Nov. 26, 2003), at http://jama.ama-assn.org/cgi/reprint/290/20/2693.pdf.

1523 *See generally* Tunis et al., *supra* note 597, at 1626. *See also* Public Citizen Health Research Group, Comments on the Prescription Drug User Fee Act (PDUFA), at point 1, (Jan. 25, 2002), at http://www.citizen.org/congress/reform/drugsafety/articles.cfm?ID=6689.

1524 Me-too drugs are drugs which differ only very slightly from existing products. Me-toos are not generics (i.e., exact copies of the active ingredients), but they do not bring forth a significant therapeutic advantage.

1525 See the mild support offered by the European Commission in: A Call for Action, *supra* note 787, at 10-11.

1526 *See, e.g.,* Bailey, *supra* note 725, at 10; Thomas H. Lee, *"Me-Too" Products – Friend or Foe?*, 350 NEW ENG. J. MED. 211-12 (Jan. 15, 2004), at http://content.nejm.org/cgi/content/full/350/3/211; Joseph A. DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22(2) PHARMACOECONOMICS 1 (2004), at http://www.who.int/intellectualproperty/submissions/Submission_DiMasi.pdf.

1527 *See* Charles Marwick, *Federal funding for comparative drug studies not in US budget*, 328 BMJ 603 (Mar. 13, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7440/603?ecoll (describing the successful efforts of the pharmaceutical industry to prohibit the (U.S.) Centers for Medicare and Medicaid Services from using comparative evidence of efficacy to decide which drugs to reimburse).

1528 This effect is sometimes referred to as the carry-over effect.
On the other hand, the placebo effect of previously taken drugs can rarely be washed out. *See* Robert Ader, *The Role of Conditioning in Pharmacotherapy, in* THE PLACEBO EFFECT 138, 150 (Harvard University Press 1997)

1529 For instance, the effects of corticosteroids taken against allergic rhinitis generally need a long time to vanish.

1530 *See* Martyn Evans, *Justified deception? The single blind placebo in drug research*, 26 J. MED. ETHICS 188, at 188 (2000), at http://jme.bmjjournals.com/cgi/content/full/26/3/188.

A washout period can be combined with a "placebo run-in" period, during which all subjects are given a placebo.[1531] The placebo run-in period allows to exclude subjects who react very strongly to the placebo (called "high placebo responders").[1532] A placebo run-in period must be carefully designed so as to avoid bias, particularly with respect to the implementation of exclusion criteria.[1533] Placebo run-in periods also entail ethical difficulties, since subjects are neither told that they are *all* receiving a placebo nor the *purposes* of this "procedure."[1534]

Washout periods pose ethical problems analogous to those involving the use of placebos; as is true of placebo-controlled trials, subjects receive no treatment during the initial washout period. Thus, the investigator must duly explain to her ethics committee why a washout period is necessary and how the subjects' health is to be safeguarded.[1535] Subjects must receive specific information about the risks they incur during this period of time.

6.3.3.5. Hiding the control

This subsection examines how the participants in a clinical trial need to remain ignorant (i.e., blind) as to the nature of the drug administered to subjects.

6.3.3.5.1. Blinding

6.3.3.5.1.1. Single-blinding

Single-blinding refers to the fact that subjects are not to know whether they are receiving the test drug or the comparator product. Sometimes, the word "masking" is used instead of "blinding."[1536] Studies that are not blinded are referred to as "open-label" studies.[1537]

Blinding is necessary for at least two reasons. These two arguments also hold, albeit to a lesser extent, when an active control is used instead of a placebo.

First, the placebo truly works only if patients believe that they are taking a "real" drug. If subjects were to know with certainty that they are being given a placebo, the

---

1531 Only once this period is over, will they receive either the investigational treatment or the comparator product (an inert placebo or an active comparator).

1532 *See, e.g.,* Vered Stearns et al., *Paroxetine Controlled Release in the Treatment of Menopausal Hot Flashes*, 289 JAMA 2827, at 2828 (June 4, 2003), at http://jama.ama-assn.org/cgi/reprint/289/21/2827.pdf; IRB Guidebook, *supra* note 411, at chapter IV.J. There is however no guarantee that this preliminary study will succeed in identifying all high responders. *See* THE SHAPIROS, *supra* note 4, at 170-71.

1533 *See* Ariel Pablos-Mendez et al., *Run-in periods in randomized trials: implications for the application of results in clinical practice*, 279 JAMA 222 (Jan. 21, 1998), at http://jama.ama-assn.org/cgi/reprint/279/3/222.pdf.

1534 *See* M. Evans, *supra* note 1530, at 189-94.

1535 *See, e.g.,* University Hospitals Center for Clinical Research, Use of Placebos and Washout Periods in Research Studies, (July 2003), at http://www.uhhs.com/download/research/IRB_Policy_21_Placebos_72003.rtf.

1536 *See also* Kenneth F. Schulz et al., *The Landscape and Lexicon of Blinding in Randomized Trials*, 136 ANN. INTERN. MED. at 256-57 (Feb. 5, 2002), at http://www.annals.org/cgi/reprint/136/3/254.pdf (on a possible explanation for the use of the word "mask").

1537 *See, e.g.,* Costal Connecticut Research, Clinical Trial, at http://www.coastal-research.com/glossary.htm; MarshallBlum, Clinical Trial Glossary, at WebMDHealth, http://my.webmd.com/content/pages/13/65826.htm?z=1104_08950_8900_ct_09.

placebo effect would be ruined.[1538] This could result in the investigational compound being thought effective, while in fact its true measure of efficacy is limited to the placebo effect. Similarly, if subjects know whether they are receiving the investigational drug or the comparator drug, their expectations of respective efficacy may influence the results observed.

Second, if subjects were to know they are receiving a placebo, they could choose to drop out of the trial in order to receive a "real" treatment in an ordinary medical setting. By blinding the study, their continued participation is facilitated. Likewise, subjects who know that they are receiving the placebo are less likely to comply with the investigator's instructions not to self-medicate.[1539] Schulz explains that these less-than-ethical grounds were what initially motivated the United States and Britain to introduce blinding.[1540]

6.3.3.5.1.2. **Double-blinding**

Double-blinding refers to the fact that, not only do subjects ignore whether they are receiving the investigational drug or the control product, but the *investigator and her team* are also kept ignorant.[1541] Several justifications warrant double-, and not just single-blinding.

The first justification of double-blinding is to maintain single-blinding. Subjects have a natural interest in guessing whether they are receiving "the real drug" or the control product.[1542] One way for them to find this out would be to observe how the medical staff treats them. Subjects feeling neglected (compared to others) could infer that they are receiving the control product. If the medical staff knows who is receiving the real drug, it might – consciously or not – bestow greater attention, care and time on the group of subjects receiving the "real" medicine (the "treatment bias").[1543] One reason for this different attitude could be that the investigator and her staff want to please the sponsor who, in turn, would be satisfied and grateful if the subjects on the active arm of the trial performed better. Another reason could be the researchers' curiosity and desire to discover the effects of a new interesting drug.

1538 Of course, subjects know that they have a 50% chance of receiving a placebo. However, this knowledge is insufficient to dispel the placebo effect.

1539 Schulz et al., *supra* note 1536, at 255. See also the explanation accompanying point 11(a) from the CONSORT Statement, at http://www.consort-statement.org/examples11a.htm.

1540 The initial reasons for introducing controls varied among countries. "The rationale in Germany for blinding centered on the elimination of bias. In contrast, the interest in Britain and the United States initially centered on preventing attrition problems." Schulz et al., *supra* note 1536, at 254.

1541 *See* section 1.2.2 (p.3) ICH E10 and section 1.10 (p.3) ICH E6. Placebo-controls generally go hand in hand with double-blinding. *Id.* at 2.1.1 (p.13) of ICH E10.
For a possible origin of the word "blind," see THE SHAPIROS, *supra* note 4, at 154. *See also* Edison Pharmaceutical Co. v. Food and Drug Administration, 600 F.2d 831, at 838 (D.C. Cir. 1979).

1542 Subjects who believe that they are receiving the placebo may choose to withdraw from the study so as to avail themselves of better treatment alternatives. Such withdrawals are clearly problematic for the sponsor and the investigator: comparison between the test treatment and the control arm is made progressively more difficult as subjects drop out of the trial. *See* chapter 2.1.7.2 (p.19) ICH E10.

1543 Not only may the attitude of the medical team accidentally reveal to subjects which type of product they are receiving, but it may also affect their recovery. If subjects receiving the investigator's preferred drug are given more attention and more care, they will get better, in part because of the placebo effect and, in part, because of the superior medical supervision.

The second justification of double-blinding is to maintain the investigator's integrity. If investigators are partial to one of the treatments; their desire to be proven right might unduly influence (even unconsciously) the way in which they conduct the trial.[1544] Tus, double-blinding prevents possible bias in the collection of data.[1545]

When certain members of the study team are not kept blind, these persons should be shielded from any contact with subjects and blinded team members.[1546] For example, those who prepare the products to be administered should not administer them.[1547]

Normally, the *sponsor* is also among the parties kept ignorant of treatment allocation.[1548] The FDA requests such extensive blinding to maintain the study's validity. When the sponsor does not know whether its investigational drug is "working" or not, it can implement necessary changes to the protocols with less risks of being accused of manipulating the results to favor its own treatment.[1549] The FDA recommends that the sponsor notify the Agency whenever the sponsor intends to break its blind.[1550] The blind should only be broken to the narrowest extent necessary. For example, "the sponsor should formulate written question, preferably with yes/no rather than numerical answers."[1551] The answers should be given in writing, so as to document the extent of the break.[1552]

6.3.3.5.1.3. Other types of blinding

Blinding is frequently extended to clinical team members who are not in contact with subjects. For instance, individuals performing the initial assessment of the data ("outcome assessors") are generally kept blind.[1553] Thus, the team that analyzes the study results does not know if specific sets of data they examine relate to a subject on the treatment or on the control arm of the trial.[1554] *A contrario,* analysis of study results, if done with the advantage of hindsight regarding treatment attribution, may lead to bi-

---

1544 *See, e.g.,* IRB Guidebook, *supra* note 411, at chapter IV.J.

1545 If a doctor expects the investigational treatment to perform better (or worse), he may be led (consciously or unconsciously) to report better (or, conversely, worse) results for subjects receiving that treatment. When the collection of data is not purely machine-made, but leaves some room for discretion (e.g., interpretation of EKG), the doctor's knowledge and expectation could distort the result. *See more generally* ICH E9, at section 2.3.1, p.8.

1546 When not all investigators or members of the medical team are blinded, there should be a mechanism to shield blinded participants from the ones that are not. Partial blinding may be necessary for example, to allow the unblinded investigator to adjust the medication's dosing. *See* Chapter 9.4.6 (p.9) of the ICH E3.

1547 *See, e.g.*, FDA warning letter to Harry D. Bear, *supra* note 931.

1548 *See* section 3.2.2.5.b ICH E8 Guidance.

1549 *See* FDA (DMC), *supra* note 920, at 20.

1550 *See id.* at 21.

1551 *Id.*

1552 *Id.* at 21-22.

1553 *See* section 2.1.2 (p.13) of ICH E10 Guideline and section 7.1 (p.30) of ICH E9.
Blinded assessment also emerges as a substitute for double-blinding in clinical trials where double-blinding would not be possible (e.g., because unethical).

1554 For example, biopsies may be assessed by an expert who does not know whether the biopsies are those of a subject taking the investigational drug or the control. *See, e.g.,* Gilead (Briefing Document), *supra* note 1240, at 22. *See also* BAZELL, *supra* note 673, at 156.

ased assessments.[1555] The data themselves should preferably originate from automatic measuring instruments. This is sometimes referred to as a triple- or quadruple-blind.[1556]

More extreme versions of blinding suggest that the staff treating the subjects be ignorant of the study design.[1557] Other versions call for the test article and the control article to be administered commingled with food so as to reduce subjects' placebo response.[1558] To curtail conscious or involuntary influences from the medical team, it has also been recommended that a third party should be appointed to provide the necessary information to prospective subjects during the informed consent process.

6.3.3.5.2. Two almost identical products

As noted above, if the subject knows or guesses that he did not receive the "real" drug, the placebo effect ceases to operate.[1559] In clinical trials, guessing is a straightforward game if the placebo (or the active comparator) does not "look and feel" like the test drug. It is therefore very important that the sponsor arrange for the control product to correctly copy the drug.[1560] The two products should have exactly the same appearance.[1561] Because patients can – and will – discuss the taste and other characteristics of the products, it may also be necessary to give the two products the same taste or other noticeable characteristics.[1562]

Yet selecting an adequate control product is not as easy as it may appear.

Certain studies require the use of an "*active*" placebo, that is an inert product combined with *active* substances selected to imitate the side effects of the investigational product.[1563] This prevents subjects from guessing what product they are receiving, based on the different side effects they can detect (e.g., a dry mouth). However, using an "active placebo" is a difficult choice. It might not be ethical to provoke purely artificial side effects. Designing an "active placebo" that really mimics the effect of the tested drug is not a straightforward task.[1564] Active placebos make it harder to determine whether the effects observed are due to the placebo's inactive or active ingredients.

1555 "Only after the results [of the trial] are analyzed should the code be revealed." THE SHAPIROS, *supra* note 4, at 210.

1556 "When investigators use the term "triple-blind," they usually mean a double-blind trial that also maintains a blind data analysis. Some investigators, however, denote trials as triple-blind if investigators and assessors are distinct people and both, as well as participants, remain unaware of assignments. Investigators rarely use the term "quadruple-blind," but some use it to denote blinding of participants, investigators, assessors, and data analysts." *See* Schulz et al., *supra* note 1536, at 256.

1557 *See* THE SHAPIROS, *supra* note 4, at 171.

1558 *See id.* at 171.

1559 The patient must believe in the treatment: he must trust – consciously or unconsciously – that the treatment will be efficacious. *See* D. B. Morris, *supra* note 1454, at 187.

1560 *See* chapter 2.1.1 ICH E10 Guideline. This obligation was explicitly stated under the former intercantonal system. *See* Article 2.3.d) of the GCPs accompanying the (former) IOCM 1995 Regulation.

1561 *See* THE SHAPIROS, *supra* note 4, at 202; Public Citizen, *Ginkgo Biloba Is Found Ineffective for Dementia and Age-Associated Memory Impairment in the Elderly*, 7(2) WORST PILLS, BEST PILLS, at 15, (Feb. 2001), at http://www.citizen.org/documents/ginko201.pdf.

1562 *See, e.g.*, chapter 9.4.6 (p.9) ICH E3.

1563 *See* THE SHAPIROS, *supra* note 4, at 35, 206-207.

1564 See the examples provided by the SHAPIROS, *id.* at 207.

Second, differences in treatment regimes, in particular when *active comparator* drugs are used, can preclude successful blinding.[1565] For example, if the control drug must be taken as a tablet after meals, while the investigational drug has to be taken in liquid form before meals, blinding may require the introduction of multiple placebos. When the toxicity profiles of the two products are different (e.g., the investigational drug causes rashes, while the active comparator causes drowsiness), maintaining perfect blinding becomes impossible.

6.3.3.5.3. Inadvertent unblinding

Despite the importance of proper blinding, studies have shown that both physicians and subjects often succeed in guessing what product is administered.[1566] Why is this?

First, most placebo products regrettably fail to mimic the characteristics of the tested drug. As alluded before, the nature of the treatment can be inferred based on the specific adverse events associated with the active treatment (e.g., fever).[1567] However, the problem could be even more worrisome. There are sponsors that fail to supply a placebo that *looks* identical to the tested drug;[1568] Shapiro and Shapiro intimate that pharmaceutical companies may not be taking their responsibility seriously enough.[1569]

Second, deliberate "cheating" may result in unblinding a study. "Methods [to ascertain the nature of the treatment administered] included holding envelopes containing the assignments up to a light bulb,"[1570] leading to increased precautionary measures to hide the assignment code. In early AIDS trials, enrolled subjects felt morally entitled to know what their treatment was and to receive the active drug. Consequently, they had their pills analyzed by laboratories;[1571] they also exchanged drugs to make sure that all subjects would receive, at least from time to time, the active drug.[1572]

Well-conducted clinical trials have to incorporate tests to verify whether the blind was maintained throughout the study.[1573] For example, investigators and subjects should be asked to guess which treatment they gave, respectively received. If they guess corectly, this means the blind was not maintained properly. When this is the case or when no tests are performed, the reliability of the study findings must be called into

---

1565 *See* ICH E9, at section 2.3.1, p.8-9; EMEA (Biostatistical Methodology), *supra* note 1382, at 143-44.

1566 *See* THE SHAPIROS, *supra* note 4, at 197-198.

1567 "The variables that appear to affect guessing include patient improvement, adverse effects, dosage units of active drug and placebo, differences among raters … and occasionally the length of the study." *Id.* at 205, and also at 149.

1568 *Id.* at 205.

1569 *Id.* at 205.

1570 Kenneth F. Schulz, *Subverting randomization in controlled trials*, 274 JAMA 1456 (Nov. 8, 1995) ("Randomized controlled trials appear to annoy human nature – if properly conducted, indeed they should.").

1571 ARNO & FEIDEN, *supra* note 125, at 52.

1572 *Id.*

1573 *See, e.g.,* Paul S. Aisen et al., *Effects of Rofecoxib and Naproxen vs Placebo on Alzheimer Disease Progression*, 289 JAMA 2819, at 2823-24 (June 4, 2003), at http://jama.ama-assn.org/cgi/reprint/289/21/2819.pdf. *See also* CONSORT Statement, at point 11(b), at http://www.consort-statement.org/examples11b.htm.

question.[1574] Unfortunately, many published reports of clinical trials fail to mention how well the blind was kept.[1575]

6.3.3.5.4. Permissible unblinding

Normally, the blind is removed only at the end of the trial ("unblinding"). Yet, the investigator may have to remove the blind during the study if a specific patient experiences serious side effects;[1576] unblinding is then necessary to allow the administration of the correct remedial treatment.[1577] The protocol may also anticipate other situations where the blind must be broken.[1578] Cases where the blind is broken should be directly observable,[1579] duly recorded and reported.[1580]

The decision to break the blind is a major one. A subject whose blind has been lifted is normally withdrawn from the trial.[1581] Conversely, the investigator faces liability if she waits too long to lift the blind and if this delay results in injuries for the subject.[1582]

Ethics committees should be closely involved in the decision to lift the blind.[1583] RECs might advise the investigator as to the abstract or case-specific circumstances where the blind should be removed. In practice, RECs are often not notified.

1574 *See, e.g.,* Dean Fergusson et al., *Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials*, 328 BMJ 432-34 (Feb. 4, 2004), at http://bmj.bmjjournals.com/cgi/reprint_abr/328/7437/432.

1575 "Only 15 of the 191 trials (8%) provided such information [i.e., the success of blinding], be it qualitative or quantitative. Of the 15 trials, only five trials reported that blinding was successful, and of these, three did not present any quantitative data analysis to support their claim." *Id.* at 433-34. *See also* Jon N. Jureidini et al., *Efficacy and safety of antidepressants for children and adolescents*, 328 BMJ 879, at 881, (Apr. 10, 2004), at http://bmj.bmjjournals.com/cgi/reprint/328/7444/879.pdf (focusing on this specific population).

1576 For example, the emergency code that discloses for each patient, whether he is taking the drug or the placebo, is placed in a sealed envelope or appears below a scratch-off label on the product. *See also* Christopher M. O'Connor et al., *Azithromycin for the Secondary Prevention of Coronary Heart Disease Events: The WIZARD Study: A Randomized Controlled Trial*, 290 JAMA 1459, at 1460 (2003), at http://jama.ama-assn.org/cgi/reprint/
290/11/1459.pdf. Thus, blinding cannot be broken without the monitor and sponsor's knowledge. If feasible, the investigator should obtain the monitor's prior approval before breaking the code. Every occurrence of code-break should be recorded and justified. *See* BAZELL, *supra* note 673, at 150.
The ICH also allows the clinical trial to be designed around such code-breaking adverse events so that their occurrence becomes a study endpoint. This type of clinical trial is referred to as "early escape." *See* chapter 2.1.5.2.2 (p.16) ICH E10 Guideline. *See also* Temple & Ellenberg, (Part 1), *supra* note 1493.

1577 *See* ICH E9, at section 2.3.1, p.9.

1578 *See* section 4.7 (p.15) ICH E6.

1579 *See* section 5.13.4 (p.24) ICH E6.

1580 *All* instances of unblinding before the normal completion date must be reported. *See* ICH E9, at section 2.3.1, p.9.

1581 He may continue to receive the treatment but outside the trial.

1582 *See, e.g.*, the complaint by U.S. law firm SSKR&P in the case of Hamlet v. Genentech, July 2003, at http://www.sskrplaw.com/gene/hamletcomplaint.pdf.

1583 Of course, when an internal committee is specifically appointed for this task, as is often the case in large trials, ethics committees need to be involved.

6.3.4. Randomization

If one wanted to cheat and show that a drug is very efficacious, a good way to go about it would be to select for the treatment group subjects who are not very sick, not very old, not taking other medication – and do the exact opposite selection for the control group. With this "pre-arranged luck" (called "selection bias"), the subjects in the control group would all die, and the treatment group miraculously heal…

To avoid this obvious bias,[1584] assignment of subjects to the study's different arms must be randomized.[1585] In other words, chance alone decides assignment to the treatment group or to the control group.[1586] Neither the sponsor nor the investigator are to exert any influence on this process.[1587] This is sometimes also referred to as "allocation concealment."[1588]

Another purpose of randomization is to distribute characteristics (e.g., sex, age, size of tumor) evenly between the two groups.[1589] Randomization operates on both known (e.g., age) and unknown factors.[1590] For example, many years after the trial, it can be discovered that gene "g" was responsible for multiple asthmatic crises. However, because subjects have been randomized, the outcome of the trial should not be affected by this discovery since there should be an even number of subjects with gene "g" in the two groups.

1584 *See* Schulz et al., *supra* note 1536, at 258 (evaluating the average bias effect on non-blinding at 19% and that of inadequate randomization at 41%).

1585 There are alternatives to randomization, but regulatory authorities view them with caution because of reliability concerns. However, in some cases, randomization is unethical or impossible. One alternative is historical or external controls. See chapter 1.3 (p.3) of ICH E10 Guideline. "The external control can be a group of patients treated at an earlier time (historical control) or a group treated during the same time period but in another setting. The external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome)." *Id.* at chapter 1.3.5 (p.5), *see also* chapter 2.5 (p.24-27). External controls are among the least reliable of study design because the potential for bias of all kinds is the highest. *Id.* at p.24. "The inability to control bias restricts use of external control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized." *Id.* at 25.

1586 *See* section 1.21. (p.2-3) of ICH E10 Guideline; section 1.48 (p.7) of ICH E6.
Randomization is generally done on an individual basis, that is each subject is allocated to one group or another. Some trials have to use a different study design such as cluster randomization, whereby groups of subjects are allocated to a given treatment (e.g., all patients of investigator X). *See* Suzeann Puffer et al., *Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals*, 327 BMJ 785 (Oct. 4, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7418/785.pdf.

1587 Randomization was slow to be adopted in clinical practice. *See* THE SHAPIROS, *supra* note 4, at 130.

1588 "Allocation concealment seeks to prevent selection bias, protects the allocation sequence before and until assignment … In contrast, blinding seeks to prevent ascertainment bias, protects the sequence after allocation …. Thus, allocation concealment up to the point of assignment of the intervention and blinding after that point address different sources of bias and differ in their practicability." Schulz et al., *supra* note 1536, at 257.

1589 "The test and control group should be similar with regard to all baseline and on-treatment variables that could influence outcome, except for the study treatment." Chapter 1.2 (p.2) of ICH E10 Guideline

1590 *See* ICH E9, at section 2.3.2, p.9; EMEA (Biostatistical Methodology), *supra* note 1382, at 144; *Warner-Lambert*, 787 F.2d at 159.

The two groups need not be exactly of the same size. As said before, the test group is often bigger than the control group.[1591] In all cases however, the two groups must have a sufficiently large number of subjects so that randomization can operate correctly.

The study protocol must describe in details how randomization is to be achieved[1592] (e.g., a computer-generated code with an interactive voice response system[1593]). Once the trial is completed, the study report summarizes the key characteristics of subjects in the two groups, including their age, race, sex and initial health status.[1594] This information is usually presented in a table of so-called "baseline characteristics." This table allows verification that the groups were indeed comparable.[1595] If that is not the case, statistical adjustments must be made.

Randomization is not the *only* technique to compose an equivalent test and control groups. Matching (also referred to as "stratification") is one of the alternative methods. In matching, the investigator verifies that, for each subject receiving the experimental compound, another individual with similar characteristics (e.g., sex, age, severity of the disease) receives the comparator product. However, this method is not as highly regarded because it is subject to greater bias.[1596]

6.3.5. Ethical problems related to controls and randomization

In "ordinary" medical care, the physician selects the most suitable treatment following discussion with her patient. The patient gets the individual health care that corresponds best to his needs. In contrast, in a clinical trial, neither the investigator-physician, nor the subject-patient, has its say as to the choice of treatment. The treatment options are delineated in the protocol and all participants are obliged to abide by it. Obviously, the

---

1591 *See, e.g.,* Jacob P. Lalezari et al., *Enfuvirtide, an HIV-1 Fusion Inhibitor, for Drug-Resistant HIV Infection in North and South America*, 348 NEW ENG. J. MED. 2175, at 2176 (May 29, 2003), at http://content.nejm.org/cgi/reprint/348/22/2175.pdf (describing the Fluezon study which had a 2:1 allocation ratio).

1592 The randomization procedures should be managed centrally in multicentric trials. *See* ICH E9, at section 2.3.2, p.10; EMEA (Biostatistical Methodology), *supra* note 1382, at 145.
The manner in which treatment allocation was achieved must also be reported in publications. *See* CONSORT Statement, at point 10, at http://www.consort-statement.org/examples10.htm.

1593 This is an example of randomization procedure: "[a]t the third screening visit (baseline), patients who remained eligible for study entry were randomly assigned to double-blind receipt of either sertraline or matching placebo for 10 weeks in a 1:1 ratio using a computer-generated randomization code. To ensure that each treatment group included similar numbers of younger and older children, patients were stratified into 2 age groups: children (aged 6-11 years) and adolescents (aged 12-17 years)." K. D. Wagner et al., *supra* note 973, at 1034. *See also* Kathleen Squires et al., *supra* note 577, at 314.

1594 To have really representative groups, the protocol may even need to know and control for socioeconomic status, geographic location, family history or motivation.

1595 This table allows an evaluation of how similar the two groups are: "If differences judged to be important are present, appropriate statistical techniques should be used to adjust the primary outcome comparison for these discrepancies." Slinger, *supra* note 1434. *See also* Trisha Greenhalgh, *Statistics for the non-statistician*, 315 BMJ (Aug. 9, 1997), at http://bmj.bmjjournals.com/archive/7104/7104ed.htm; Martyn Evans, *supra* note 1530, at 188.

1596 *See* John Worrall, *Controlling Clinical Trials: Some Reactions to Peter Urbach's Views on Randomisation*, (Discussion Paper 41, 2000), at http://www.lse.ac.uk/collections/CPNSS/pdf/DP-withCoverPages/DP51/DP51F-00_C.pdf (setting forth the advantages and disadvantages of matching versus randomization).

absence of choice creates ethical quandaries, which are further examined in this subsection.

6.3.5.1. The notion of equipoise

6.3.5.1.1 Theoretical and clinical equipoise*

In a controlled trial, enrolled subjects are not all treated in the same way. On the contrary, one arm receives the investigational compound, while the other arm receives either a placebo or an active comparator drug (on these two notions, see subsection 6.3.3. above).[1597] Clearly, if one arm of the study is known to be preferable all subjects would want to get this treatment. Subjects receiving the "worse" treatment would be unfairly cared for; they would reasonably object to random allocation.

Consequently, ethical considerations require that, at the beginning of a controlled trial, the two treatment arms be thought equivalent.[1598] *A contrario*, it would be unethical to give subjects a product (either the drug or the comparator) *known* to be inferior. The patient's primary care provider would have to recommend against his patient's participating in a randomized study if, as a result, the latter could receive an inferior drug.

A partial solution to this moral difficulty is *theoretical equipoise*: the belief *by all* participating investigators that the two treatment arms (here: "A" and "B") are equivalent;[1599] in other words, they offer exactly equivalent therapeutic chances for the patients-subjects.[1600] This is sometimes also referred to as the "honest *null hypothesis*"[1601] or the "moral uncertainty principle."[1602]

However, the human mind does not work in this way but tends to take side. Hence, this strict benchmark had to be loosened to tolerate a lower standard:[1603] clinical

---

1597 The two-arm trial (or parallel group design) does not represent the only possible trial design, but it is most the frequent. *See* ICH E9, at section 3.1.1, p.11.

1598 *See, e.g.,* IRB Guidebook, *supra* note 411, at chapter IV.J.

1599 Freedman defines theoretical equipoise as the situation where "the evidence on behalf of the trwo alternative treatment regimens is exactly balanced. This evidence may be derived from a variety of sources, including data from the literature, uncontrolled experiences, considerations of basic science and fundamental physiologic processes, and perhaps a "gut feeling" or "instinct" resulting from (or superimposed on) other considerations." Benjamin Freedman, *Equipoise and the ethics of clinical research*, 317 NEW. ENG. J. MED. 141, at 143 (July 16, 1987).
Since a study can have more than two arms, equipoise must exist for all of them. *Id.* at 141.

1600 Because this equivalence has to be *exact*, "we may say that theoretical equipoise is balanced on a knife's edge." *See* Freedman, *supra* note 1599, at 143.

1601 *Id.* at 141. This null hypothesis should not be confused with the statistical null hypothesis, which is the hypothesis to be confirmed or refuted by the experiment.

1602 *See* Charles Weijer et al., *Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial*, 321 BMJ 756 (Sept. 23, 2000), at http://bmj.com/cgi/reprint/321/7263/756; Don Marquis, *How to Resolve an Ethical Dilemma Concerning Randomized Clinical Trials*, 341 NEW. ENG. J. MED. 691-693 (1999), at http://content.nejm.org/cgi/content/full/341/9/691; Benjamin Djulbegovic et al., *The uncertainty principle and industry-sponsored research*, 356 LANCET 635-38 (2000).

1603 "Many researchers, however, make compromises with this ethical requirement [equipoise]. Sometimes these compromises involve self-delusion in that researchers convince themselves that they do not know what they really do know. Sometimes the compromises involve ingenious methods of denying themselves access to information that would make the trial ethically impossible to continue." Angell (Publication), *supra* note 898,

equipoise.[1604] *Clinical equipoise* is the situation in which *at least some scientists* – and not necessarily the investigator herself – believe that treatment A is better than treatment B, while at least some other scientists are convinced of the contrary.[1605] Under clinical equipoise, an investigational drug should *not* be administered when the medical community is *generally convinced* that the drug is worse than the comparator product (whether active or inert), or vice versa.[1606] How large the majority and how small the minority can be is a solemn question yet unresolved. A survey indicates:

> half the respondents [human research subjects] perceived a trial as unethical when clinical equipoise was disturbed beyond 70:30, and less than 3 percent [of subjects] would consider trials morally justifiable when clinician equipoise is disturbed beyond 80:20.[1607]

This controversy surrounding equipoise is related to the axiom that the *interests of subjects* must always *prevail* over those of patients, of the community as a whole, or of science.[1608]

Although this principle may be appealing in theory, it is difficult to handle in practice. There is no use denying that research subjects are indeed consenting to special sacrifices for the good of the entire community. This should be acknowledged and duly appreciated rather than maintaining an hypocritical stance.

These sacrifices are most evident in *phase I trials on healthy volunteers*. Aside from the payments they receive, these subjects have nothing to gain personally from participation. The interests of science and society clearly prevail over the interests of these volunteers. Yet, the Helsinki Declaration acknowledges that participation of *healthy* volunteers in clinical trials is admissible, even though these volunteers incur only risks, with no benefits.[1609]

---

at 280. *See also* Murray W. Enkin, *Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial*, *Against*, 321 BMJ 757 (Sept. 23, 2000), at http://bmj.com/cgi/reprint/321/7263/756. *See also* SPRUMONT, *supra* note 16, at 45.

1604 Clinical equipoise was proposed by Benjamin Freedman, *supra* note 1599, at 141.

1605 *See id.* at 144 (requiring, for clinical equipoise to be present, "an honest, professional disagreement among expert clinicians about the preferred treatment"). *See also* Steven M. Grunberg & William T. Cefalu, *The Integral Role of Clinical Research in Clinical Care*, 348 NEW. ENG. J. MED. 1386-1388 (Apr. 3, 2003), at http://content.nejm.org/cgi/reprint/348/14/1386.pdf ("[I]f numerous other factors, including the physician's preference and the patient's preference, are allowed to enter into play [to gauge equipoise], then it is indeed difficult to conceive of a situation in which the choice between two treatment groups is ever exactly balanced"); Miller & Rosenstein, *supra* note 1293.

1606 Exceptions can be – and are certainly – made when the condition under study is rather trivial (e.g., hair loss).

1607 *See* Howard Mann & Benjamin Djulbegovic, *Choosing a control intervention for a randomised clinical trial*, 3 BMC MEDICAL RESEARCH METHODOLOGY 7 (2003), at http://www.biomedcentral.com/1471-2288/3/7 (citing to a study by Johnson et al).

1608 *See, e.g.*, paragraphs 5 and 10 Helsinki Declaration; CIOMS 2002 Guidelines, *supra* note 105, at Guideline 8 (commentary); Article 2 of the Biomedicine Convention, *supra* note 107. *See also* DHA (Ordinance Comments), *supra* note 522, at 45; Article 3 COE Research Protocol. In the United States, see AMA, Subject Selection for Clinical Trials, at point (5)(a) (Policy E-2.071), at http://www.ama-assn.org/ama/pub/category/8423.html.
In Switzerland, the Fédération Romande des Consommateurs ("FRC") requested in vain that this principle – the precedence given to research subjects over scientific goals – be set in the OClin itself; FRC (OClin comments), *supra* note 792.

1609 *See* paragraph 16 Helsinki Declaration and also paragraph 18.

This clash is not the exclusive province of nontherapeutic studies. For instance, a subject enrolled in a therapeutic trial could reasonably want to drop out as soon as some preliminary evidence indicates that the treatment he is receiving is not the most effective. Similarly, it is in the subject's best interest to have his pill analyzed to determine whether it is a placebo or the active drug. Yet, subjects are expected to play the game "fairly," and accept the corresponding sacrifices. Greenberg has correctly framed this problem in terms of *game theory*: While all (i.e., the community, including the subjects as a group) are better-off if everyone cooperates, an individual derives a better pay-off by defecting.[1610]

6.3.5.1.2. Personal equipoise

Clinical equipoise may not be sufficient to protect the subjects' interest. There may be scientific uncertainty in situations where, nonetheless, only insane subjects would risk their health and enroll in the proposed trial![1611] Cheng and others have described such a real-world situation and argued that clinical equipoise is not sufficient where personal equipoise is lacking.[1612] In their illustration, doctors were confronted with the following problem: A new drug treatment had been introduced at a hospital to reduce mortality from septic shock. After a while, it was noticed that the drug seemed extremely effective. But because no randomized clinical trials had been conducted, it could not be ruled out that this drastic reduction in mortality was not attributable to some other causes (e.g., closer monitoring of patients, different patient clientele coming to the hospital). Worse, the scientific underpinning for the drug's effects could not be ascertained using in vitro or animal models. Hence, the situation was one where scientific uncertainty indisputably persisted. Therefore, the condition of clinical equipoise was satisfied. Yet, the hospital physicians had to give up the idea of conducting a randomized clinical trial because they could not ethically propose that the control group be randomized to a placebo. The risk of dying from untreated septic shock was so high that no reasonable subject would accept it. Similarly, no doctor could ever recommend to his patient enrollment in such a randomized trial.

This case shows that scientific uncertainty (i.e., clinical equipoise) is not a sufficient condition if personal equipoise is obviously lacking.[1613] The consequences are sometimes unfortunate: A drug's efficacy may remain unproven – at least by strict scientific standards. This illustrates that ethics can operate to bar socially desirable research.[1614]

1610 *See* M. D. Greenberg, *supra* note 129, at 332-33 and 335-36 (introducing this game theory model in the context of facilitated treatment access for HIV patients-subjects).

1611 See also the critical comments by Brody, *supra* note 447, at 123 and at 127-28 (finding Freedman's approach exceedingly subjective).

1612 *See* Allen C. Cheng et al., *Ethical problems of evaluating a new treatment for melioidosis*, 327 BMJ 1280-82 (Nov. 29, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7426/1280.

1613 *See also* BEAUCHAMP & CHILDRESS, *supra* note 16, at 323.

1614 Cheng and others did suggest that the placebo-controlled trial might be deemed ethical in developing countries, because their lack of financial resources implied that only treatments whose efficacy had been duly demonstrated have a chance of being implemented. Cheng et al., *supra* note 1612, at 1282. This argument is not entirely convincing.

6.3.5.1.3. Duration of equipoise

Another problem with equipoise, is *how long* should it last? What happens if a few weeks or months after the beginning of the trial it is realized that one treatment arm is better than the other? Such a realization may come long before the available data prove the given outcome with the necessary statistical significance ($p < 0.05$; see subsection 6.3.10.3. below). This realization may also arise following reports by *other* researchers doing distinct clinical trials of the same drug. The interval between this first realization and the desirable statistical proof is an ethical limbo.[1615] On the one hand, the protocol states that the trial should proceed until a given point in time and the importance of making subsequent medical decisions based on strongly reliable results speaks for the continuation of the trial. On the other hand, subjects could be harmed because they were ascribed to the less effective arm of the trial.

Unfortunately, by that stage, ethics committees find themselves on the sidelines.[1616] Although RECs do receive adverse event reports (see below subsection 9.1.2.), they are normally kept blind and find it exceedingly difficult to interpret these reports (when they do try…). RECs are also not provided with positive findings or reports stemming from different clinical trials. The responsibility to end the trial prematurely may rest with the DSMB if there is one (see subsection 5.8. above).[1617] This board is confronted with the same ethical quandary regarding how to reconcile scientific and ethical considerations. Most authors admit that a trial should be stopped as soon as the more effective treatment is identified with some certainty, that is the certainty which would be enough to cause a reasonable person to refuse his consent at this point or to withdraw it if already enrolled. However, clinical trial practice appears significantly more tolerant and inclined toward scientific and statistical certainty.

In my view, subjects – provided they are fully competent adults – should be allowed to make their own decisions, of course based on full and comprehensible information. They may choose to drop out of the trial, particularly if they can access the more effective treatment outside the trial. However, they may also decide to maintain their participation, notably if the best drug is only available through the clinical trial and they are satisfied with the health care they are receiving. One should accept that competent and fully informed subjects may choose to make sacrifices in the interests of future patients and society. Although they can never be forced to make this sacrifice, they can decide to do so as long as their choice is not coerced.

Yet, insisting on statistical proof at $p=0.05$ is simply impractical once there is strong evidence of likely *life-saving* benefits. In such a case, marketing authorizations should be granted even if the clinical evidence provided falls below the ordinary standards; phase IV commitments may address the statistical gap.

[1615] *See* Angell (Publication), *supra* note 898, at 277. *See also* 21 C.F.R. § 312.7(c), according to which a "sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application."

[1616] *See also* OIG (Reviewing), *supra* note 1187, at 6.

[1617] *See also* Freedman, *supra* note 1599, at 142.

6.3.5.1.4. Consequences

The equipoise requirement has obvious consequences for researchers' *liability*. In lawsuits initiated by subjects injured by the experimental drug, it is doubtful that a physician could justify allowing random selection of a patient to a treatment she believed – for good or bad reasons – to be suboptimal. However, to my knowledge, the issue has never been submitted to the courts.

Imbalance in treatment arms (i.e., lack of equipoise) may also affect the attitude of subjects. As we saw earlier, subjects enrolled in the first AIDS trials felt that they were mistreated, because they had no therapeutic alternatives to enrollment. As a result, they felt justified in cheating; they lied to satisfy the strict entry requirements; they tested their drug to make sure they were not receiving a placebo; they did not adhere to the treatment regimen.[1618] As in any other aspect of life, people feel considerably less scruples in breaching an "agreement" they see as unfair.

Ethics committees should verify that trials truly take place in a situation of equipoise, at least when they are risky.[1619] Ideally, they should request independent demonstration of equipoise, for example based on a systematic literature review.[1620] RECs should not rely only on information presented by the investigators. They may have to survey practitioners to assess the degree of uncertainty surrounding the various arms of a trial.[1621] Others have replied that RECs are already overwhelmed by their "classic" set of duties, making it impossible to intensify their review (see subsection 7.1.3. below). This is only one more illustration of the inherent limitations of the scientific and ethical review entrusted to RECs.

6.3.5.2. The placebo controversy

Placebos have always been immensely controversial. Even outside clinical trials, giving a dummy pill to a sick patient is contentious.[1622] Some doctors may think this is the best and cheapest technique to cure patients whose symptoms are not serious or who are branded as hypochondriacs.[1623] Since the placebo does work, the patient is happy, the doctor is happy and even the insurance company is satisfied!

[1618] *See* Udo Schüklenk & Carlton Hogan, *AIDS Clinical Trials: Ethical and Design Issues*, 8(3) INTERN. J. OF BIOETH. 127-32 (1997).

[1619] *See* Paul Little, *Commentary: presenting unbiased information to patients can be difficult*, 325 BMJ 770 (Oct. 5 2003), at http://bmj.com/cgi/reprint/325/7367/766. *See also* WHO (Operational Guidelines), *supra* note 1379, at point 6.2.1.3 (p.10).

[1620] *See* Mann & Djulbegovic, *supra* note 1607.

[1621] *Id.* Surveys may be particularly helpful to displace the mistaken impression of clinical *certainty* and thus to justify a clinical trial.

[1622] Additionally, "[m]any physicians prescribe drugs with known pharmacological effects that are irrelevant to the clinical problem, a practice referred to as impure placebo. Thus, an antibiotic might be prescribed for a cold, even though doing so lacks scientific merit, or a suboptimal dose might be given and considered a harmless intervention." Wick & Zenni, *supra* note 1445, at 526-27; *see also* C. Hart, *supra* note 1435.

[1623] The Shapiros conducted a survey of physicians' point of view with regard to the use of placebos and found that older physicians not involved in research were more critical of such a practice. *See* THE SHAPIROS, *supra* note 4, at 177-78.

Bioethicists and some physicians nevertheless argue that this is not fair.[1624] The physician should not trick her patient, even in the latter's best interest. For them, patient autonomy and trust are far more important than medical achievements (i.e., the principle of beneficence). Patients are bestowed with a "legalistic" right to make informed decision; this right prevails over likely therapeutic benefits stemming from ignorance and blind trust in the physician.[1625] Even when patients declare explicitly and in advance their wish to be kept in ignorance, many physicians will nonetheless choose to provide detailed information for fear of liability.[1626]

6.3.5.2.1. The controversy in developed countries

In clinical trial settings, placebos became a particularly divisive issue with the AIDS calamity.[1627] Early AIDS clinical trials tested new compounds against placebo, largely because no effective drugs had yet been discovered, let alone received marketing approval. In addition, as I mentioned above (subsection 6.3.3.3.1. above), having one group take no medication at all made it easier to assess the effects of the tested compounds. However, the consequences were often unacceptable: Subjects died because they were receiving a dummy drug, while the investigational drug was saving the lives of subjects assigned to the other arm of the trial. Worse, subjects died because, under the condition imposed to participate in the trial, they were prohibited from taking *any other* ancillary treatment even if prescribed by their primary care doctor. Sure enough, AIDS patients protested. After rumors of effective though unapproved treatments started circulating, they refused to enroll in placebo-controlled trials.[1628]

In part due to their protests, the use of placebo is now restricted whenever there exists a life-prolonging effective treatment (aside from the investigational drug). When this is the case, placebos cannot be used as controls in clinical trials of serious diseases.[1629] What diseases are to be considered "serious" is occasionally open to discussion.[1630] Mental conditions pose particular problems as denying an active treatment

---

1624 *See, e.g.,* BEAUCHAMP & CHILDRESS, *supra* note 16, at 85-86. *See also Pantron I Corp*, 33 F.3d at 1090 (where the Court held that it was a deceptive practice and misleading advertisement for a manufacturer to claim "effectiveness" that arises exclusively out of the placebo effect); United States v. An Article … Acu-Dot, 483 F. Supp. 1311, at 1315 (D.Ohio 1980) ("The strong placebo effect may save the res from claims of 'false labeling' … but it does not protect the device from the charge that the labeling is 'misleading'… and that is all that is required to warrant condemnation of the res.").

1625 "The thing is, we live in an age in which, from a legal point of view and a moral point of view, autonomy trumps everything else." *See* Alan Stone, *Placebo: Conversations at the Disciplinary Borders*, *in* THE PLACEBO EFFECT 208, 237 (Harvard University Press 1997).

1626 *See* Howard Spiro, *Placebo: Conversations at the Disciplinary Borders*, *in* THE PLACEBO EFFECT 208, 241 (Harvard University Press 1997).

1627 Long before the AIDS drama, Beecher had criticized placebo-controlled trials in his famous 1966 article. *See* Beecher (Ethics), *supra* note 232. See also in the 1980s clinical trials of thrombolytical agents, BRODY, *supra* note 447, at 43.

1628 ARNO & FEIDEN, *supra* note 125, at 50-52, also at 93 and at 187.

1629 *See* chapter 1.3.4 of ICH E10 Guideline. Active controls may get in the way of double-blinding if the two drugs (the test treatment and the active control) are not administered in a similar fashion (e.g., a pill versus an injection). *Id.*

1630 *See* Susan Ellenberg & Robert Temple, *Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments: Part 2: Practical Issues and Specific Cases*, 133 ANN. INTERN. MED. 464-470 (Sept. 19, 2000), at http://www.annals.org/cgi/reprint/133/6/464.pdf [hereinafter Ellenberg & Temple (Part 2)]. *See also* the complaint filed by the U.S. law firm of SSKR&P in the case of Hamlet v. Genentech, in July 2003, *at* http://www.sskrplaw.com/gene/hamletcomplaint.pdf.

may place the subjects at risk of suicide. The dilemma is accentuated by the fact that mental patients (e.g., depressive patients) often exhibit a strong positive reaction to placebos.[1631]

Choosing the appropriate *active control* is not easy either. There may not be a consensus as to what constitutes the current most effective treatment, perhaps due to the paucity of reliable scientific information.[1632] When an active control is used despite the fact that little is known about it, the two arms of the study are in a way "experimental," making the study results hard to interpret.[1633]

Even when *no approved drug* exists (for the studied medical condition), doing a placebo-controlled trial may be unethical, especially when preliminary evidence suggests that the investigational compound is particularly effective.[1634] In such cases, the trial design may need to be adapted to test different doses of the experimental drug against each other. A crossover design is another possible solution; in a crossover trial, two groups are formed, the first receives the investigational product, while the second receives a control (generally a placebo); after a while, the second group gets the investigational drug, while the first group either stays on the drug or is switched to the control.[1635]

Another issue is whether the use of a placebo transforms a therapeutic trial in a *nontherapeutic* trial for the subjects enrolled in the placebo arm of the study (on the distinction between therapeutic and nontherapeutic trials, see subsection 6.1.1.3. above).[1636] This question is important when the law sets forth additional protection for nontherapeutic clinical trials.[1637] Traditionally, the delineation between therapeutic and nontherapeutic trials is made on the basis of the study design *as a whole*. Hence, if the general aim of the study is to test the efficacy of a treatment that the investigator deems promising, the study is labeled as therapeutic, even though certain subjects only receive a placebo.

1631 *See, e.g.,* CCNE N°34, *supra* note 1493. The problem is made even more complex given that certain antidepressants have been associated with suicide.

1632 Information may be lacking about the effectiveness of the proposed active control or about its risk profile (i.e., it is effective but its side effects appear very serious).

1633 If the two arms perform equally well, is it because both work or because both do not work? *See, e.g.*, Robert Steinbrook, *How Best to Ventilate? Trial Design and Patient Safety in Studies of the Acute Respiratory Distress Syndrome*, 348 NEW. ENG. J. MED. 1393-1401 (Apr. 3, 2003); Ellenberg & Temple (Part 2), *supra* note 1630.

1634 *See* ARNO & FEIDEN, *supra* note 125, at 115.

1635 A crossover design makes it harder to distinguish the effect of the investigational drug from the effect of the control product, especially if the investigational drug's efficacy is not clear-cut. Interim washout periods can be introduced to address this problem. *See* ICH E9, at section 3.1.2, p.11; FDA, Review of NDA for Celgen's Thalidomid (July 7, 1998), at http://www.fda.gov/cder/news/thalinfo/20785medr.htm.

1636 *See* SPRUMONT, *supra* note 16, at 34-36. *See also* OHRP, Protections for Children in Research, A Report to Congress, at 10, (May 2001), at http://www.hhs.gov/ohrp/reports/ohrp502.pdf [hereinafter OHRP (Children)].

1637 For example, Article 55.2 LPTh introduces additional safeguards for clinical trials on children when the research does not entail "direct benefit" for the subjects.
In the past, the standard of liability for therapeutic and nontherapeutic clinical trials could be significantly different: liability was usually stricter when researchers engaged in nontherapeutic experimentation.

6.3.5.2.2. The placebo controversy in developing countries

Deciding between a placebo or an active control is hard enough in industrialized countries; it becomes an even more complex issue in developing countries.

Until the mid-1990s, many researchers contended that placebo-controlled trials ought to be permissible in countries where the standard of "care" is no treatment anyway. They argued that such trials can yield information which is highly relevant for these countries. For example, testing a cheaper therapy (e.g., a cheaper drug, a standard drug but used at lower dosages or at greater intervals of time) may help decision-makers in a country which cannot afford the more expensive treatment.[1638] The results may lead the developing country to embrace the cheaper course of treatment, whereas previously it had provided no health care at all, invoking the exceedingly onerous costs of the standard treatment.

Going to the other end of the spectrum, the situation is admittedly quite different when Western sponsors' reason for conducting clinical trials in developing countries is purely commercial. For example, the sponsor aims to save time and money by moving the trial in a developing country, even though the drug will be offered for sale only to patients of developed countries.[1639] Bioethicists view such motivation as inherently unethical.

6.3.5.2.3. The revised Helsinki Declaration

Scandals involving placebo-controlled AIDS trials in developing countries led to amendments of the existing bioethical guidelines in order to forbid or limit use of placebos throughout the world.[1640]

Amid heated debates and over a three-year period ending in 2000, a revision of the Helsinki Declaration was negotiated.[1641] The pharmaceutical industry fought to keep placebos and relax other ethical rules (see also subsection 8.6.2.3. below).[1642] It argued that

---

1638 See the example provided by Angell (Publication), *supra* note 898, at 283-84.

1639 To get a proper perspective, it should be mentioned that drug sales in developing countries represent only about 10% of total worldwide sales revenues. *See* IMS Health (Lipitor), *supra* note 670.

1640 In 2002, the CIOMS has adopted a position similar to that of the 2000 Helsinki Declaration on the choice of comparator products. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 11.
According to the Council of Europe, "[t]he use of placebo is permissible where there are no methods of proven effectiveness, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden." Article 23.3 COE Research Protocol.

1641 See for historical background on the 2000 revision, Human & Fluss, *supra* note 72, at 13-18. *See also* Flaherty & Struck, *supra* note 844; Ibarreta et al. (controversy), *supra* note 846, at 167-68.

1642 Public Citizen describes the industry's initial proposal. "The proposed [amendment to the] Declaration [of Helsinki] greatly extends the use of placebos, even when known effective interventions exist, as long as the condition under study does not lead to 'death or disability.' This change will have adverse effects on the health of study participants in both developing and industrialized countries. … The 'death or disability' standard also invites the defining of surrogate markers (which may not themselves be directly associated with disability) as the outcome of interest, justifying the withholding of effective therapy. … The draft Declaration also proposes that placebo-controlled trials 'may be justified on the basis of their efficiency.' This appears to be a reference to the notion that the speed of completing a clinical trial is related to the sample size required. … Whereas the current Declaration assures research participants of 'the best proven diagnostic and therapeutic method', the corresponding section in the proposed Declaration adds the phrase 'that would otherwise be available to him or her,' condemning most residents in developing countries to potentially receiving second-rate medical care when they participate in experiments. … Furthermore, if the logic of this section is to be followed, it will only be a matter of time before it is applied to poor residents in developed

placebos are more valid from a scientific point of view and they also allow for the development of treatments that take into account the reduced financial means of developing countries.[1643] Patients advocacy group fought back to protect, and even extend, subjects' rights. Eventually, the latter won and the Declaration was amended to make it unethical to use placebo where efficacious treatments exist. The industry's proposal to rely on the *local* standard of care was turned down; such an exception could have led to refusal of known medical treatments where most of the local population cannot afford it.

Thus paragraph 29 of the Declaration now reads:[1644]

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the *best current* prophylactic, diagnostic, and therapeutic method. This does not exclude the use of placebo, or no treatment, in studies where *no proven* prophylactic, diagnostic or therapeutic method exists.[1645]

This provision was further clarified – but also toned down[1646] – by a 2002 note.[1647] Pursuant to this note, placebo-controlled trials are permissible when "necessary to determine the efficacy or safety" of a treatment, provided this use is also justified by "compelling and scientifically sound methodological reasons."[1648] Placebos are also allowed in drug studies targeted at minor conditions provided the subjects are not exposed "to any additional risk of serious or irreversible harm." *A contrario*, a level of discomfort is deemed acceptable.[1649] In other words, two alternative criteria[1650] are set forth to choose between a placebo and an active control: i) strict scientific necessity, and ii)

---

countries as well. Particularly in countries like the United States, which does not have universal health coverage, it is inevitable that this principle will ultimately be used to deny uninsured or underinsured persons access to medical care in human experiments. Already we have seen studies in which opiates users are randomized to placebo instead of active therapy, presumably because, due to the drastic underfunding of drug treatment, 'they wouldn't have gotten it anyway,' as many researchers argued in the perinatal HIV transmission case." Public Citizen's letter to the World Medical Association dated March 29, 1999, at http://www.citizen.org/hrg/PUBLICATIONS/1477.htm. *See also* Troyen A. Brennan, *Proposed Revisions to the Declaration of Helsinki – Will They Weaken the Ethical Principles Underlying Human Research?*, 341 NEW. ENG.J. MED. 527-31 (Aug. 12, 1999).

1643 In the case of the aforementioned HIV/AIDS studies, the placebo clinical trials proved that pregnant mothers infected with HIV could be treated effectively by a *shorter* treatment of AZT; this shorter treamtent was significantly more affordable for the patients and governments of these developing countries. *See, e.g.,* Ibarreta et al. (controversy), *supra* note 846, at 166 and 170.

1644 The 1966 version was only slightly different, using the words "best proven diagnostic and therapeutic method." The word "proven" is exceedingly vague since the necessary level of proof is open to discussion. *See* W. T. Carpenter et al., *supra* note 1517.

1645 Emphasis added.

1646 *See, e.g.,* Letter of Public Citizen to the World Medical Association (Aug. 28, 2003), at http://www.citizen.org/publications/print_release.cfm?ID=7272 (criticizing the note of clarification).

1647 *See* Note of clarification on paragraph 29 of the Helsinki Declaration, at http://www.wma.net/e/policy163.htm#note1.

1648 *Id.* However, even in this case, the risk/benefit ratio as a whole must be favorable. *See also* Reidar K. Lie et al., *The standard of care debate: the Declaration of Helsinki versus the international consensus opinion*, 30 J. MED. ETHICS 190 (2004), at http://jme.bmjjournals.com/cgi/content/full/30/2/190 (arguing that, even where there are "compelling and scientifically sound methodological reason," there should also be no risk of "serious or irreversible harm."); Schüklenk, *supra* note 857, at 194-96.

1649 *See* chapter 2.1.3 (p.14) ICH E10 Guideline.

1650 Shapiro proposes that placebo could also be used when the alternative treatments are of limited efficacy. However, even if these alternatives are only marginally better than no treatment, they should still be preferred to placebo when the studied disease is of a serious nature. *See also* Lie et al., *supra* note 1648, at 190.

the absence of *irreversible harm*.[1651] Many commentators view the introduction of condition i) as a mistake – albeit a very serious one.[1652]

6.3.5.2.4. Consequences in developed countries

The Helsinki placebo rule continues to be contentious. If interpreted strictly, it would forbid almost all placebo-controlled trials, since for nearly all medical conditions it is possible to find treatments with at least some degree of efficacy. Even though the researcher may have serious misgivings as to the true degree of efficacy of these other treatments, she would be obliged to incorporate them as control in her study.[1653] Placebo-controlled trials would be admissible only in the rare situations where there is no evidence of a favorable treatment. The upshot would be a considerably less reliable demonstration of new drugs' efficacy: One would only know whether the new drug works better than a treatment that may or may not work. Moreover, it is unclear whether the Declaration allows placebo trials on patients who have not responded to existing, and usually effective, therapies.

A strict interpretation of Paragraph 29 would also ban certain trials with *active* controls.[1654] Indeed, if there is good evidence that the active control is effective, then it becomes the best current therapeutic method, while the investigational drug represents a much more risky alternative given the lack of knowledge about its risks and benefits. Studies of new me-too products for mild conditions that already respond well to existing treatments would be impossible to conduct.[1655]

Conversely, when the sponsor has sound reasons to believe that its investigational compound is clearly better than all available treatments, clinical trials with an *active* control (i.e., with anyone of these other treatments thought to be less efficacious) also raise ethical problems. In that case, the only solution may be to adopt some historical or external control, despite the important scientific limitations of such a study design (see also subsection 6.3.1. above).[1656]

1651 *See* chapters 2.1.3 (p.13) and 2.1.7.1 (p.18) of ICH E10 Guideline (use of placebo is unethical when available treatment would "prevent death or irreversible harm.").
In the United States, see AMA (E-2.071), *supra* note 1608, at point (2).
In the European Union, see EMEA/CPMP's Position Statement on the Use of Placebo, *supra* note 1514.
Following the same rule, subjects should not be assigned to a less effective treatment (e.g., a lower dose of the investigational drug) when a more effective treatment is known to be available. *See also* chapter 2.3.3 (p.20) of ICH E10.

1652 *See* Lie et al., *supra* note 1648, at 190-91; Schüklenk, *supra* note 857, at 194-96.

1653 *See* Richard Simon, *Are Placebo-Controlled Clinical Trials Ethical or Needed When Alternative Treatment Exists?*, 133 ANN. INTERN. MED. 474-475 (Sept. 19, 2000), at http://www.annals.org/cgi/reprint/133/6/474.pdf.

1654 *See* Temple & Ellenberg (Part 1), *supra* note 1493.

1655 Temple and Ellenberg give the example of hair-growing products: why should a placebo-controlled test of such products be unethical? *See id.*

1656 *See* chapter 2.5.4 (p.26) of ICH E10. "It is well documented that externally controlled trials tend to overestimate efficacy of test therapies." *Id.* at chapter 2.5.7 (p.27). *See however* John Concato et al., *supra* note 1438, at 1887-1892 (suggesting ways to improve the reliability of observational studies).
Such situations are however infrequent. They occur principally when a new disease appears and there are no existing treatments.

The scientific community rejects these excessively strict interpretations of the Helsinki Declaration, a permissible stance since the Declaration is not legally binding.[1657] However, drug agencies and ethical commissions can theoretically stop clinical trials when the sponsor does not confirm compliance with the Helsinki Declaration, including its paragraph 29. Similarly, editors are not supposed to publish reports of clinical trials which did not follow the rules of the Declaration. Thus, through these mechanisms, the Declaration carries considerable moral clout.[1658]

Despite this moral authority, U.S. authorities are not easily persuaded.[1659] Prompted by the industry, the FDA proposed a new guideline on placebo and active controls to the ICH.[1660] For Public Citizen:

> The Draft Guidance on Choice of Control Group in Clinical Trials, prepared as part of the International Conference on Harmonisation (ICH), is a clear attempt by FDA to spread its pro-placebo-controlled trial ideology globally. This proselytizing intent was made clear at an FDA meeting on the use of placebos in clinical trials in which we participated in April of this year. … The zeal to expand the use of placebos in clinical trials has resulted in a document that is so unbalanced that its credibility is undermined. … The Draft Guidance is a transparent attempt to legitimize evasions of the clear requirements of the Declaration of Helsinki … .
>
> In addition to its attempt to water down the existing ethical codes, the document places undue emphasis on the supposed needs of regulators and pharmaceutical companies (who together make up the ICH) and places these above the needs of patients or physicians. Most patients and physicians have little need for information addressing whether a new drug for a disease for which there already is an effective therapy is better than nothing; they would like to know whether the new drug is better than the existing drug.[1661]

Similarly, the E.U. has also criticized paragraph 29 of the Helsinki Declaration.[1662] The EMEA insisted that for many products, it is indispensable to use placebo controls to demonstrate their efficacy. Rather than forsaking placebos, the EMEA recommends applying general ethical safeguards such as informed consent.

An accepted alternative to active-controlled trials is to have both the treatment and the control group take additional medicines to manage their medical conditions.[1663] The

---

1657 Under U.S. law, "there is no private right of action for an alleged violation of international law for the protection of human research subjects under the Declaration of Helsinki and the Nuremberg Code." Robertson v. McGee, 2002 U.S. Dist. LEXIS 4072 (N.D. Okl. 2002) (citing notably to White v. Paulsen, 997 F. supp. 1380, 1388 (E.D. Wash. 1998).

1658 *See* W. T. Carpenter et al., *supra* note 1517, at 365-362.

1659 *See generally* BRODY, *supra* note 447, at 105.

1660 *See* ICH E10.

1661 Public Citizen's letter to FDA (Dec. 23, 1999), at http://www.citizen.org/hrg/PUBLICATIONS/1503.htm.

1662 The European EMEA is not partial to active control either: "[p]rovided that the conditions that ensure the ethical nature of placebo-controlled trials are clearly understood and implemented, it is the position of the CPMP and the EMEA that continued availability of placebo-controlled trials is necessary to satisfy public health needs." EMEA/CPMP, Position Statement on the Use of Placebo, *supra* note 1514.

1663 The ICH calls this study design an "add-on" study. *See* chapters 1.3.1 (p.4), 2.1.3 (p.14) and 2.1.5.2.1 (p.15) of ICH E10 Guideline. *See also* Temple & Ellenberg (Part 1), *supra* note 1493. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 11 (commentary).

ICH notes that clinical trials for "anticancer, antiepileptic, and heart failure drugs" commonly follow this methodology (an "add-on" design).[1664] The difficulty is that the trial will only demonstrate efficacy of the tested compound *along with* these other drugs taken during the trial.[1665] Another strategy is to shorten the duration of the placebo period, and then give all subjects the active substance during the follow-up period.[1666]

In my opinion, the risks and benefits for both current subjects and future patients must be balanced. If an active controlled trial would not yield reliable data, future patients risk incurring harm (and correspondingly being deprived of the benefits of strong therapeutic evidence).[1667] This risk should be balanced with the risks borne by subjects who would receive a placebo. Hoping to reduce risks incurred by subjects to nil amounts to wishful thinking. Clinical trials are always the product of a compromise between the interests of society and the interests of enrolled subjects. Finding the proper balance is obviously not simple especially when the study participants in the placebo group will experience pain, but neither serious nor permanent harm. It is a delicate balance that must be stricken between ethical principles and the necessity of sound science. In some cases, clinical research will be impossible, while in others sacrifices will be asked of subjects.[1668]

6.3.5.2.5. Consequences in developing countries

The new language in the Helsinki Declaration makes it unethical to conduct placebo-controlled trials in developing countries if such trials would be unethical in developed countries. The issue of treatment accessibility in developing countries is no longer pertinent and the standard should refer to the treatments available in industrialized countries.[1669] For instance, if a treatment would have been prescribed to the control group in Switzerland, it should also be used in a trial conducted in Ghana.

The initial version of paragraph 29 of the Helsinki Declaration was criticized on this issue. It could have the excessive effect of banning clinical trial designs that would have answered important scientific questions relevant for the host country. With the "clarified" version of paragraph 29, the agitation has lessened.

In addition to the hypotheses mentioned in the note of clarification, exceptions to the rule against placebos are tolerable when the purpose of the study is to test a less costly or simpler treatment (e.g., less pills to take) made necessary by the constraints on

---

1664 *See* chapter 2.1.5.2.1 (p.15) of ICH E10 Guideline.

1665 *See* chapter 2.1.5.2.1 (p.16) of ICH E10 Guideline.

1666 K. Squires et al., *supra* note 577, at 314 ("After week 24, all patients received open-label tenofovir DF for the remainder of the 48-week study.").

1667 For instance, for hypertension, a medical condition with potentially serious consequences (e.g., risk of stroke), the ICH has come to the conclusion that the use of placebos is necessary to ensure that the trials yield useful and reliable results. "Because blood pressure readings … are subject to systematic error (bias), because spontaneous changes in blood pressure can be large, and because the effect of active drugs is often small (diastolic blood pressure change of 4-5 mm Hg more than placebo), studies conducted in a blinded fashion and with placebo controls are essential (See ICH E10)." Chapter 3.1 of ICH E12A; also chapter 2.1.3 (p.14) of ICH E10 Guideline.

1668 It must also be accepted that in some cases, ethical principles may effectively block or hinder the development of potentially helpful drugs. *See* chapter 2.1.7.1 (p.18-19) of ICH E10.

1669 *See* EGE, *supra* note 110, at 18 (point 2.10); Shapiro & Meslin, *supra* note 245, at 140.

available financial or health resources.[1670] However, the disease under study should not be life-threatening or debilitating.[1671] When, for example, it is known that patients are unable to visit their doctor periodically to receive treatment, a study can evaluate whether a monthly treatment given by a nurse is as effective as a weekly treatment administered by the doctor. Nonetheless, pharmaceutical companies should be very circumspect in their use of this exception, since their predominantly commercial motives can easily cast a damaging shadow on all their research in developing countries.[1672]

6.3.6. The study's endpoints

A protocol must necessarily state the hypothesis that the trial is to confirm or refute (see subsection 6.2.1. above). This hypothesis is generally stated as a percentage of response (effect) to a given variable. An example would be whether drug X reduces the number of death by 30% in patients suffering from severe heart failure.[1673] In this case, death (i.e., mortality), the "output" being measured, is called the studied endpoint, variable or outcome.[1674] An endpoint may have to do with safety, for example, during early trial phases, or with efficacy during a phase III trial. The chosen endpoint must be duly described in the protocol, along with a justification for its selection.[1675]

Indeed, the selected endpoint must be scientifically valid.[1676] In particular, it should truly have the expected and direct influence on the disease.[1677] In other words, relevant and valid endpoints are strongly correlated with the disease.[1678] Preferably, the end-

---

1670 *See* EGE, *supra* note 110, at 18 (point 2.10).

1671 *See, e.g.,* Shapiro & Meslin, *supra* note 245, at 139.

1672 Despite the revision of the Helsinki Declaration, a 2004 study found that only a minority of clinical trials conducted in sub-Saharan Africa truly provided the best current standard of care. The authors found that adherence to the Helsinki Declaration depended on the disease being studied. "In general, patients with HIV disease enrolled in trials received care that did not conform to clinical guidelines;: neither control nor intervention groups received 'best current' antiretroviral therapy, even when they had symptomatic or advanced disease." *See* David M. Kent et al., *Clinical Trials in Sub-Saharan Africa and Established Standards of Care, A Systematic Review of HIV, Tuberculosis, and Malaria Trials*, 292 JAMA 237-42 (July 14, 2004), at http://jama.ama-assn.org/cgi/reprint/292/2/237.pdf.

1673 The *experimental* hypothesis must be distinguished from the *statistical* null hypothesis. The first generally presupposes that the tested treatment has a favorable effect. In contrast, the null hypothesis states that the effect is equal to zero. In a trial comparing two products (e.g., the investigational drug versus a placebo or an active comparator), the null hypothesis is that they have the same effect.

1674 The two notions are synonymous. "Study endpoints are the response variables that are chosen to assess drug effects that are related to pharmacokinetic parameters, pharmacodynamic measures, efficacy and safety. A primary endpoint(s) should reflect clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess other drug effects that may or may not be related to the primary endpoint. Endpoints and the plan for their analysis should be prospectively specified in the protocol." ICH E8, at section 3.2.2.4.

1675 *See* ICH E9, at section 2.2.2, p.5.

1676 Bias can also be due to the endpoints selected (e.g., comparing a striking reduction of pain versus prolonged reduction of pain. *See* chapter 1.4.3.3 (p.7) of ICH E10 Guideline. *See also* ICH E9, at section 2.2.2, p.5.

1677 For example, the question asked to the subjects should not be: "do you feel better?"

1678 For example, the EMEA's CPMP recommended not to grant a marketing authorization to Serono's Serostim, because "[d]oubts remain about the clinical relevance of the primary endpoints studied. The clinical relevance of the positive effect of Serostim on work output and lean body mass (LMB) in terms of an improvement in daily activities is questionable. Although the questionnaire on the Quality of Life (QoL) showed improvements across all the domains, it is still unclear what kind of a benefit might be expected from treat-

point should be objective, in that it can be "measured" by a third party using impartial measurement instruments.[1679]

For life-threatening diseases, the favored endpoint is mortality (i.e., how many patients taking the drug survive during a given period);[1680] this endpoint is, by definition, scientifically valid.[1681] For less serious disease such as insomnia, the endpoint cannot – of course – be death (but rather, for example, the duration of uninterrupted sleep).

6.3.6.1. Primary and secondary endpoints

Many trials have more than one studied outcome; the main endpoint is called the "primary endpoint," while the others are "secondary endpoints."[1682] For example, in an asthma trial, a first endpoint could be the number of crisis during a set period; the secondary endpoint would be the severity of the crises. A protocol may also define *composite* endpoints, that is an ensemble of related outcomes.[1683]

Some clinical trials have a *short-term* endpoint followed by a *long-term* endpoint. The short term endpoint is normally studied under strict conditions (e.g., double-blinding, controls), whereas the long-term endpoint is monitored during the follow-up part of the trial and under somewhat relaxed protocol conditions. Often, the blind is lifted for this follow-up period and all subjects are given the treatment found most effective.

The more hypotheses set forth by the protocol, the more difficult the conduct of the trial. For instance, the investigator may need a larger medical team; the trial may require more patients or have them go through more medical interventions. Adding hypotheses also lengthens the trial, making it more expensive. Hence, drafting a protocol implies balancing divergent interests. Instead of having one very long, costly and complex protocol, the sponsor may opt for conducting several shorter and simpler clinical trials.

---

ment with Serostim in a clinical setting." CPMP, Summary of Opinion for Serostim, (Sept. 3, 2003) (CPMP/4475/03), at http://www.emea.eu.int/pdfs/human/opinion/447503en.pdf [hereinafter CPMP (Serostim)].

1679 *See* ICH E9, at section 2.2.4, p.6.

1680 The protocol should specify how mortality should be measured (e.g., how many patients taking the drug survive during a given period). *See* ICH E9, at section 2.2.2, p.5.

1681 Of course, deaths not due to the disease or the treatment (e.g., a car accident) must be excluded from the analysis.

1682 *See* ICH E9, at section 2.2.2, p.5-6; EMEA (Biostatistical Methodology), *supra* note 1382, at 146.

1683 A composite outcome is a combination of two or more outcomes. *See* Nick Freemantle et al., *Composite Outcomes in Randomized Trials*, 289 JAMA 2554 (May 21, 2003), at http://jama.ama-assn.org/cgi/reprint/289/19/2554.pdf. *See also* ICH E9, at section 2.2.3, p.6; EMEA, CPMP, Points to Consider on Multiplicity Issues in Clinical Trials, at 8-10, CPMP/EWP/908/99 (Sept. 19, 2002), at http://www.emea.eu.int/pdfs/human/ewp/090899en.pdf [hereinafter CPMP (Multiplicity)].

6.3.6.2. Tracking endpoints

The protocol must determine the best way to track the selected endpoint. While this is relatively easy for death, this gets more complicated for certain conditions, such as psychological disorders. If the protocol only plans for the investigator to ask depressed patients "how did you feel last week?," the answers may not objectively match the various psychological states the patient went through over the past period. Bias from both sides must be minimized: first patients may forget or have an unconscious desire to please the scientist's team; second scientists may want to hear only the "good side." Therefore, tools are devised to secure accurate reports.[1684] In the case of depression, patients are often asked to fill a diary with a summary of their daily moods. However, this does not solve all problems as the way the collected data are combined, categorized and scaled can influence the apparent magnitude of the treatment's effect.[1685]

Outcomes (other than mortality) should preferably be expressed on a quantitative scale, since qualitative assessment (e.g., less pain) are less reliable. There are a variety of scales to evaluate diseases, some of them being used primarily for clinical trial purposes.[1686] When endpoints are subjective, protocols often call for a special committee to evaluate them.[1687] The committee is kept blind so as to make an objective assessment of the evidence presented.

6.3.6.3. Surrogate endpoints

As mentioned above, the mortality/survival rate is the most reliable endpoint for serious diseases.[1688] But its use makes it more difficult to conduct the trial, if only because it takes time for subjects to die.[1689] To avoid this difficulty, sponsors – with the support of drug agencies, most notably the FDA – have turned to "simpler" outcomes.[1690] For example, in cancer trials, an alternative endpoint can be the size of the tumor, because large tumors are more deadly.[1691] For AIDS trials, the number of CD4 cells has become a

---

1684 *See* Saul Shiffman & Michael R. Hufford, *Ecological Momentary Assessment*, APPLIED CLINICAL TRIALS, (Mar. 2001), at http://www.phtcorp.com/pdf/EPDI.pdf ("Patients who become subjects in drug trials are being asked to observe their own symptoms, relief, quality of life – and report their observations to investigators. Devising a way to capture their experience reliably and validly requires a deep understanding of the way people observe and report information about themselves and their behavior. … Clinical research is meant to be relevant to real-world subject experience. Ecological validity refers to data that accurately reflects that experience.").

1685 See the interesting observations made by Jon N. Jureidini et al. in their analysis of antidepressant clinical trials in pediatric populations, *supra* note 1575, at 881.

1686 *See, e.g.*, Hamilton Depression Scale, at http://healthnet.umassmed.edu/mhealth/HAMD.pdf.

1687 These committees are sometimes called Endpoint Assessment/Adjudication Committees. *See* FDA (DMC), *supra* note 920, at 5.

1688 *See e.g.,* ASCO/FDA, *supra* note 572, at 4 ("Survival is obviously the "gold standard" endpoint for clinical benefit."). However, a study of a benign medical conditions (e.g., hair loss) would – of course – not have mortality as the primary endpoint.

1689 Another difficulty is that a greater number of subjects need to be enrolled to achieve statistical significance. *See, e.g.,* BRODY, *supra* note 447, at 23 and at 36. See also subsection 6.3.10. below.

1690 In the European Union, see EMEA (Biostatistical Methodology), *supra* note 1382, at 146.

1691 *See* John R. Johnson et al., *End Points and United States Food and Drug Administration of Oncology Drugs*, 21 JOURNAL OF CLINICAL ONCOLOGY 1404, at 1404-1405 (Apr. 1, 2003), http://www.jco.org/cgi/reprint/21/7/1404. *See however* FDA, Questions and Answers on Iressa, (June 17, 2005), at http://www.fda.gov/cder/drug/infopage/iressa/iressaQ&A2005.htm.

classic study point.[1692] The majority of important new drugs approved through accelerated procedures had their efficacy demonstrated using such endpoints.[1693]

These endpoints are called *surrogate* endpoints.[1694] Clinical trials focusing on surrogate endpoints are faster, easier, and hence cheaper, to complete.[1695] They result in earlier marketing approval and market entry.[1696] This, in turn, benefits patients who get earlier access to the drugs.[1697] Pharmaceutical companies also are set to gain, since earlier approval translates in an earlier return on investment.

"A surrogate endpoint is an endpoint that is intended to relate to clinically important outcome but does not in itself measure a clinical benefit."[1698] A surrogate endpoint should be chosen based on its ability to "predict" whether the subject is going to die or survive (of course, in relation to a serious diseases).[1699] One then says that the surrogate endpoint correlates with survival. Surrogate endpoints can consist in a risk factor (e.g., high blood pressure for cardiovascular disease) or in a given measurement.[1700] They should be well defined (i.e., standardized); the investigator must know exactly what to measure and how.

Using surrogate endpoints is not without problems, as the chosen endpoint may not be a good indicator of the most important prognosis (e.g., a link between self-

---

1692 *See* ARNO & FEIDEN, *supra* note 125, at 15 (a normal CD4 count is between 800 and 2,200, while an unsafe count is below 500). *See also* M. D. Greenberg, *supra* note 129, at 323; FDA (Critical Path), *supra* note 708, at 21.

1693 *See* J. R. Johnson et al., *supra* note 1691, at 1404. *See also* FDA, New Drug, Antibiotic and Biologic Drug Product Regulations: Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992), at http://www.fda.gov/cder/fedreg/fr19921211.txt.

1694 *See id*. The opposite of the surrogate endpoint is sometimes called the "hard" clinical endpoint. *See* Rosenkranz, *supra* note 1364, at 31.

1695 "Clinical trials evaluating surrogate end points require smaller sample sizes, and they can sometimes be completed in weeks or months rather than years." Bruce M. Psaty et al., *Surrogate End Points, Health Outcomes, and the Drug-Approval Process for the Treatment of Risk Factors for Cardiovascular Disease*, 282 BMJ 786 (Aug. 25, 1999). *See also* ARNO & FEIDEN, *supra* note 125, at 221; Rosenkranz, *supra* note 1364, at 31.

1696 "Frequently, clinical trials include several outcome measures, raising the problem that the likelihood of finding a statistically significant result by chance alone increases with the number of tests undertaken." Nick Freemantle, *Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic?* 322 BMJ 989 (Apr. 21 2001), at http://bmj.com/cgi/reprint/322/7292/989.

1697 The broader acceptance by drug agencies of the use of surrogate endpoints in clinical trials is another side effects of the AIDS crisis and the social activism of AIDS patient groups. *See, e.g.*, Grow, *supra* note 249, at 2. *See also* FDA (Cancer Guidance), *supra* note 1418.

1698 ICH E8, at section 3.2.2.4. *See further* Robert Temple, *Are Surrogate Markers Adequate to Assess Cardiovascular Disease Drugs?*, 282 JAMA 790- (Aug. 25, 1999), at http://jama.ama-assn.org/cgi/content/full/282/8/786.

1699 For Trisha Greenhalgh, "[t]he surrogate end point should be reliable, reproducible, clinically available, easily quantifiable, affordable, and show a "dose-response" effect (the higher the level of the surrogate end point, the greater the probability of disease). It should be a true predictor of disease (or risk of disease). … The relation between the surrogate end point and the disease should have a biologically plausible explanation." *How to read a paper: Papers that report drug trials*, 315 BMJ 480-483 (1997), www.bmj.com/cgi/content/full/315/7106/480. *See also* ICH E9, at section 2.2.6, p.7; ICH E3, at chapter 9.5.2 (p.10). *See also* Rosenkranz, *supra* note 1364, at 31 (stressing the "clinical relevance," "sensitivity, specificity," "reliability," "biological plausibility," "practicality and simplicity" of good surrogate endpoints).

1700 Because a surrogate endpoint generally consists in a given measurement, it is also sometimes referred to as a biomarker. However, not all biomarkers are surrogate endpoints. *See also* Rosenkranz, *supra* note 1364, at 31.

reported quality of life ("QOL") and survival in cancer patients[1701]). There have been cases where a clinical trial proved the "effectiveness" of a drug on a given surrogate endpoint, while subsequent trials nevertheless showed an increase – not a decrease – in mortality![1702] This illustrates the importance of a thorough scientific justification for the choice of surrogate endpoints.[1703] Similarly, surrogate endpoints should not distract the investigators from other important observations. For example, a drug may lower blood pressure, but simultaneously augment the risk of death due to diabetes complications.[1704]

6.3.6.4. Post hoc analysis

In order to avoid bias, all endpoints should be stated in advance in the protocol. When a sponsor realizes too late that its initial hypothesis was not aptly stated or that the compoud is effective on another endpoint, it may try to "re-arrange" its data to prove another hypothesis.[1705] However, the reliability of subsequent unplanned analyses leaves much to be desired.[1706] The practice of highlighting relationships discovered *post facto* is referred to as data milking or retrospective analysis.[1707]

The same problems arise with unplanned *subgroup* analysis (also called post-hoc stratification).[1708] In such a situation, efficacy is observed for a subgroup of subjects after the results have been gathered (e.g., greater efficacy for white male subjects, subjects younger than 60, or subjects suffering from a severe form of the disease).[1709] Post-hoc stratification is considered artificial and scientifically flawed (e.g., too small sample

---

1701 *See* ASCO/FDA, *supra* note 572, at 23.

1702 Clinical trials have sometimes studied *wrong* endpoints, for example "ventricular premature beats as a predictor of death from serious cardiac arrhythmias, blood concentrations of antibiotics as a predictor of clinical cure of infection, and plaques seen on magnetic resonance imaging in monitoring the progression of multiple sclerosis." *Id.* The anti-arrhythmia drugs encainide and flecainide are mentioned as another case where approval on the basis of a surrogate marker proved to be flawed. *See* Tabarrok, *supra* note 433, at 37; ICH E9, at section 2.2.6, p.7; Remarks by Jane E. Henney, Commissioner of FDA, International Conference on Surrogate Endpoints and Biomarkers, National Institutes Of Health, (Apr. 15, 1999), at http://www.fda.gov/oc/speeches/surrogates8.html. *See* BÉRAUD, *supra* note 1452, at 31 and 35; Rosenkranz, *supra* note 1364, at 33-34.

1703 The FDA pays heightened attention to the choice of surrogate endpoints. Other countries may take more flexible approaches and allow a whole array of different endpoints to be taken into consideration. *See* ASCO/FDA, *supra* note 572, at 11.

1704 See the examples provided by Bruce M. Psaty et al., *supra* note 1695.

1705 An author describes such action as "raking data for 'interesting results' (retrospective subgroup analysis)." Trisha Greenhalgh, *How to read a paper: Statistics for the non-statistician, I: Different types of data need different statistical tests*, 315 BMJ 364-366 (1997), at http://www.bmj.com/cgi/content/full/315/7104/364.

1706 "[S]paring use should be made of unplanned analyses." Section 7.1 (p.31) of ICH E9.

1707 *See* THE SHAPIROS, *supra* note 4, at 120. *See also* Jon N. Jureidini et al., *supra* note 1575, at 882 (criticizing the way pediatric trials of antidepressant medicines were reported).

1708 *See* Kulynych, *supra* note 541, at 141-42.

1709 *See* Salim Yusuf et al., *supra* note 1292; Mike Mitka, *Critics Bash HIV Vaccine Trial Analysis*, 290 JAMA 1491 (Mar. 26, 2003), at http://jama.ama-assn.org/cgi/reprint/289/12/1491.pdf (criticizing VaxGen's subset analysis of its HIV Vaccine Trial); Mike Mitka, *Efforts Needed to Foster Participation of Blacks in Stroke Studies*, 291 JAMA 1311 (Mar. 17, 2004), at http://jama.ama-assn.org/cgi/content/full/291/11/1311?etoc (on subset ethnic analysis of clinical trial data). *See also Warner-Lambert*, 787 F.2d at 155.

size).[1710] Even when subgroup analysis is performed in accordance with planned steps of the protocol, the results must be considered with caution.[1711]

Because the protocol must describe all the tests that will be conducted, it is normally not permissible to introduce additional tests or measurements. Similarly, since the protocol says how data and subjects will be pooled, it is not possible to subsequently modify the classification.

Hence, these practices described above are rightly frown upon. The fact that the initial protocol was not meant to test that hypothesis (but a distinct one) may lead to the drug agency's refusal to take that set of data into account.[1712]

6.3.7. Control of eligibility criteria

The unusual settings in which clinical trials take place rarely match those of the "real world."[1713] In the real world, patients are often sicker than those selected to participate in the study.[1714] They tend to suffer from other diseases ("comorbidities"), for which they may be taking other drugs simultaneously, including in self-medication.[1715] Other patients may not even be aware of their concomitant medical conditions which therefore remain untreated. "Real world" patient population may comport greater ethnic diversity than the subject population tested during the clinical trial.[1716] Rates of treatment compliance are normally lower in ordinary settings;[1717] patients do not always follow the drug's notice of use, thus taking too much or too little of the drug.

In contrast, subjects in clinical trials receive very close medical attention – and sometimes also better general health care.[1718] The simple fact that subjects are surrounded by a study team dedicated to their health and well-being may help "spontaneously" improve their medical status. Clinical studies also take place in a clean environment; the patient is encouraged to eat a balanced diet and to avoid dangerous activities

---

[1710] See for example the explanations accompanying point 12(b) of the CONSORT Statement, at http://www.consort-statement.org/examples12b.htm.

[1711] *See, e.g.,* CPMP (Multiplicity), *supra* note 1683, at 7.

[1712] For example, "'Data dredging' should be avoided during analysis. For example, researchers may put participants into new groups in an attempt to answer additional questions, but randomization is lost in the process. Adding more unplanned analyses increases the risk of finding statistically significant differences purely by chance." Slinger, *supra* note 1434, at 182-186.

[1713] *See* BÉRAUD, *supra* note 1452, at 30 and 33-34.

[1714] *See* Astrid Fletcher et al., *Implications for trials in progress of publication of positive results*, 342 LANCET 653 (Sept. 11, 1993). Conversely, for some trials (e.g., depression), the selected subject tends to be sicker than the average patient.

[1715] *See, e.g.,* James M. Wright, *Why don't we initiate more large simple randomized controlled trials?* 169(11) CANADIAN MEDICAL ASS. J. (CMAJ) 1170 (Nov. 25, 2003), at http://www.cmaj.ca/cgi/reprint/169/11/1170.pdf.

[1716] *See* Antonio L. Dans, *How to decide on the applicability of clinical trial results to your patient*, 279 JAMA 545 (Feb. 18, 1998).

[1717] On patient compliance, see for instance Iona Heath, *A wolf in sheep's clothing: a critical look at the ethics of drug taking*, 327 BMJ 856-858 (Oct. 11, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7419/856.

[1718] *See, e.g.*, Interview with Henri Bounameaux, President of the Central Ethics Committee of the Geneva University Hospitals (HUG-REC), in Geneva, Switzerland (Aug. 22, 2003). *See also* SPRUMONT, *supra* note 16, at 81.

(e.g., smoking, drinking). All these factors tend to enhance the efficacy of the studied treatment.[1719]

While some of the above-mentioned sources of bias are unavoidable, others can be deliberately introduced in the trial by the sponsor or the investigator. For example, the sponsor can hope that its drug will fare better if all subjects are young and relatively healthy, bearing also in mind that it never looks good when a subject dies during the trial. Similarly, the sponsor normally prefers to recruit a *homogenous* subject population since this facilitates the interpretation of the study results.[1720] Furthermore, sponsors know that drugs typically produce better outcomes when no other pharmaceuticals has been taken in the past or is being taken concurrently.[1721] For instance, sponsors for AIDS clinical trials prefer enrolling treatment-naïve patients,[1722] that is patients who have not yet taken any treatment;[1723] they know that drugs perform better on such a population. Of course, once the drug is marketed, very ill AIDS patients may also be taking it, but with no guarantee of similar efficacy.[1724]

This explanation illustrates the importance of selection criteria, in addition to randomization.[1725] Clearly, compromises have to be made: for instance, it may be understandable to exclude from participation very old patients with multiple diseases (except if the studied disease affects them particularly). However, it may *not* be legitimate to exclude anyone taking additional medications, because, though such an exclusion might be based on a rational wish to avoid potentially dangerous drug-drug interactions, it may also be a way to screen out sicker patients. Therefore, guidelines request that – at least phase III – trials enroll subjects who are *representative* of the patient population.[1726]

1719 *See, e.g.,* Victoria Stagg Elliott, *Statins found to work better in studies than in practice*, AMEDNEWS.COM, (Dec. 10, 2001), at http://www.ama-assn.org/amednews/2001/12/10/hlsb1210.htm (placing the blame on lack of patient compliance).

1720 *See generally* Tunis et al., *supra* note 597, at 1626.

1721 Similarly, the ICH criticizes study designs whereby only subjects who had already been taking the comparator drug but failed to respond positively to it would be enrolled. Such a trial design could prove only that the investigational drug is efficacious in patients having failed with the comparator drug, but would not show comparative efficacy for patients having previously taken neither of them. *See* chapter 1.4.3.2 (p.7) of ICH E10 Guideline.

1722 Public Citizen's Comments, *supra* note 906.

1723 The second can easily be found in Third World countries where no therapy is sadly the standard treatment. Even in developed countries, naïve patients can be found among poorer and uninsured populations. For non-serious diseases, this is probably as well since recruitment will be easier due to direct or indirect financial incentives.

1724 *See* Emily Bass, *FDA Gives Salvage Therapy Testing a Push Forward*, AIDS Treatment News, (Mar. 2001), at http://www.findarticles.com/cf_dls/m0HSW/2001_March_23/73181591/p1/article.jhtml.

1725 The initial selection criteria stated in the protocol should normally not be modified in the course of the trial. *See* ICH E9, at section 4.2 (p.19).

1726 It is only if the subject pool is a representative sample of the population (i.e., all patients which will be using the drug) that conclusions drawn from the sample (i.e., the subjects participating in the trial) can be generalized to the population (the patients). *See* ICH E9, at section 2.2.1, p.4-5. *See also* P. Allmark, *Should research samples reflect the diversity of the population*, 30 J. MED. ETHICS 185-89 (2003), at http://jme.bmjjournals.com/cgi/reprint/30/2/185.pdf.

6.3.8. Dropouts*

In all clinical trials, a number of subjects decide at one point or another to leave the study. This can be a source of bias, if the subjects who withdraw are those who experienced the worse outcome (compared to subjects who stayed in the trial). For example, the dropouts may be patients who suffered greater side effects or who felt the drug to be ineffective.[1727]

If their withdrawal (also called subject attrition) is not duly acknowledged, this could create the false impression that the drug is 100% safe and effective. To preclude bias, every subject must be accounted for;[1728] this is sometimes referred as an *intention-to-treat* principle.[1729] The study report must explain the reasons behind each drop-out. Subjects are not obliged to say why they withdrew from a clinical study. However, this is an important information that investigator should at least attempt to obtain. Moreover, the researcher should try to obtain follow-up medical information about the subjects who dropped out, to make sure that their condition did not deterioriate.[1730] Drug agencies must be told who started the trial (in this case, received a first dose of the trial), who was there at the end, and what happened to the drop-outs.[1731] The numbers of drop-outs for the active and the control group are compared to determine whether the treatment received had any influence on full protocol adherence.[1732] The agency must then determine whether the number of drop-outs affects the reliability of the trial; high percentage of withdrawal or withdrawal clustered among a given group of subjects (e.g., all are women over the age of 65) are typically issues of concern at the drug approval stage.

1727 *See, e.g.,* Sarah Boseley, *The Riddle of the Drug Regulators*, THE GUARDIAN, Mar. 13, 2004, at http://society.guardian.co.uk/mentalhealth/story/0,8150,1168505,00.html (regarding failure of the authorites to take into proper consideration the higher number of dropouts in subject groups taking high doses of Seroxat).

1728 *See* section 7.1 (p.31) of ICH E9. *See also* Slinger, *supra* note 1434.

1729 This principle "implies that all randomised patients should be included in the analysis." Even patients who took only one dose of the medication should be included. Applying the intention-to-treat principle ensures that the results thus obtained are closer to those which will be observed in ordinary clinical practice. See *generally* EMEA (Biostatistical Methodology), *supra* note 1382, at 148; ICH E9, at section 5.2.1, p.22-23.

1730 *See* Jon N. Jureidini et al., *supra* note 1575, at 881 (criticizing the way high drop-out rates were reported in clinical trials of antidepressants in pediatric populations).

1731 In publications of randomized clinical trials, the explanation may be along these lines: "Forty-six sertraline-treated patients (24%) and 31 placebo patients (17%) discontinued the study early. Among patients treated with sertraline, the most common reasons for discontinuation were adverse events (n = 17; 9%), withdrawal of consent (n = 9; 5%), and loss to follow-up (n = 8; 4%). Similar proportions of placebo patients discontinued from the study because they withdrew consent (n = 11; 6%) or were lost to follow-up (n = 5; 3%); fewer placebo patients (n = 5, 1 of whom had not received study drug; 3%) discontinued because of adverse events. This difference was more apparent in children, among whom 13 sertraline-treated patients but no placebo patients discontinued because of adverse events." K. D. Wagner et al., *supra* note 973, at 1036. *See also* K. Squires et al., *supra* note 577, at 316. Ideally, the type of adverse events should also be described.

1732 *See e.g.*, Salim Yusuf et al., *supra* note 1292, at 498. For example, the treatment may be so complicated to follow that many subjects fail to follow properly the instructions they have been given. *See generally* ECRI (Guide), *supra* note 869, at 36.

6.3.9. Duration of the trial

Bias can reside in the trial's duration. For diseases that require treatment over a long period (e.g., depression, hypertension, diabetes), the question arises as to how long the investigational compound should be studied. Ideally, commercial sponsors want to stop the trial just when their product has reached its efficacy peak (as compared to the comparator product).[1733] Letting the trial proceed for a longer period implies the risk that the comparator product will "catch up" with the sponsor's drug. Moreover, adverse reactions may multiply over a long period.

On the contrary, drug agencies, physicians and patients value having as much information as possible in order to decide whether to allow and use the new treatment. Trials that are stopped "too soon" do not yield all desirable information. Several stories have been reported where sponsors or study authors were criticized for presenting clinical results deriving from an inappropriately short clinical trial or short review period.

6.3.10. Statistics

The precedent subsections on bias and the means to avoid it have already underscored the crucial role of statistics in medical research.[1734] This subsection goes over additional statistical concepts not previously reviewed. It begins by reviewing the various benefits of statistical analysis.

Statistics are helpful to unearth mistakes in the trial's execution. For example, if a number was incorrectly recorded (e.g., adding by mistake a zero), the statistical analysis would rapidly detect the outlier (i.e., a number manifestly outside the normal range).[1735] Statistics can also uncover deliberate maneuvers to improve the trial's outcome. For example, if the quantity of experimental drug administered is suddenly increased during the trial, statisticians may notice an abnormal change in the data recorded. They can also detect misleading presentation of the facts or intentional deviations from protocol. In some situations, these methods can also correct both types of mistakes.

It is not enough for a study to make use of good statistical tools. Equally important is how this use is explained in the study report or the publication available to the public. Often, reports and articles do not contain sufficient indications to infer whether or how statistics were used to assess the reliability of the study.[1736] The problem may not only have to do with calculations, but also with upstream factors. For example, the article may not state the study's inclusion and exclusion criteria for enrollment, thus raising the possibility that only comparatively healthy patients were enrolled. Lack of adequate explanations can throw doubts on a study's reliability:

1733 *See* Burls & Sandercock, *supra* note 789, at 1446.

1734 On the emergence of biomedical statistics in the 1950s, see the fascinating book by MARKS, *supra* note 536, particularly its part II.

1735 On the notion of "outlier," see section 5.3 (p.25) of ICH E9.

1736 *See* Douglas G. Altman et al., *How Statistical Expertise is Used in Medical Research*, 287 JAMA 2817-20 (June 5, 2001), at http://jama.ama-assn.org/cgi/reprint/287/21/2817.pdf.

The general rate of erroneously used statistical methods and/or insufficient explanation of their explication is currently estimated to affect between 60% and 80% of reviewed articles (20% to 40% of the articles contain even serious errors).[1737]

6.3.10.1. Sample size

The first "rule" of statistics is that truth is in the numbers. The greater the number of subjects enrolled (i.e., sample size), the more reliable the findings (i.e., smaller error margin).[1738] Moreover, randomization is efficient only if a large subject pool is randomized; if the pool is too small, negative or positive factors may not be distributed evenly.

Protocols should state in advance the number of subjects necessary to get the desired level of significance.[1739] To calculate the necessary sample size in simple situations, one "medical" factor needs to be known, a second "medical" factor must be decided, and two "statistical" measures need to be set, typically by reference to generally admitted conventions.[1740]

The first medical factor is the prevalence of the *event (or base) rate* in the population being studied. For example, in a placebo-controlled trial of fatal strokes in obese elderly people, one needs the percentage of persons (having these two characteristics) who "normally" suffer fatal strokes (without treatment). This percentage acts as a reference point *against which* any positive effect of the treatment administered in the clinical trial must be measured. The event rate can be determined based on earlier trials or on a medical literature review.

The second medical factor is the *desired size of the treatment effect*. This desired treatment effect is set at a level that is held be to sufficiently significant. Going back to our above-mentioned trial, imagine that the trial aims at testing the efficacy of drug D in reducing the number of fatal strokes in two groups of subjects, one being given drug D, the other group receiving the placebo. Reducing death by only 1% may be deemed insufficient. A reduction of 2% assumes that 3 patients (out of 100) taking drug D will suffer a fatal stroke (3%), as opposed to the 5% of those taking the placebo. As we will see below, the 2% (5% minus 3%) can be expressed in terms of *relative risk reduction* by dividing 2% by the "baseline" percentage of 5%, giving here a 40% reduction.

1737 Norbert Banik, Biostatistical methodology: part 2, Clinical trials in the 21st century- a means of knowledge generation or self-fulfilling prophecy, DRUGDEV123.

1738 Once the number of subjects enrolled satisfies statistical significance tests, it may become unethical to enroll more than this necessary number of subjects. This is chiefly the case when the trial is thought to entail significant risks for the subjects.

1739 The protocol should also state how the sample size was calculated. *See* ICH E9, at section 3.5, p.17.

1740 *See* Adrienne Kirby et al., *Determining the sample size in a clinical trial*, 177 MJA 256 (Sept. 2, 2002), at http://www.mja.com.au/public/issues/177_05_020902/kir10425_fm.pdf; ICH E9, at section 3.4, p.17; EMEA (Biostatistical Methodology), *supra* note 1382, at 142. These four factors should normally be recapped in publications of study results. *See* Moher (Sample), *supra* note 633, at 122-24 (finding that most trials reporting negative results, first, do not properly disclose sample size calculations and, second, were not adequately powered).

It is important to evaluate correctly these two factors.[1741] If the *event rate* is overestimated (here, 5% each year), while the true rate is much smaller (only one such patient out of a hundred suffers a fatal stroke), the sample size calculated will be too small, with the consequence that the trial results will not be reliable. Similarly, if an unrealistically large treatment size is selected at the beginning (here 40%), while the *real* effect (as measured during the study) is much smaller (e.g., 15%), the sample size calculation made at the inception of the study will be off the mark, with the consequence that the trial will not demonstrate this smaller effect (15%) in a *reliable* manner.

The first statistical factor is called the *power*, that is the ability to detect a real difference between the treatment group and the control group. Usually clinical trials are powered at 80%, meaning that they accept a 20% risk of not detecting this difference (a false negative result or Type I error).[1742] Conversely, the trial has at least an 80% chance of detecting a clinically significant effect when one exists.[1743] In our example, this translates into an 80% chance of noticing a reduction in the number of strokes.

The last statistical factor is the *level of significance*. It is usually set at 5%, meaning that there is only a 5% chance of falsely detecting a significant effect (a type I error).[1744] In our example, this implies that if the trial concludes in a reduction in the number of subjects suffering a stroke, there is only a small chance (5%) that this reduction was "caused" by chance, as opposed to caused by the drug.

The sample size is a function of the power, the significance level divided by the squared absolute difference. Accurate calculations of sample size take into account additional factors such as the expected number of subjects who decide to drop out of the study or the number who do not follow the prescribed treatment regime.[1745] When the allocation to the two arms is not equal (50% each), the sample size calculation must be adapted.[1746]

6.3.10.2. Underpowered studies

Because of subject recruitment problems, sponsors sometimes have to accept smaller sample size than initially hoped for. It is then no surprise that many trials are too small to make reliable deductions.[1747] Studies that fail this standard are said to be *underpow-*

1741 *See* Kirby et al., *supra* note 1740, at 256.

1742 *See* EMEA (Biostatistical Methodology), *supra* note 1382, at 142.

1743 *See* Scott D. Halpern et al., *The continuing unethical conduct of underpowered clinical trials*, 288 JAMA 358, 359 (July 17, 2002), from http://jama.ama-assn.org/cgi/content/abstract/288/3/358 ("This exact value [80%] is arbitrary; higher power will always be preferable and should be set with consideration of the importance of limiting both false-negative conclusions (ie, type II errors) and false-positive conclusions (ie, type I errors)."). *See however* S. J. L. Edwards et al., *Why "underpowered" trials are not necessarily unethical*, 350 LANCET 804-807 (Sept. 13, 1997).

1744 *See, e.g.,* EMEA (Biostatistical Methodology), *supra* note 1382, at 142.

1745 *See* Kirby, *supra* note 1740, at 257.

1746 *Id.*

1747 Robert Slinger mentions that "a review found that 67 (945) of 71 statistically 'negative' RCTs had a sample size too small to detect moderate (25%) or large (50%) differences between treatment groups." *Supra* note 1434, 182-186.

ered.[1748] "Underpowered trials can do great scientific harm if their results are misinterpreted as demonstrating that an intervention has no effect."[1749]

Moreover, it is considered unethical to enroll subjects in a trial likely to be of limited scientific validity. Hence, subjects should be explicitly informed if asked to participate in a study known to be underpowered.[1750] An underpowered study may be admissible when the pool of potential subjects is small due to the rarity of the disease.[1751]

Early clinical trials (e.g., phase I and phase II) are frequently underpowered, but they are meant to be "completed" by a phase III trial; in addition, their objectives are usually more limited (e.g., identification of a safe starting dose).[1752]

Typically, underpowered studies can be saved by pooling them with other clinical trials in what is called a meta-analysis.[1753] However, meta-analyses cannot address all limitations of underpowered trials.[1754]

This should be taken as far as to state that the more subjects are enrolled, the better it is. On the contrary, the statistical analysis may also reveal that too many subjects have been enrolled. Past a certain point, adding more subjects results in diminished returns, that is the margin of error decreases, but by an ever tinier percentage. Moreover, a needlessly large subject pool is ethically unacceptable since too many subjects are forced to incur the risks of the trial. Given that the investigator and the REC must take all measures to minimize risks borne by subjects, they must also make sure that the sample (i.e., the number of enrolled subject) is large enough, without being larger than necessary.[1755]

6.3.10.3. The p-value and confidence interval

The most frequently encountered statistical measure in clinical trials is the "p" measure. Whenever a study reaches a conclusion, it will – or should – say what the p-value is. This figure tells you what the odds are that the result is due to chance.[1756] If we say "the drug causes mitigation of the symptoms" with a p-value < 0.02, this translates in a less than 2% chance that mitigation is not due to the drug, but to another cause for example random chance. This is equivalent to a 98% confidence interval. If $P \leq 0.5$, this means that there is 50% chance that the drug is not the cause of the symptoms' mitigation. The

---

[1748] A trial can also be underpowered for a specific patient population. For instance, a trial can be adequately powered for white patients aged 20 to 65, while underpowered to infer any reliable conclusion for Asian patients and for seniors.

[1749] Julie E. Buring, *Women in Clinical Trials – A Portfolio for Success*, 343 NEW. ENG. J. MED. 505-506 (2000), at http://content.nejm.org/cgi/content/full/343/7/505. *See also* COE Explanatory Report, *supra* note 417, at paragraph 37, p.8.

[1750] *See* Halpern et al., *supra* note 1743, at 359 and 360.

[1751] *See id.* at 359 and 360-61.

[1752] *See id.* at 361.

[1753] *Id.* See *also* Simon G. Thompson & Stuart J. Pocock, *Can meta-analysis be trusted*, 338 LANCET 1127 (Nov. 2, 1991); section 7.2.1 (p.32) of ICH E9.

[1754] *See* Halpern et al., *supra* note 1743, at 359-60.

[1755] *See also* WHO (Operational Guidelines), *supra* note 1379, at point 6.2.1.1. (p.10).

[1756] *See however Variability, supra* note 45.

p-value is generally deemed statistically significant if p = 0.05 and highly significant if p = 0.01.[1757]

The p-value is linked to the *confidence interval*, abbreviated CI.[1758] The CI indicates how precise the results are, by stating the range (margin of error) within which the true outcome (that which would obtained if the entire population was tested instead of just a sample) is most likely to lie. For example, in a study that found a reduction in deaths of 6% in the control group, the 95% confidence interval might indicate that the real effect is a reduction of between 2% and 8% (expressed as 95% CI 2% to 8%). In other words, if the study was repeated over and over with different samples, 95% of the sample mean (here the mitigation proportion) would lie within this range (2% and 8%). Trial results with narrow confidence intervals (e.g., 95% CI 5.5% to 6.5%) allow to draw more reliable inferences. If an investigator wants to narrow the CI, she must increase the sample size, that is the number of enrolled subjects.

6.3.10.4. Causation

When an investigational drug is administered to subjects to see whether their condition improves, the underlying assumption is that it is the drug, and not some other factors, that *caused* the improvement. In other words, a clinical trial should prove causality – and not just correlation – between (or from) the test product and (or to) the outcome measured. The clinical trial design should isolate and eliminate confounding factors, that is the other reasons that could have influenced or caused the measured outcome.[1759] Only by doing a controlled experiment can the variables of interest (i.e., administration of treatment x) be isolated. For instance, in a clinical trial of depression, it would be important to exclude the possibility that the diminution of depressive symptoms was the result of the high level of care provided by the medical team. A confounding factor such as this one can be addressed through controls and randomization.

6.3.10.5. Presentation of results

There are several different ways to summarize clinical trial results. The four principal ones are the absolute risk reduction, the relative risk reduction, the percentages of event-free subjects, and the number needed to treat.[1760]

1757 *See e.g.,* R. E. Becker, *supra* note 1444.

1758 The CONSORT Statement recommends that confidence interval be systematically provided in publications of clinical trial findings. See the explanations accompanying point 12(a) of the CONSORT Statement, at http://www.consort-statement.org/examples12a.htm. *See also* section 5.5 (p.26) of ICH E9.

1759 *See* Marcus Müllner et al., *Reporting on Statistical Methods To Adjust for Confounding*, 136 ANNALS OF INTERNAL MEDICINE 122-26 (Jan. 15, 2002), at http://www.annals.org/cgi/reprint/136/2/122.pdf.

1760 The risk of a certain outcome in the control (or no-treatment or placebo) group is CER (for "control event rate"). The risk of a certain outcome (e.g., death) in the treatment (or experimental) group is EER (for "experimental event rate"). The relative risk reduction is equal to (CER- EER)/CER. The absolute risk reduction is CER – EER. The odds ratio is the [odds of dying (here the outcome) versus the odds of surviving for the treatment/ experimental group] divided by [the odds of dying versus the odds of surviving for the no-treatment / control group]. *See, e.g.,* Trisha Greenhalgh, *How to read a paper: Statistics for the non-statistician. II: "Significant" relations and their pitfalls*, 315 BMJ 422-425 (Aug. 16, 1997), at http://bmj.bmjjournals.com/cgi/content/full/315/7105/422.

The *relative risk* ("RR") indicates how much more (un/)likely subjects taking the experimental drug are to suffer from an adverse outcome, compared with patients not taking it. So if we consider a trial of 200 subjects divided in two groups of 100 and suppose that there were 3 deaths in the group taking the investigational drug D (r_{tg}= 3%) and 5 death in the control group (r_{cg} =5%), the RR is 0.6 (.03/.05). In other words, subjects taking drug D are 0.6 times as likely (i.e., less likely) to die than subjects taking the placebo.

The *relative risk reduction* ("RRR") marks a reduction in the percentage of deaths (here the outcome) in the treatment group versus the group receiving the control product. It is calculated by subtracting r_{tg} from r_{cg} and dividing it by r_{tg} (RRR= (r_c – r_{tg})/ r_{cg}; or RRR=(1-RR)). In our example, RRR is 40%. This suggests that the risk of death is dwindled by 40%!

The *absolute risk reduction* ("ARR") takes better account of the fact that deaths were altogether rare in the two groups.[1761] It is equal to r_c – r_t or, in our example, 2%. This means that, for every 100 patients who receive the investigational treatment, 2 deaths would be avoided.

The *number needed to treat* ("NNT"), as its name indicates, states the number of patients who must be treated to avoid, in our example, one death. The NNT is calculated by dividing 1 by the ARR (here 1/.02 = 50 Thus, a doctor would have to treat 50 patients with drug T to prevent one death.

Usually, results using RRR "look better" than results presented using ARR or NNT (here compare 40% and 2%).[1762] Unfortunately, physicians tend to rely excessively on data framed in terms of relative risk reduction.[1763] To get a fairer idea of the contribution of a new drug, especially as compared to existing alternatives, the NNT is probably the most revealing measure. It facilitates the incorporation of economic, comparative and ethical perspectives into ordinary clinical practice.[1764] This number "more usefully expresses the therapeutic effort that is needed to get a therapeutic result."[1765]

1761 *See* Bandolier, Number needed to treat (NNT), at http://www.jr2.ox.ac.uk/bandolier/band59/NNT1.html.

1762 *See* Burls & Sandercock, *supra* note 789, at 1446.

1763 In one study, 148 physicians participating in the study were given the *same* results, only expressed according to different statistical methods, but none realized it. Moreover, physicians paid little attention to the fact that the treatment, while generally beneficial for a given medical condition, had nonetheless increased the number of deaths. *See* Marco Bobbio et al., *Completeness of reporting trial results: effect on physicians' willingness to prescribe*, 343 LANCET 1209 (May 14, 1994). *See also* Bandolier, Framing, at http://www.jr2.ox.ac.uk/bandolier/booth/glossary/framing.html.

1764 *See* Gian Franco Gensini & Andrea A. Conti, *Evidence-based evaluation of benefits in therapeutic interventions: methodologically controlled and non-randomly assigned reflections on the number needed to treat*, 4 ITAL. HEART J. 80-83 (2003) at http://www.italheartj.org/pdf_files/20030026.pdf. *See also* Richard Smith, *The drugs don't work*, 327 BMJ (Dec. 13, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7428/0-h.pdf ("NNTs under 5 are unusual, whereas NNTs over 20 are common.").

1765 Bandolier, *supra* note 1763.

6.3.11. Quality assurance

The importance of "clean data" cannot be stressed enough. Especially when a study has a commercial sponsor, clean data is the latter's chief goal. "Data are a product, with customers, to whom they have both cost and value."[1766] When the data are not reliable, the consequences for the commercial sponsor are harsh: The national drug agency may turn down the sponsor's application for marketing approval. Millions of invested dollars will be literally lost as the sponsor will have to either repeat trials or abandon its application altogether. Hence, at every step of the clinical trial, the sponsor must make sure that accurate observations are accurately entered and maintained. Although errors in the *analysis* of accurate information can have adverse consequences on the fate of the sponsor's marketing application, these consequences are by far not as dramatic as errors pertaining to the *entry* of information.

To ensure that the investigator collects reliable data, the sponsor must have quality assurance plans. These plans describe the various methods used to attain this goal. One key method consists in issuing standard operating procedures (SOPs) for the benefit of the investigator's team.[1767] These SOPs complement the protocol in specifying how each piece of data is to be acquired and controlled.[1768] SOPs are helpful to make sure that all personnel, including new employees, abide by a uniform set of rules.[1769] They are particularly important in multicentric trials, where they are, along with the protocol, often integrated into a Manual of Procedures ("MOPs").[1770]

Depending on the drug and disease studied, the recording of observations will be made easier or harder. When the studied endpoint is survival rate, it is straightforward to determine who is alive and who is dead at the end of the trial – although there may be some difficulty in determining the cause of death. However, when the endpoints used to prove efficacy are more subjective (such as for an antidepressant drug), obtaining accurate data proves to be more challenging. As we saw, one of the means to achieve this objective is to ask subjects to make a daily record of their symptoms. Subjects are given a journal or diary (increasingly in electronic format such as handheld devices/PDAs) in which they must regularly note how they feel.[1771] More broadly, elec-

---

1766 NISS, *supra* note 1426, at 1.

1767 *See, e.g.,* SPRUMONT, *supra* note 16, at 176.

1768 FDA (Computerized), *supra* note 1426, at IV.
In the European Union, see E.U. Guidance (Adverse Reaction), *supra* note 270, at 4.

1769 *See, e.g.*, National Institute of Neurological Disorders and Stroke (NINDS), Quality Assurance Guidelines, (reviewed June 12, 2003) at
http://www.ninds.nih.gov/funding/clinical_trials/quality_assurance_guidelines.htm.

1770 The MOP "details the study organization, the definitions of data elements to be collected, visit procedures, data management, case flow, case report forms (CRFs), safety monitoring, and quality control procedures." *Id. See also* ICH E9, at section 3.2, p.13.

1771 According to Teri Stokes and Jean Paty, diaries are used "in about 25% of all clinical trials." *Developing and Validating Electronic Diaries, Roles for the Technical and Clinical Teams*, APPLIED CLINICAL TRIALS 68 (June 2003), at http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/222003/58534/article.pdf.
Electronic diaries (compared to paper diaries) are believe to result in better subject compliance with the reporting requirements. *See* ASCO/FDA, *supra* note 572, at 24. *See also* Teri Stokes & Jean Paty, *What Is a Subject Diary, and How Do Regulations Apply? Part 1,* APPLIED CLINICAL TRIALS 38-43 (Sept. 2002), at http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/342002/29336/article.pdf. See also by the same authors, *The Role of the Clinical Protocol in Developing and Implementing Electronic Diaries, Part 2*, APPLIED CLINICAL TRIALS 46-56 (Mar. 2003), at

tronic data capture (EDC), is viewed as a key tool in reducing the high costs of conducting clinical trials.[1772]

Sponsor may chose to submit data in electronic format to the agency.[1773] For clinical trials using computerized systems, the FDA has issued a specific guideline explaining how the general requirements should be met.[1774] One of the FDA's concerns is that electronic data can be modified more easily and inconspicuously than "paper data." The general principle is that post-facto changes should not be entered without a clearly stated and valid reason.[1775] In this context, electronic data represent added risks. Therefore, the FDA asks that each instance of use of computerized systems be stated in advance in the protocol.[1776] Changes made to the data should be duly recorded so as to allow identification of the *original* entry.[1777] All changes should leave a permanent audit trail, so that the sponsor, the investigator and the agency can verify when, how, why and by whom original entries were modified.[1778] Initial and subsequent digital entries should be signed and protected by electronic signatures.[1779]

When electronic methods are used, software utilized in trials must first be validated[1780] – as is true for any other piece of equipment. Validation demonstrates that the software consistently achieves its intended performance, notably recording complete, accurate and reliable data.[1781]

6.4. Manufacturing controls and labeling

One important assumption of clinical development is that the drug being tested remains always the same. It must have the same active ingredient, the same strength, the same dosage form. If, on the contrary, the product differed from trial to trial, then the scientific conclusion could be fully contingent on a particular product form used. Fifty

---

http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/092003/47853/article.pdf.

1772 *See* Rod M. Saponjic et al., *What Monitors Think of EDC*, APPLIED CLINICAL TRIALS, May 2003, at 50 at http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/222003/58185/article.pdf. According to a survey of clinical trials monitors, "the best-liked characteristics of EDC were the reduced number of queries and reduced time on site" while the least-appreciated characteristics were "the training and the technology support provided by the EDC vendor and the "slowness" of some systems." *Id.* at 52. However, ultimately, 96% of the monitors surveyed were ready to recommend use of EDC. *Id.* at 54.

1773 See, on this topic, section 5.5.3 (p.21) of ICH E6.

1774 FDA (Computerized), *supra* note 1426, at chapter I.

1775 *See* section 4.9.3 (p.18) of ICH E6. It is also the responsibility of the monitor to verify that changes to the CRF are made according to procedures. *See* section 5.18.4(n) (p.28) of ICH E6.
See, e.g., FDA warning letter to Harry D. Bear, *supra* note 931.

1776 FDA (Computerized), *supra* note 1426, at chapter III.A.

1777 *Id.* at III.D.

1778 *Id.* at V.B. and II. This is also called reconstruction of the course of events leading to the final submitted data.

1779 *Id.* at V.

1780 The publisher and seller of the software is usually responsible for performing the main validation steps, with the sponsor only doing more basic functional testing. *Id.* at VIII.B.1.

1781 *Id.* at VIII.

years ago, this problem affected many clinical studies: Drug agencies were never quite sure that the study results they received pertained to exactly the same product.

Before phase I begins, the sponsor must arrange for the investigator to have a sufficient quantity of the investigational drug (as well as the control product). Even though the drug has already been manufactured for animal studies, the manufacturing requirements become more severe when the drug is administered to humans.

A drug administered in the framework of a clinical trial does not require a marketing authorization,[1782] which is only logical since the purpose of clinical trials is to gather evidence in order to obtain one. Although the clinical trial itself requires an authorization (or clearance) (see section 7. below), the product is not the object of this authorization.

Drugs used in clinical trials must nonetheless be manufactured by the holder of a *manufacturing authorization*.[1783] However, experimental drugs which are imported into Switzerland do not require an importation authorization.[1784]

Experimental drugs used in Swiss clinical trials must be manufactured according to Good Manufacturing Practices ("GMP").[1785] Switzerland has chosen to defer to European GMP.[1786]

The GMP requirement has important consequences given that abidance by GMP standards significantly increases the cost of the trials.[1787] A sponsor contracting out the manufacturing of GMP-grade compound for clinical trials faces costs starting at an estimated $500,000.[1788] This adds another barrier to entry for small research institutions that can hardly invest such an amount just for the manufacturing of the compound. These institutions also face difficulties in convincing potential commercial partners to enter collaborative agreements as long as they cannot present persuasive study results showing efficacy. The upshot is a "catch-22" situation.[1789]

1782 Article 9.2.d LPTh.

1783 Article 5 LPTh. *See also* e-mail from Méroz (Sept. 2003), *supra* note 517 (confirming that such an authorization is indeed necessary).

1784 *Id.*

1785 Article 4 OAMéd contains no exception for pharmaceuticals used for clinical trials. *See also* sections 2.12 (p.9) and 5.13.1 (p.24) of ICH E6.
In the European Union, GMP is also applicable to pharmaceuticals used in clinical trials; Article 13.3 of Directive 2001/20/EC; E,U, Guidance (Request), *supra* note 270, at 5.

1786 Point 1.a. of Annex 1 of the Swiss OAMéd still refers to the former EU Directive 91/356/EEC, which has now been replaced by the Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, text at http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/GMP_19_09_03.pdf (see in particular Article 16 of Directive 2003/94/EC). *See also* the Annex 13 of the European Commission's Guide to Good Manufacturing Practice, regarding the manufacture of investigational medicinal products, (July 2003), at http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/anx13en030303Rev1.pdf; this Guide is also incorporated by reference under Swiss law, pursuant to point 1.c. of Annex 1 of the OAMéd.

1787 Katherine Uraneck, *No Trials Without Money, No Money Without Trials*, 16[11] THE SCIENTIST 49, (May, 27, 2002), at http://www.the-scientist.com/yr2002/may/prof1_020527.html.

1788 *See id.*

1789 *See id.*

Abidance by GMPs also implies that the sponsor must decide on the dose[1790] and dosage form[1791] of its drug fairly early, usually before starting phase III trials. If the final product is not identical to the one administered during phase III, the sponsor faces the risk of having to conduct additional trials to prove to the drug agency that the same study results would have been obtained had the final dosage form been used (instead of the preparation administered during the trials).[1792] These problems at the clinical stage lead to flexible interpretations of GMP requirements.[1793]

In the United States, a drug at the clinical trial stage does not need to be manufactured according to GMP standards. Instead, the FDA has elaborated extensive guidance on the topic.[1794] The manufacturing requirements are made to increase as the clinical development progresses and the studies extend over a longer period of time.

Neither the LPTh nor the OClin indicate how an investigational compound must be labeled. Labels are the key to avoid confusion risks and similar errors committed either by the physician or by the patient. When a product is administered by the investigator or her team in a medical settings (e.g., an hospital), the risk of errors is reduced, since the person administering the product can refer to the protocol and the brochure; the requirements pertaining to labels can therefore be loosened.[1795] In the United States, investigational drugs should bear a label stating "Caution: New Drug – Limited by Federal law to investigational use."[1796] The FDA receives for review a copy of the labels to be affixed on, or used in connection with, the products.[1797]

The sponsor should adopt Standard Operating Procedures (SOPs) regarding the distribution of the experimental product to investigators participating in clinical trials. These SOPs should serve to curtail shipment mistakes.[1798]

Whereas the sponsor is responsible for supplying the tested products, including the comparator product, to the investigator,[1799] the responsibility shifts to the investigator once the products are at the research site.[1800] However, the sponsor should issue written procedures to guide the investigator in her use of the products.[1801] There should be an inventory of products received, administered and disposed of. In particular, the investigator must make sure that subjects are administered drugs that are within their shelf

---

1790 The dose is the amount to be administered (e.g., 10 mg).

1791 The dosage form is the drug's delivery system (e.g., tablet, capsule).

1792 *See, e.g.,* BRODY, *supra* note 447, at 47 (in the case of the thrombolytic agent tPA).

1793 *See* Peter O'Donnell, *EU to Put the IT into Clinical Trials*, APPLIED CLINICAL TRIALS 20, at 21, (Sept. 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=79877 [hereinafter O'Donnell (IT)]. *See also* VASELLA, *supra* note 127, at 95-99 (on the decision to scale up manufacturing of Gleevec very early in its clinical development process).

1794 *See* in the United States 21 C.F.R. § 312.23(a)(7).

1795 The European Union's 2001/20/EC Directive at its Article 14 leaves it up to the Commission's guidelines on good manufacturing practice to set the requirements for labeling.

1796 See in the United States, 21 C.F.R. § 312.6(a).

1797 See in the United States, 21 C.F.R. § 312.23(a)(7)(iv)(*d*).

1798 *See, e.g.*, FDA warning letter to Louis R. Bucalo, Titan Pharmaceuticals, (Apr. 15, 2002), at http://www.fda.gov/foi/warning_letters/g3180d.pdf.

1799 *See* section 5.14.1 (p.24) and also sections 5.14.4&5 (p.25) of ICH E6.

1800 *See* section 4.6.1 (p.14) of ICH E6.

1801 *See* section 5.14.3 (p.25) of ICH E6.

life.[1802] She has to account for the disposition of each and every drug product.[1803] In turn, the sponsor must make sure that the investigator properly disposes of, or returns, all unused supplies.[1804]

The ethics committee is responsible for verifying that the investigational drug comes from a reputable source; it must check that the drug has been prepared and tested so as to minimize risks for subjects. The less is known about an investigational product, the more information about its preparation should be requested.[1805]

1802 *See, e.g.*, FDA warning letter to Harry D. Bear, *supra* note 931.

1803 *See* section 4.6.3 (p.14) of ICH E6.
In the United States, see 21 C.F.R. § 312.62(a). The FDA mentions failure to do so as one of the five most frequent deficiency unearthed during inspections. FDA, CDER, 2002 Report to the Nation: Improving Public Health Through Human Drugs, 23, at http://www.fda.gov/cder/reports/rtn/2002/Rtn2002.pdf.

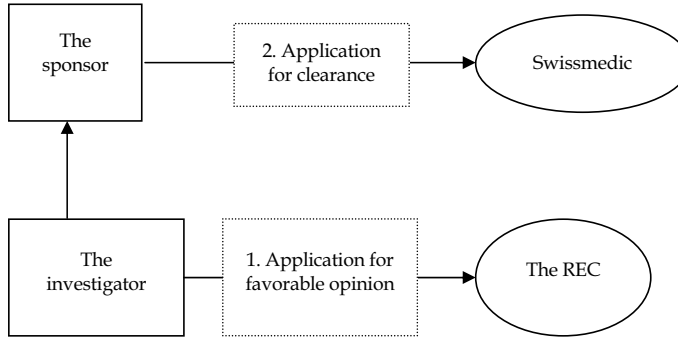
1804 "The sponsors shall maintain written records of any disposition of the drug …." See in the United States, 21 C.F.R. § 312.59 and also § 312.62(a).

1805 *See, e.g.,* John Hopkins Internal Committee Report, *supra* note 378.

Part III

7. Approval of clinical trials

As was the case with IOCM Regulation, a clinical trial governed by the OClin requires two prior "green lights": one from the ethics committee and another from Swissmedic.[1806] I shall review these two requirements successively. Without these approvals, a trial cannot begin;[1807] the sponsor should not even start delivering the experimental product to the investigator.[1808] It goes without saying that before issuance of the approvals, the investigator cannot enroll any subjects, nor even screen them for eligibility.[1809]



This graph shows how the investigator is the one applying for the REC's favorable opinion (see subsection 7.1.) and how the sponsor applies for Swissmedic's clearance (see subsection 7.2.).

[1806] Article 54 at paragraphs 1.c and 3 LPTh; Articles 9.1 and 13.1 OClin.
The situation is similar in that respect in the European Union; Article 9.1 of Directive 2001/20/EC.

[1807] Some other countries have comparatively lower requirements for phase I clinical trials.

[1808] *See* section 5.14.2 (p.25) of ICH E6.

[1809] *See* FDA, Screening Tests Prior to Study Enrollment, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators (1998 update), at http://www.fda.gov/oc/ohrt/irbs/toc4.html. *See however* ECRI (Guide), *supra* note 869, at 29 (pointing out that standard health care treatment that would be given anyway, that is regardless of enrollment, can be administered before the subject's consent is given).

7.1. Approval of clinical trials by ethics committees

Article 54.1.c LPTh states that a clinical trial cannot start until a research ethics committee ("REC")[1810] has granted its favorable opinion.[1811] This has become a fundamental requirement throughout the world.[1812] One should not forget however that, until a recent past, many research projects escaped review by a REC.[1813]

REC approval pertains to a given trial *by a given investigator*.[1814] Although the language of LPTh suggests that the trial *itself* must receive the REC's favorable opinion,[1815] the OClin makes it clear that the obligation to secure this approval rests on each principal investigator.[1816] Hence, if a study is conducted by several private-practice doctors, each acting as independent investigator, each doctor should seek the favorable opinion of his or her ethics committee.[1817] Similarly, if a study is conducted by two investigators from two different cantons, the trial will be reviewed twice, that is separately by each cantonal REC. If several investigators involved in a research project are located within a single REC's jurisdiction, the latter's bylaws determine how the REC is to rule on the issue (e.g., does it issue one main decision for all investigators or as many decisions as there are investigators?).

7.1.1. Organization of Swiss RECs

Before examining how RECs reach their decisions (subsection 7.1.2. below), we need to know how they are organized in Switzerland; we also consider whether their present organization is adequate.

1810 The full name is "research ethics committee" (in French: "*comité d'éthique de la recherche*"; in German: "*Ethikkommission für klinische Versuche*"; in Italian: "*Commissioni d'etica per le sperimentazioni cliniche*"). The LPTh and the OClin use a shorter expression: "ethics committee." Swissmedic abbreviates it "CER." The ICH E6's abbreviation is "IEC" for independent ethics committee. The SAMS uses the term "*comité d'éthique pour la recherche expérimentale*" [ethics committee for experimental research] or "CERE." *See* SAMS 1997 Guideline, *supra* note 110, at point C.1., at 6.

1811 *See* sections 2.6 (p.9), 4.4.1 (p.13), 4.8.1 (p.15) of ICH E6. *See also* paragraph 13 Helsinki Declaration.

1812 In the United States, see 21 C.F.R. § 56.103(a); *but see* 21 C.F.R. § 56.105 (authorizing the FDA to waive the IRB review requirement).

1813 *See* SPRUMONT, *supra* note 16, at 99 (commenting on the interesting results of a survey conducted by the Swiss Academy of Medical Sciences).

1814 *See* FDA, Guidance for Institutional Review Boards and Clinical Investigators, Frequently Asked Questions (updated 1998), at question 54, at http://www.fda.gov/oc/ohrt/irbs/faqs.html [hereinafter FDA (FAQ-IRB)].

1815 *See* Article 54.1.c LPTh.

1816 *See, e.g.*, Article 9.2 OClin.

1817 If all the investigators belong to the same research site, there should be only one ethics committee with jurisdiction over the trial. Then, one of the investigators, the principal or lead investigator, will ask for the REC's approval on behalf of all listed co-investigators.

7.1.1.1. Historical perspective

Before 1995, drug clinical research in most Swiss cantons could theoretically be conducted without the intervention of RECs since cantonal laws did not impose this requirement.[1818] The situation was not very different in Europe.[1819] In fact, in several countries, pressure to set up RECs came from American medical journals that required REC protocol review as a prerequisite to the publication of clinical study reports.[1820]

First in 1971, and then more clearly in 1989, the SAMS issued guidelines mandating review of protocols by ethics committees.[1821] It is not known how widely obeyed the guidelines were. The 1995 IOCM Regulation, for the first time, obliged all cantons to set up ethics committees.[1822] However, even the intercantonal regulatory system was not truly compulsory: cantons had to implement the obligations they had subscribed under the IOCM system in their own legislation. Subsequent to these two sets of initiatives, cantons began setting up their RECs. These initiatives could not avert significant variations in the organization of cantonal RECs.[1823] Some cantons adopted a comprehensive system whereby all research protocols were submitted to a REC, but most cantons only had vague provisions. A strict obligation to create standardized RECs was lacking.

7.1.1.2. Role of the canton under the LPTh

7.1.1.2.1. Cantonal appointment of RECs

Under the LPTh, each canton has to appoint an ethics committee.[1824] The canton has the choice between establishing one or several ethics committees. If there is only one REC, it reviews all clinical trials taking place within the canton. If there are more than one, the canton has to set the principles according to which clinical trials are allocated

---

1818 Not all cantonal laws had provisions mandating review by ethics committees and the SAMS Guidelines were not mandatory. However, several ethics committees were set up in the early 1970s. For example, the ethics committee for the canton of Vaud's Medical School was created in 1976. *See* Jacques Diezi, *La commission d'éthique de la recherche clinique: A la recherche de l'éthique*, 39(1) Cahiers médico-sociaux 91 (1995). At the Geneva HUG, RECs were established in the early 1970s. *See* Dayer (Limites), *supra* note 74, at 65.

1819 For example, in Germany, ethics committees became compulsory in all federal states ("Länder") in 1995. *See Bioethics Newsletter*, 7(2) INTERN. J. OF BIOETH. 137 (June 1996).
In France, they were made compulsory by a 1988 law ("Huriet" law) which entered into force at the end of 1990. *See* J.-P. Demarez, *Les Comités de Protection des personnes dans la loi française relative à l'expérimentation biomédicale sur l'être humain*, 2(3) INTERN. J. OF BIOETH. 137 (July-Sept. 1991); CHRISTIAN BYK & GÉRARD MÉMETEAU, LE DROIT DES COMITÉS D'ÉTHIQUE 208-210 (Eksa & Alexandre Lacassagne 1996) (on the history of French ethics comittees). *See also generally* Ivan Berlin & David A. Gorelick, *The French Law on "Protection of Persons Undergoing Biomedical Research": Implications for the U.S.*, 31 J. L. MED. & ETHICS 434-40 (2003).
The Huriet law was recently revised. *See* French Health Ministry, Direction générale de la Santé, draft law on public health policy ("*projet de loi sur la politique de santé publique*"), especially its Articles 42 to 45, at http://www.sante.gouv.fr/htm/actu/sante_publique/2sante_publique.htm.

1820 See for France, GUY DURAND, INTRODUCTION GÉNÉRALE À LA BIOÉTHIQUE, 512 (Fides Cerf 1999). *See also id.* at 507 (for Canada). *See generally* ROUZIOUX, *supra* note 1270, at 64, and also at 36-39 (Masson 1978). In Switzerland, see Ummel (1990), *supra* note 74, at 33.

1821 On these SAMS Guidelines, see *supra* subsection 2.2.1.2. above.

1822 On the former 1995 IOCM Regulation, see *supra* subsection 2.2.1.4. above.

1823 *See* Ummel (CMS), *supra* note 134, at 86.

1824 Article 57.4 LPTh. For an overview of the system prior to the LPTh, see SPRUMONT, *supra* note 16, at 96.

among them. Cantons can also join their efforts to share one ethics committee.[1825] A canton may also delegate responsibility for reviewing clinical trials to another canton's ethics committee.[1826]

Since most RECs were created some years before the LPTh, several cantons have simply recognized their existing RECs, instead of setting up new ones "from scratch." Hence, many RECs owe their legal existence not to a law or regulation, but simply to an executive decision acknowledging their existence.[1827] For similar reasons, REC members are appointed essentially through co-optation. In Geneva for example, RECs propose existing or new members for formal appointment by the cantonal Department of Social Action and Health.[1828] The Department seeks the prior endorsement of the cantonal Pharmacist.[1829] For practicity, I nevertheless write "the canton sets up/creates its REC" even though creation in the traditional sense of the word has not necessarily taken place.

Presently, there are 19 RECs in Switzerland.[1830] In the mid-90s, there were about 70.[1831] These numbers can be contrasted with the 3,000 to 5,000 IRBs in the United States;[1832] the precise number of U.S. IRBs is not known because they are neither registered nor authorized by public authorities.[1833]

About half of the Swiss ethics committees are tied to a medical institution, whether public or private. Cantons that host a public academic hospital typically have one REC just for their hospital. This main hospital REC may then be further divided into sub-

---

1825 For instance, the three cantons of Fribourg, Jura and Neuchatel share the same ethics committee as do the cantons of Luzern, Nidwald, Obwald, Schwitz, Uri, and Zoug. *See* Article 29.1 OClin; Swissmedic's list of ethics committees, at http://www.swissmedic.ch/files/pdf/Liste_Ethikkommissionen-f.pdf. There are four other intercantonal RECs for 12 cantons.

1826 This is presently the case of the cantons of Appenzell Innerrhoden, Glaris and Shaffhausen.

1827 *See, e.g.*, Article 6.1&2 of the Geneva Regulation K 4 05.18, *supra* note 517.

1828 Article 6.3 of the Geneva Regulation K 4 05.18.

1829 Article 6.2&3 of the Geneva Regulation K 4 05.18. *See also* the website of the service of the Cantonal Pharmacist, at http://www.geneve.ch/pharmacien/accueil/welcome.html. The Cantonal Pharmacist receives a list of REC members and REC's bylaws. On this basis, the Cantonal Pharmacist performs an essentially formal verification; he makes sure that the objective prescriptions of the OClin are met (e.g., at least one unaffiliated member). *See* Telephone Interview with Christian Robert, Geneva Cantonal Pharmacist, (Apr. 8, 2004).

1830 The number varies depending on how ethics committees are to be counted. Some cantonal ethics committees are divided in sub-committees. This is for example the case in Geneva, Vaud and Zurich. See the list, *supra* note 1872.

1831 *See* ASSM Bulletin 3/2000 (Sept. 2000), http://www.samw.ch/content/bulletin/f_Bulletin3_2000.html; Hermann Amstad, *Der Schutz des Patienten im Zentrum*, 82(37) BULLETIN DES MÉDECINS SUISSES 1975 (2001), at http://www.saez.ch/pdf/2001/2001-37/2001-37-950.PDF [hereinafter Amstad (Zentrum)]. *See* Ummel (1990), *supra* note 74, at 28-57 (commenting a 1988 survey by the SAMS in 1988 identifying 51 ethics committees); Ummel (CMS), *supra* note 134, at 86-87 (referring to a 1978 survey coming across some 50 ethics entities).

1832 *See* Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360-66 (July 16, 2003), abstract at http://jama.ama-assn.org/cgi/content/abstract/290/3/360?etoc; OIG (Reviewing), *supra* note 1187, at 13 (the number of IRB reviewing FDA-regulated clinical trials is smaller: between 1,500 and 1,700); OIG (Reform), *supra* note 877, at 3; FDA (FAQ-IRB), *supra* note 1814.
This corresponds to roughly one IRB per 360,000 persons for Switzerland (Swiss population: 7.2 million) and to one IRB per 73,250 persons in the United States (U.S. population: 293 million).

1833 *See, e.g.,* Goldman & Choy, *supra* note 491, at C-26.

RECs.[1834] For instance, at the Geneva University Hospital ("HUG"), half a dozen sub-RECs have been set up across medical specialties.[1835] All of these sub-RECs are assembled under the authority of the central ethics committee (here referred to as the HUG-REC). Geneva has also authorized a REC for physicians in private/outpatient practice (hereafter referred to as the outpatient REC). The outpatient REC has been in existence for more than 15 years, long before it received formal recognition by the Geneva government ("*Conseil d'Etat*"). [1836] Collaboration between the Geneva outpatient REC and the HUG-REC is reported to be good, with each committee referring to the other protocols that extend beyond its respective jurisdiction.[1837]

7.1.1.2.2. Further cantonal responsibilities

According to the LPTh, the canton selects its ethics committee(s) and designates its members.[1838] The canton reports its choice of RECs and RECs members to Swissmedic.[1839] All designated RECs are registered in a list maintained by Swissmedic.[1840] The latter also ascribes each REC a reference number.[1841]

The canton must take the necessary measures to fund its REC(s).[1842] RECs receive no funds from or through Swissmedic. The canton must also ensure that REC members receive appropriate training (e.g., continuing education programs).[1843] Swissmedic assists the canton in discharging this obligation; the agency can supply RECs with "specialized information" ("*Fachinformation*").[1844]

Although the OClin does not state other duties for cantons (aside from surveillance obligations reviewed in subsection 7.1.5.1. below), cantons can further regulate their

---

1834 The hospital RECs of the cantons of Zurich, Vaud and Geneva have sub-RECs. *See* Swissmedic's list of ethics committees, *supra* note 1872, at 1.

1835 *See also* Jean Fabre, *Genève, Quelle est l'activité d'une commission d'éthique de la recherche clinique ?*, 39(2) CMS 251-56 (1995).
It is possible that, in the future, the total number of sub-RECs at the HUG will be reduced down to four. Interview with Bounameaux, *supra* note 1718.

1836 *See* Interview with Ciaroni, *supra* note 1338. The justification for this REC is mainly historical. Private practitioners in Geneva have always been numerous and intent on safeguarding their independence. Having their "own" REC contributes to their autonomy. *Id.*

1837 *Id.*

1838 Article 29.1 OClin.

1839 Article 29.1 and Article 34.3 OClin.

1840 Article 57.5 LPTh. Under the SAMS 1997 Guidelines, ethics committees must also be reported to the SAMS. *See supra* note 110, at point C.2.c) at 7.

1841 *See, e.g.,* Swissmedic's form for the reporting of ethics committees' opinion on a clinical trial.

1842 Article 29.2 OClin. During the OClin comment period, one canton proposed that RECs be funded by fees collected by Swissmedic. This was not accepted. *See* DHA (Ordinance Comments), *supra* note 522, at 47. See however Article 57.3 LPTh which gives the Federal Council, and not the cantons, the power to further specify how RECs are to be funded.

1843 Article 29.3 OClin. According to the Geneva Cantonal Pharmacist, Geneva RECs have been invited to communicate their needs for training so that requests can be pooled and courses organized on an intercantonal basis. Not only would this reduce the costs of organizing the courses, but it would ensure that sufficient participants (i.e., REC members from different cantons) are present to share their perspectives. See Telephone Interview with Robert (April 2004), *supra* note 1829.

1844 Swissmedic assists the canton. Article 19.3. OClin. *See also* WHO (Operational Guidelines), *supra* note 1379, at chapter 4.7 (p.6).

RECs.[1845] To the extent that the canton has not laid down detailed regulations, RECs have the power of setting their own organizational structure.[1846] The REC's internal bylaws should be sufficiently detailed so as to explain how it plans to meet each of its obligations.[1847] For example, the bylaws should state how the REC will review adverse reaction reports.[1848] The canton receives a copy of the bylaws.[1849] These must also be published, along with the list and qualifications of ethics committees' members.[1850] Although the LPTh unambiguously requires publication, this rule is disregarded; for example, Geneva does not publish the bylaws of its two RECs.[1851]

In practice, cantons allow RECs considerable autonomy. For instance, in December 2003, Geneva enacted a new Regulation on clinical trials of therapeutic products,[1852] which contains practically no constraints on RECs' organization.[1853].

7.1.1.2.3. Difficulties with the cantonal organization

Having Swiss RECs organized on a cantonal basis, as opposed to a federal and centralized basis, has its advantages and disadvantages. Among the pros is the assumption that cantonal RECs have a better understanding of local factors (see subsection 7.1.1.3.5. below); they should be familiar with the research site, know the credentials of the investigator, be sensitive to the concerns of the population.[1854] The present system also satisfies the cantons' demand for independence vis-à-vis the federal government.[1855]

Yet the system has its drawbacks. A research project taking place in several cantonal university hospitals will require the favorable opinion of several RECs, each theo-

---

1845 *See, e.g.,* Geneva Regulation K 4 05.18, *supra* note 517. *See also* the recommendations of the VanTx Working Group in the VanTx Report, *supra* note 148, at 27.

1846 Article 34.1 OClin. These internal regulations must be submitted to the canton; Article 34.2 OClin. *See* DHA (Ordinance Comments), *supra* note 522, at 49.
In the United States, see 21 C.F.R. § 56.108.

1847 Section 3.3 of ICH E6 Guideline (at p.11-12) describes the written procedures that ethics committees should adopt. See also for an example of bylaws, Council of Europe, Povl Riss, Ethical Review of Biomedical Research in Europe: Suggestions for best national practices, at 11-15, (DEBRA project) (CDBI/INF (98) 6) (June 23, 1998), at http://www.coe.int/T/E/Legal_Affairs/Legal_co-operation/Bioethics/Activities/Biomedical_research/CDBI-INF(1998)6E-ManualDebra.pdf [hereinafter Council of Europe (Riis)].

1848 This obligation appears not to be systematically followed. See, in the United States, FDA warning letter to Dan F. Ausman, CEO of Irvine Regional Hospital and Medical Center (June 14, 2002), at http://www.fda.gov/foi/warning_letters/g3353d.htm; FDA warning letter to Terry Fredeking, Antibody Systems, (Apr. 14, 2003), at http://www.fda.gov/foi/warning_letters/g3960d.htm; FDA warning letter to Matthias McGuire, Catholic Health Partners, (Dec. 9, 2003), at http://www.fda.gov/foi/warning_letters/g3746d.htm.

1849 Article 34.2 OClin.

1850 Article 34.3 OClin.

1851 For examples of Swiss REC bylaws, see those of the Lausanne University and the Canton of Ticino, available on-line respectively at http://www2.unil.ch/cercfbm/docs/Regl_cercfm_2000.pdf, and at http://www.ti.ch/DSS/DSP/SezS/ComEC/PDF/RegolamentoInternoCE.pdf.

1852 *See* Geneva Regulation K 4 05.18, *supra* note 517.

1853 As an example, the Geneva Regulation K 4 05.18 does not state the maximum term that Geneva REC members can serve, nor how these members can be forcibly removed.

1854 *See* Amstad (Reden), *supra* note 794, at 1733.

1855 For example, the Swiss central REC (when it was still in existence) had problems convincing cantonal RECs to surrender part of their jurisdiction over multicentric clinical trials. *See* Truniger et al., *supra* note 1337, at 2400.

retically allowed to examine the protocol in details and insist on its own set of corrective measures (see also subsection 7.1.2.2. above). This extra layer of "bureaucracy" slows down research and may discourage, if not infuriate, sponsors.[1856] A related disadvantage is the lack of uniformity. Some RECs review many protocols, while others receive very few each year;[1857] some tackle complex protocols and others assess phase IV clinical trials. Since the dialogue among RECs is constrained by many factors, not least of them linguistic obstacles, RECs cannot pool their resources and expertise to agree on a set of best practices. Worse, in multicentric trials, errors or flaws detected by one REC may go unnoticed by another REC.

Efforts are underway to optimize efficiency by improving communication between RECs.[1858] Regular meetings of members from different RECs are to take place.[1859] A couple of such intercantonal meetings have already been organized, to the great satisfaction of REC members.[1860] Electronic tools are to be used to maintain effective channels of communication.[1861]

In my view however, there remains a need for a central federal REC for multicentric clinical trials of significant scientific importance.[1862] This federal REC could also issue recommendations for cantonal RECs. It would bring forward uniform practices much more rapidly than the above-mentioned meetings are able to. Furthermore, it would reduce the procedural burden and costs for research projects that deserve it.

7.1.1.3. Composition of RECs

It is often said that ethics committees must satisfy four principles: competence, pluralism, independence, and transparency.[1863] These principles are reviewed in the following subsections, though not in this order.

7.1.1.3.1. Qualifications of REC members

To ensure both independence and scientific expertise, the OClin outlines the mandatory composition of ethics committees in Switzerland.[1864] Each ethics committee must have i) at least three *physicians* with experience either in the evaluation of safety and efficacy of therapeutic products or with clinical trials;[1865] ii) at least three *non-physicians* with expe-

---

1856 *See* Amstad (Reden), *supra* note 794, at 1734; Truniger et al., *supra* note 1337, at 2401.

1857 *See id.* at 1733, table 1.

1858 *See id.* at 1735.

1859 *See id.*

1860 *See* Hermann Amstad, *Coordination oui, association non*, 2 BULLETIN ASSM 5 (May 2002), at http://www.samw.ch/content/Bulletin/f_bulletin2_2002.pdf [hereinafter Amstad (Association)].

1861 *See* Amstad (Reden), *supra* note 794, at 1735.

1862 Until April 2001, the SAMS offered the services of a central ethical committee. *See* Margrit Leuthold, *La CES disparaît*, 82 BULLETIN DES MEDECINS SUISSES 817 (2001), at http://www.saez.ch/pdf/2001/2001-17/2001-17-398.PDF. *See also* Interview with Dominique Manaï, Professor at the Geneva Law School and then member of this central ethical committee, (Mar. 23, 2001).

1863 *See* EFGCP (Auditing IECs), *supra* note 163, at 3.

1864 Article 30.1 OClin.

1865 It is unclear whether a one-time physician member remains so, for the purpose of Article 30.2, even after he retires.

rience in the ethical, legal or social field;[1866] iii) at least one member with expertise in *biometry* (i.e., biomedical statistics);[1867] iv) at least one member with *no affiliation* with the institution hosting the ethics committee.[1868] While members listed under i) logically cannot be also listed under ii), nothing prevents a physician to act as the biometric expert or as the non-affiliated member, or the non-physician to be the non-affiliated member and so on.[1869] The requirements of Article 30.2 OClin result in RECs having at least six members. The Swiss OClin does not fix a maximum number of members for RECs.[1870]

According to Article 30.1 OClin, RECs must have members who hold the necessary qualifications and experience to review clinical trials, from a scientific, medical and ethical standpoint.[1871] It is unclear how the "scientific" and "medical" evaluations of a clinical trial are to be distinguished.[1872] The scientific evaluation probably refers to the statistical appraisal to which Article 30.2 OClin alludes. This provision makes no mention of a *legal* assessment of clinical trials, despite the fact that regulatory stipulations are becoming more comprehensive than ethical guidelines.[1873]

While the experience of the physician members must be extensive,[1874] the OClin sets no equivalent standard for the experience of the *non-physician* members.[1875] It only mentions that the latter must have expertise in the legal, social or ethical realm. Why can a member not combine experience in both the medical and the ethical/social/legal field? It seems that the OClin intended to curtail the power that physicians could acquire over ethics committees. This concern is underscored in Article 30.3 OClin, which states that RECs must have an equivalent number of health care professional versus non-professionals.[1876] By using the expression "health care professionals" in this provi-

---

In British NHS ethics committees, an individual is also considered a "lay member" if he has not practiced [his] profession for a period of at least five years." However, at least half of the lay REC members must never have exercised a medical profession. *See* COREC, *supra* note 1379, at points 6.6 and 6.7, p.13.

1866 Article 30.2 OClin. There is no need that there be one person coming from each field (one ethicist, one social worker and one lawyer). *See* DHA (Ordinance Comments), *supra* note 522, at 48.

1867 The term most usually employed is not biometrician, but rather "statistician." See CACR (Dictionary), *supra* note 956.
According to the VanTx Working Group, Switzerland is the only country to have such a requirement. *See* VanTx Report, *supra* note 148, at 27.

1868 Article 30.2 OClin.

1869 This is possible under U.S. law. *See* FDA (FAQ-IRB), *supra* note 1814, at question 13.

1870 According to section 3.2.1 (p.11) of ICH E6 Guideline, ethics committees must have at least five members. According to Article 5 of the Geneva Regulation K 4 05.18, Geneva RECs must have at least 9 members. For the SAMS, the ideal number of members is between 9 and 12. *See* SAMS 1997 Guideline, *supra* note 110, at point C.2.a) at 6. In the United States, IRBs must have at least five members. *See* 21 C.F.R. § 56.107(a); 45 C.F.R. § 46.107.a.

1871 In the United States, see 21 C.F.R. § 56.107(a).

1872 Article 10.1 OClin also distinguishes between scientific and medical aspects.

1873 This is in any case true of the United States where the FDA and other federal agencies have issued numerous guidances. Mello further observes that, with the risk of subjects raising legal claims against IRBs, the latter "may be pushed into a legalistic mode in which slavish attention to regulatory detail crowds out reviewers' ability to ask real questions about the risks and benefits of research studies." Michelle M. Mello et al., *The Rise of Litigation in Human Subjects Research*, 139 ANN. INTERN. MED. 40-45 (July 1, 2003), at http://www.annals.org/cgi/reprint/139/1/40.pdf.

1874 Article 30.2 OClin ("*expérience approfondie*," "*vertiefter Erfahrung*," "*con provata esperienza*").

1875 Article 30.2 OClin ("*justifiant d'une expérience*," "*con esperienza*," "*mit Erfahrung*").

1876 Article 30.3 OClin. Compare with Article 30.2 OClin which only refers to physicians versus non-physicians.
In the United States, see 21 C.F.R. § 56.107(b) and (c); 45 C.F.R. § 46.107.b.

sion, the OClin presumably intends to encompass not only physicians, but also others groups such as nurses, pharmacists, biologists or chemists.[1877] This creates a contradiction with Article 30.2 OClin which distinguishes between physicians and non-physicians – and not between health care professionals and non-health care professionals. In Geneva, the non-physician members are often health care professionals (e.g., nurses, pharmacists).[1878] The only member with no involvement in health care tends to be the jurist. Whether the biometry "expert"[1879] belongs to the health care group is not entirely clear although the answer is probably positive.

The OClin also does not go as far as requiring that the non-physician members be "lay" members of the community.[1880] On the contrary, several provisions suggest that all members must have some kind of specialized expertise.[1881] This is unfortunate as a purely "lay" member (e.g., a patient or a research subject) could help other REC members realize what it feels like to be sick or to be "experimented upon." He may give a more realistic assessment of the consent form;[1882] while high-level professionals may believe the consent form to be perfectly appropriate, the lay member may notice unnecessarily convoluted language. The trend in other countries is to acknowledge the important role that purely lay members play.[1883]

Bioethics bodies in the United States have pointed out that having *only one* member unaffiliated with the institution is probably insufficient.[1884] This member assumes an important role because he is the one less likely to be subject to institutional conflict of interest. For example, he should have no desire to boost the reputation or the scientific notoriety of the institution by approving cutting-edge clinical trials. However, he may be at pain to fulfill his duty if he is surrounded by a massive majority of REC members affiliated with the institution. Since there is no maximum REC membership, the unaffiliated member may have to face a dozen or more "affiliated" members intent on defending their institution. While it was deemed necessary to have a balance between physicians and non-physicians,[1885] a similar need should have been felt with respect to affiliated and unaffiliated members.[1886]

1877 In the United States, see FDA (FAQ-IRB), *supra* note 1814, at question 17.

1878 Interview with Ciaroni, *supra* note 1338.

1879 Actually, Article 30.2 OClin does not require an expert but someone "competent" in biometry. In contrast, the physician-members must have extensive experience in either the assessment of the safety and efficacy of therapeutic products or in the field of clinical trials.

1880 By contrast, the CIOMS requires that "ethical review committees" include as members "lay persons qualified to represent the cultural and moral values of the community." *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary). *See also* Sohini Sengupta & Bernard Lo, *The Roles and Experiences of Nonaffiliated and Non-scientist Members of Institutional Review Boards*, 78 ACADEMIC MEDICINE 212-218 (2003).

1881 *See* Article 57.2 LPTh and Articles 30.2 and 31.a OClin.

1882 *See, e.g.,* OIG, HHS, Institutional Review Boards: Promising Approaches, (June 1998), at 18, at http://oig.hhs.gov/oei/reports/oei-01-97-00191.pdf [hereinafter OIG (Promising)].

1883 "[A] more correct view is to consisder scientists and lay citizens to be equal in their knowledge of ethical norms, and to even consider lay citizens to be as ethically knowledgeable as philosophers and other ethicists, as long as the question is not the history of ethics or basic ethical terms, but instead reflections of contemporary ethical standards within society." Council of Europe (Riis), *supra* note 1847, at 5.

1884 *See* NBAC (Issues in Research), *supra* note 244, at 12.

1885 Article 30.3 OClin.

1886 Compare with Article 30.2 OClin.

7.1.1.3.2. Female REC members

According to Article 30.3 OClin, RECs membership must be "balanced" with respect to gender.[1887] Why is that? Indeed, the rule appears peculiar since Switzerland has rarely promoted affirmative action programs for women. This provision could even be construed as meaning that a woman with less qualifications should be selected as committee member, if this is necessary to uphold this balance between genders.[1888] The provision is all the more surprising as gender considerations should have little influence on the scientific soundness of clinical trials: It is unlikely that the choice between approving or turning down a clinical trial will ultimately depend on whether committee members are male or female.

A possible justification for this clause is that ethics committees should somehow *represent* and reflect the general population and/or the subject population.[1889] Since their decisions are to be based in part on ethical factors and since ethics is not a well-defined field, the best way to "find" ethics could be to ask a representative segment of the population. In turn, if this segment is to be representative, it should include both men and women. Yet, this seems to be an odd justification as it implies that ethics is not based on universal consensus, but more on a polling system. A related explanation is that women bring a different perspective – a more feminine or gentle one ? – to the assessment of clinical trials.[1890]

Discussion with the presidents of two Geneva ethics committees (i.e., the outpatient REC and the HUG-REC) revealed that RECs do not interpret Article 30.3 OClin as requiring an equal, or even roughly equal, number of men and women members.[1891] Swissmedic does not seem to enforce this requirement strictly either.[1892] While parity may be a goal for the distant future, these two RECs operate with far fewer women.[1893] In fact, a single woman was considered sufficient, if not ideal.[1894] Such a situation gives rise to quorum problems during REC meetings since the absence of this single female member defeats the quorum.[1895]

1887 Article 30.3 OClin. This provision does not state there should be the exact equal number, but that the composition must be balanced ("*équilibré*," "*angemessen vertreten sind*," "*adeguatamente rappresentate*"). According to Article 32.1 OClin, an ethics committee cannot vote on whether or not to approve (i.e., give its favorable opinion) a trial if its composition is not balanced as per Article 30.3 OClin.
In the United States, see 21 C.F.R. § 56.108(c); 45 C.F.R. § 46.107.b. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).

1888 Compare with the U.S. provision at 21 C.F.R. § 56.107(b): "Every non-discriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender."

1889 This justification is analogous to the one for local conditions.

1890 Interview with Ciaroni, *supra* note 1338.

1891 Interview with Bounameaux, *supra* note 1718; Interview with Ciaroni, *supra* note 1338.

1892 *Id.*

1893 In comparison, a survey conducted among U.S. IRBs has revealed that only 27% of IRB members are women. *See* Eric G. Campbell et al., *Characteristics of Medical School Faculty Members Serving on Institutional Review Boards: Results of a National Survey*, 78 ACADEMIC MEDICINE 831 (2003), at http://www.academicmedicine.org/cgi/reprint/78/8/831.pdf.

1894 Interview with Ciaroni, *supra* note 1338. This information was confirmed by the Geneva Cantonal Pharmacist, C.Robert. Telephone Interview (April 2004), *supra* note 1829.

1895 Article 32.1 OClin. *See also* interview with Ciaroni, *supra* note 1338. On quorum requirements, see further subsection 7.1.2.6. below.

7.1.1.3.3. Non-represented groups

If representation of the population was really at issue with respect to appointment of REC members, we would have to wonder why other groups are not mentioned in Article 30 OClin. The goal of representativeness could have been reached by a provision requiring that the composition of RECs reflect the patient population, the subject population, or comprise representatives of the main groups whose interests are at stake. This is not the case.

First, as already mentioned, Article 30 OClin does not require any *subject representative*.[1896] Although subjects are the ones bearing the risks of the trial, they have no spokesperson. Imagine the following hypothesis: An AIDS vaccine trial is devised at a time where no alternative treatment exists; an ethics committee could rule on the basis of preclinical safety data that scientific uncertainty is still too great to start clinical trials on humans. Yet, patients may prefer to take the risk rather than simply die of AIDS (see already subsections 2.1.4. and 2.1.5. above). If the ethics committee is composed solely of healthy persons who are not personally confronted to this dilemma, they may reach a decision that is unfair to patients.

The OClin makes no mention of age groups. Thus, a clinical trial could be conducted exclusively on seniors (or adolescents) without a representative of this group of subjects speaking on their behalf.[1897] In contrast, the French National Ethics Committee ("CCNE") recommends that different age groups be adequately represented.[1898] Similarly, the WHO stresses the importance of a balanced composition with respect to age.[1899]

In contrast with U.S. law,[1900] the OClin does not specifically make room for foreigners or minority ethnic groups.[1901] If "representativeness" was an objective, then foreigners should be appointed as REC members at least in cantons with an important non-Swiss population (e.g., Geneva). The presence of foreign REC members may also facilitate the enrollment of foreigners as subjects. For instance, foreign REC members could suggest well-tailored initiatives to make foreigners aware of the opportunity to participate in clinical trials.

1896 According to the CIOMS, ethics committees that often review protocols aimed at particular diseases should "invite or hear the views of individuals or bodies representing patients with such diseases or impairments." *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).
In 1988, the French CCNE found that the inclusion of patient representatives would often be impractical. See CCNE N°13, *supra* note 95, at 8.

1897 In the European Union, ethics committees reviewing clinical trials on children must have pediatric expertise (see further subsection 8.4.6.1. below). The same goes for clinical trials involving incapacitated persons: the ethics committee must have expertise in the relevant patient population. Articles 4(h) and 5(g). of the Directive. In the United States, an IRB that regularly reviews trials on "children, prisoners, pregnant women, or handicapped or mentally disabled persons" should have members who are "knowledgeable about and experienced in working with those subjects." 21 C.F.R. § 56.107.

1898 *See* CCNE N°13, *supra* note 95, at 8.

1899 *See* WHO (Operational Guidelines), *supra* note 1379, at 2. *See also* COREC, *supra* note 1379, at point 6.2, p.13.

1900 In the U.S., IRBs composition should also reflect *racial* diversity. *See* 21 C.F.R. §56.107(a). *See also* COE Explanatory Report, *supra* note 417, at 9, paragraph 41, (recommending that RECs be culturally balanced).

1901 Of course, the role of and the importance given to minorities is very different in Switzerland compared to the United States.

7.1.1.3.4. Accountability

The previous subsection suggests that the legislator did not hold representation as a key issue.[1902] The risk of placing the emphasis on representation is that each REC member may limit his contributions to his own "field of expertise."[1903] For instance, the subject representative at the REC would only give his ideas regarding subjects' rights; the female REC member would mainly make sure that female patients are eligible to enroll as subjects.

Instead of representativeness, *accountability* should be the decisive factor in appointing REC members. Accountability is more effective than representation. If a REC that is correctly composed reaches bad decisions, representation is not a remedy. Accountability is achieved first and foremost by *transparency*. The public should be able to obtain information as to how ethics committees operate. Upon request, the public should have access to decisions taken by ethics committee, as is the case for court decisions. Ideally, the public should be allowed to attend meetings of ethics committees, with the necessary precautions taken to safeguard sponsors' trade secrets. Presently, the OClin makes no provision for the presence of observers during REC meetings.[1904] But if the public could follow and monitor the work of RECs, it would be able to intervene when the REC's decisions are flawed. It could do so, for example, by petitioning for a change in the REC's internal regulations.

7.1.1.3.5. Knowledge of local conditions

Pursuant to Article 31.a OClin, REC members must be aware of *local conditions* ("*örtlichen Voraussetzungen*," "*condizioni locali*") in order to assess i) the qualifications of the investigator, ii) the site's medical facilities, iii) the protocol, iv) the subjects' selection criteria and v) the measures taken to guarantee confidentiality.[1905] Here again, the OClin text could have been clearer. The reader is not told what kind of knowledge is required, nor how many REC members must have it (e.g., only the physician members? Is one member sufficient?).[1906] We do not know either how the cantons will *verify* that REC members are acquainted with local conditions. Should members be domiciled in the canton? Should they have lived there during a long period? Would a foreign individual be excluded from participating in a REC because she lacks such familiarity with local conditions? What if a canton has a large percentage of foreigners (40% in Geneva): Should it have members of foreign origin to assess these local conditions?

With respect to the investigator's qualifications or the research site's suitability (points i) and ii) above), the reference to the "local conditions" adds little meaning since

---

1902 In England, the NHS-COREC guidance states: "[d]espite being drawn from groups identified with particular interests of responsibilities in connection with health and social issues, REC members are not in any way the representatives of those groups. They are appointed in their own right, to participate in the work of the REC as equal individuals of sound judgment, relevant experience and adequate training in ethical review." COREC, *supra* note 1379, at point 6.8, p.14.

1903 *See, e.g.*, OIG (Promising), *supra* note 1882, at 18.

1904 The British RECs belonging to the NHS system allow observers. *See* COREC, *supra* note 1379, at point 6.17 (p.15).

1905 Article 31.a OClin. *See also* Article 57.1 LPTh.

1906 Article 31.a OClin refers to REC members generally, but adds depending on their qualifications as per Article 30 OClin ("*selon leur qualification au sens de l'art.30 OClin*"; "*je nach ihrer Qualifikation gemäss Artikel 30*").

these two points are specific by nature.[1907] However, as alluded above, the OClin does not tell us how well the REC must know the investigator (e.g., personal acquaintance with the investigator or a review limited to her curriculum vitae?) nor how familiar it must be with the research site (is a prior visit necessary?[1908]).

The link between protocol assessment (point iii) above) and "local conditions" is even more doubtful. It is unlikely that the former ever hinges on the second. Rather, research protocols should be evaluated from a scientific point of view. The reference to "local conditions" should not be viewed as an endorsement of factors that have nothing to do with science, law or even ethics. For instance, a REC based in a Catholic canton should not refuse to give its go-ahead to a protocol whose purpose is to test a new drug to induce lawful abortion; "local feelings" should not come into play. Similarly, the reference to "local conditions" should not be taken as an invitation to apply purely relative ethical standards. What ethics is and what it dictates under different circumstances is admittedly unclear. We should not however assume too fast that ethical principles vary across national or cultural zones. Having ethical stances fluctuate along cantonal lines or even smaller local divides certainly does not help set ethics on firm ground. How sound is the REC system if a committee in the canton of Vaud can reach a different verdict than one set in Geneva? In a nutshell, ethics must strive for universality, or at least for uniformity within a small country like Switzerland.

What is the impact of "local conditions" on subject selection (point iv) above)? Could it mean that natives or residents of certain cantons are less apt to give their informed consent and to participate in research? One finds its hard to imagine which local conditions should be reason enough to call into question the protocol's selection criteria. Even citizens' religious beliefs which may be more widespread in a given canton should hardly be relevant to assess the validity of a clinical trial.[1909] One can conceive that the socio-economic status of a canton's population can have some bearing on a clinical trial: If the population from which subjects are drawn is particularly poor, payments made to them could be judged excessive given their low incomes. Similarly, if the population is known to have limited literacy skills, the written consent form should be modified so that potential subjects be given more extensive oral information. In Switzerland however, local conditions will rarely be sufficiently uniform so that only patients with these homogeneous "local" characteristics are enrolled. It is more likely that subjects' characteristics do not tie in closely with local geographical settings. Subjects may come from more than one geographical region. If the trial is viewed as a promising therapeutic opportunity, it may even attract patients from foreign countries. When this occurs, the words "local conditions" no longer mean much.

Finally, I struggle to see what "local conditions" have to do with measures aimed to guarantee data confidentiality (point v)). These measures should be roughly similar whatever the geographical location of the trial. Cantonal laws influence little the pro-

---

1907 *See however* the Federal Council's Message at FF 1999 3151, at 3232.

1908 *See* OIG (Reform), *supra* note 877, at 6 ("At the six academic medical centers we visited, officials reported that during the past year they seldom visited the research site. Five of the 11 independent boards we interviewed reported that they have no routine policy for visiting the research sites under their purview.").

1909 However, the Copernicus Group, a private independent IRB in the United States, asks "what are the community attitudes (such as religious, ethical, ethnic or economic) that may affect the conduct of clinical research at this site." The Copernicus Group, Investigator Site Questionnaire, at 2, at http://www.copernicusgroup.com/irbForms/Forms/20050523_InvSiteQues.pdf.

tection given to medical data, as these are primarily protected by federal laws (see subsection 8.6.3. below).[1910]

In conclusion, in a small country like Switzerland, local conditions should not – in my opinion – influence RECs' review of clinical trials.[1911] If RECs were to operate perfectly, they would always reach the same decision on a given protocol. In that respect, RECs and courts are alike: They leave a poor impression when two different courts or RECs reach a different conclusions from the same facts. Courts, like RECs, have several factors to weigh in order to decide a case; courts, like RECs, sometimes have to go beyond the letter of the law (e.g., divorce cases, cases involving children, criminal cases). Yet it would be absurd to explicitly encourage courts to pay heed to local conditions. Likewise, it is counter-productive to refer to local conditions in Article 31.a OClin.

A more legitimate ambition would be to develop a *uniform practice* across ethics committees. If sponsors and investigators were able to refer to published "case law" to design protocols accordingly, this would benefit everybody. Ethics committees would have less work doing routine assessments and more time to fine-tune their positions on complex issues. Subjects would benefit from the highest level of protection, because published decisions of ethics committees would – hopefully – display a meticulous analysis of all factors. The public would be in a position to review this case law. Activists would be able to comment on the decisions reached by RECs and thus exercise a greater influence on the process.

7.1.1.4. Independence of RECs

7.1.1.4.1. The legal requirements

The LPTh contains a general provision on independence in its Article 57.2.[1912] This clause is supplemented by three provisions of the OClin.

First, Article 30.2 OClin stipulates that at least one REC member must be unaffiliated with the institution conducting the clinical trial ("*indépendent de l'institution*," "*von der durchführenden Institution unabhängig*").[1913] *A contrario*, all other members can be affiliated with the institution (see already subsection 7.1.1.3.1.). For instance, they can be employees or directors of the institution. In Switzerland, the non-affiliated member is often the jurist.

Second, Article 31.b OClin states that REC members must be independent from the investigator and the sponsor ("*indépendants de l'investigateur et du promoteur*," "*von der*

1910 *See* Article 321bis of the Swiss Penal Code ("CP").

1911 ICH E6 guideline also refers to local conditions. However, the situation contemplated by ICH is quite different, since this guideline, which is the result of an harmonization effort, is to be applied by three countries/regions that still have different sets of values. Since it would be politically unfeasible to impose a unique set of values to these sovereign nations, it is reasonable to allow for variations due to local conditions. Similarly, in the European Union, which unites several still-partly sovereign States, local conditions can still reasonably have their say. Greece may still have very different laws from England on the topic of subjects' potection. Moreover, it is not politically practicable to erase all such differences by means of legal texts and guidelines. However, these reasons simply do not prevail in Switzerland where it is both desirable and realistic to progressively erase possible cantonal differences.

1912 *See also* paragraph 13 Helsinki Declaration.

1913 Compare with the U.S. rule at 21 C.F.R. § 56.107(d).

Prüferin oder dem Prüfer sowie vom Sponsor unabhängig sein," "*indipendenti dagli sperimentatori e dai promotori*").[1914] Should this provision be taken to mean that a person who has worked in the past with the investigator or consulted for the sponsor cannot be appointed on the REC?[1915] While a literal reading of the provision could support such an interpretation, it is unlikely that the legislator had such a far-reaching ban in mind. Most members of a hospital REC probably have some kind of past relationship with the hospital's investigators (e.g., they worked together on a project, the REC member was a former student of the investigator).

Third, Article 31.c OClin requires that REC members be independent from the (public) authorities.[1916] The latter are not allowed to give instructions. Should Article 31.c be taken to mean that REC members should not occupy other functions as civil servants? Probably only high-level public officers should abstain from serving as REC members.

We see that the OClin mentions independence only in connection with given entities (the institution, the investigator, the sponsor, and the authorities). Article 57.2 LPTh contains a more general requirement, but fails to define what independence entails. Thus, one still has to refer to the OClin to interpret Article 57.2.

In contrast, other international guidelines contain *more general* statements about the importance of RECs' independence.[1917] The underlying objective is that RECs reach their conclusions based only on the merits of the trial. Their decisions should not be influenced by financial considerations nor by friendship or animosity towards a participant in the trial (e.g., the sponsor, investigator, institution and even the subject).[1918]. By failing to stress the importance of general independence, in particular the need for an impartial and open-minded attitude, the OClin makes it hard to gauge the scope of the requirement.

7.1.1.4.2. What independence for institutional RECs?

In Switzerland, many RECs are affiliated with an institution (e.g., a public hospital) or organization (e.g., physicians in private practice). Research taking place in that institution is reviewed by the institution's REC. The independence of these institutional RECs is somewhat problematic. For example, in the U.S. Kennedy Kriger Institute case (see subsection 2.3.1.4. above), the ethics committee had shamelessly sided with the researchers and the University.[1919] It had largely abdicated its responsibility toward subjects in order to help the researchers circumvent ethical requirements.[1920]

[1914] Compare with section 3.2.1 (p.11) of ICH E6 (requiring that REC members *who vote* on a given clinical trial be independent of the sponsor and investigator).

[1915] See more generally on recent patterns of interaction between Pharma and bioethics, Carl Elliott, *Not-So-Public Relations, How the drug industry is branding itself with bioethics*, MSN Slate, (Dec. 15, 2003), at http://slate.msn.com/id/2092442/.

[1916] Article 31.c OClin: "*ils prennent leurs decisions en toute autonomie par rapport aux autorités*," "*nelle decisioni sono indipendenti dalle autorità*," "*Sie treffen ihre Beschlüsse ohne Weisung der Behörden*."

[1917] *See* paragraph 13 Helsinki Declaration.

[1918] *See* Article 31.b OClin.

[1919] *See Grimes*, 782 A.2d at 817.

[1920] *Id.* at 813-14.

Lack of independence of institutional RECs can be attributed to several causes.

First, several, if not most, institutional REC members are employees or high-level officers of the institution. For example, in the case of hospital RECs, physicians employed by the hospital are selected to work part-time for the ethics committees. As REC members, they have to assess and review protocols prepared (or at least submitted) by their colleagues and perhaps friends.[1921] Moreover, their institution is often set to earn money or to better its reputation by hosting clinical trials.[1922] A REC member should not take these factors into consideration, even if a refusal would hurt its institution financially or offend colleagues, hierarchical superiors, and external sponsors. Still, some REC members will feel uncomfortable adopting an intransigent attitude; others will fear reprisals. REC members may unconsciously trust colleagues who submit protocols; they would not doubt their word, nor double-check the claims made in the protocol (e.g., the favorable risk/benefit ratio).

Second, the institution's employees serve mostly as *unpaid volunteers* on the REC. They receive little credit and recognition for their services.[1923] Given the full-time position they occupy elsewhere (for example, as physicians or professors at medical schools), they have only limited time left to devote to their REC functions. Furthermore, ethics committees receive little or no staff support (e.g., secretaries) so that members may have to perform administrative tasks themselves.[1924] In Geneva, the maximum fee paid for a REC review is CHF 1,000.[1925] The outpatient REC, for example, uses this money to pay a secretary and to fund continuing education programs for its members;[1926] there is not enough left to compensate members for their time. Although independence is not directly linked to compensation, the incentive to do an excellent job wanes if no rewards are offered (whether in money or in appreciation). Overwhelmed REC members asked to review piles of adverse events reports may go for the "easy way" and not scrutinize these reports.

Third, the presence of a single unaffiliated member (on a total of at least six REC members) is obviously insufficient. While the legislator has visibly sought to balance the composition of RECs (see Article 30.3 OClin), this aspect remains clearly lopsided. As I argued before, the balance between affiliated and non-affiliated members is at least

---

1921 *See* VanTx Report, *supra* note 148, at 27.

1922 *Id.*

1923 *See, e.g.*, Jeffrey L. Kaufman, Protecting Research Subjects, Letter, 346 NEW. ENG. J. MED. 2093 (June 27, 2002), at http://content.nejm.org/cgi/content/full/346/26/2093. *See however* COREC statement, *supra* note 1379, at point 6.9 (p.14).

1924 *See* VanTx Report, *supra* note 148, at 26. *See however* WHO (Operational Guidelines), *supra* note 1379, at point 4.4 (p.5) ("REC should have adequate support staff for carrying out its responsibilities.").

1925 Article 8 of Geneva Regulation K 4 05.18, *supra* note 517. In the canton of Ticino, the maximum fee is CHF 2,000.-. *See* Article 10a.4 of the Ticino health law of April 18, 1999 (Legge sulla promozione della salute e il coordinamento sanitario); RL 6.1.1.1.; abbreviated: Ticino-Lsan; Italian text at http://www.ti.ch/CAN/argomenti/legislaz/rleggi/rl/dati_rl/f/s/185.htm.
In comparison, the U.S. Department of Veterans Affairs has just started to ask external sponsors to pay fees of up to $1,200 to "cover the costs of the human subject protection program." *See, e.g.,* GAO (Insufficient), *supra* note 893, at 10. Chairpersons of IRBs at the University of California at San Diego receive an annual stipend of $10,000; other IRB members receive a fully equipped computer. *See* UCSD-SOPP, *supra* note 485, at 21.

1926 Interview with Ciaroni, *supra* note 1338.

as important as the balance between health care professionals and non-professionals; it is more important than the balance between men and women.

Institutional RECs are not without advantages. First, its members are on-site and can more easily monitor the clinical trial. If they want to, they can meet the investigator to ask him questions or to receive information about the trial's progress. If they wanted to, they could even meet subjects to find out how the informed consent process went – regrettably, they rarely if ever do so (see subsection 7.1.3. below). Second, REC members affiliated with the institution can cultivate relations of trust with the investigators who are also their colleagues. They can educate investigators so that the latter submit better protocols. They can discuss and negotiate submissions in a less formal setting if they choose to. They can explain their work and convince the investigators of the importance of good cooperation. In turn, trust and cooperation should facilitate open and sincere assessment of research projects.

7.1.1.4.3. Conflicts of interest within RECs

The independence requirements discussed above (subsection 7.1.1.4.) do not preclude situations where REC members face conflicts of interest. Therefore, under Article 32.2 OClin, REC members with a conflict of interest should decline participation.[1927] Conflicts of interest involving a REC member encompass any circumstance that could color, bias, or cloud his reasoning. This includes any "direct participation in the research" (e.g., the REC member helped organize the trial, he participated in the drafting of the protocol, he will participate in the trial's execution or analysis) as well as any financial interest in the research (e.g., any connection with the sponsoring company, a financial stake in the product being tested).[1928] A conflict of interest concerning a close relative of the REC member should be treated as a conflict affecting the member himself.

Although the OClin does not state so explicitly, REC members should systematically disclose conflicts of interest.[1929] These disclosures should be reflected in the minutes of the meeting, which should further indicate which members recused themselves, which participated in the deliberations and which took part in the vote.[1930] Even when no member recused himself, the minutes should preferably confirm that the question was raised and answered by each REC member.

Article 32.2 OClin refers to situations where a REC member and/or his relatives have an interest in the trial under review ("*intéressés à l'essai*," "*persönlich oder in der Sache befangen ist*," "*è materialmente o personalmente implicato*"). The Italian and German versions reveal that the interest at issue is either personal or financial. This notion of

---

1927 Article 32.2 OClin: "*se récuser*," "*in den Ausstand treten*," "*si astiene*." Compare the French version to both the German and Italian version which specify that the interest can be personal or material ("*in der Sache*" "*materialmente*").

1928 *See also* UCSD-SOPP, *supra* note 485, at 71.

1929 Article 32.3 OClin.
In the United States, the HHS recommends that, at the start of REC meetings, its chairperson personally interrogate REC members regarding actual and potential conflicts of interest. *See* HHS Interim Guidance, *supra* note 938, at 3.1. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).
See also Article 10.2 COE Research Protocol.

1930 See, in the United States, HHS Interim Guidance, *supra* note 938, at 3.1. Under U.S. law, IRB members who have a conflict of interest do not participate in the discussion of the protocols unless they are asked to answer specific questions. *See* HHS Financial Guidance, *supra* note 938, at 15,459.

conflict of interest is narrow. A broader definition would have REC member declining participation whenever circumstances could suggest to a third party that this member is likely to take into consideration factors other than those set by the law and internal REC regulations. As a point of comparison, the WHO Guidelines defines a "conflict of interest" as a situation arising "when a member (or members) of the REC holds interests with respect to the specific applications for review that may jeopardize his/her (their) ability to provide a free and independent evaluation of the research focused on the protection of the research participants. Conflicts of interests may arise when a REC member has financial, material, institutional, or social ties to the research."[1931]

Potential conflicts of interest ought to be treated in the same way as actual conflicts of interest. The appearance of subjectivity, bias or partisanship can "taint" the REC's reputation. Provisions on conflicts of interest exist not only to ensure that the final decision is reached fairly, but also to convince third parties that the process is truly impartial. Potential conflicts of interest undermine the faith in ethics committees, just as would actual conflicts.

An interesting question is how to distinguish the independence provisions (Articles 30 and 31.b OClin) from the conflict of interest provision (Article 32.2 OClin)? Is independence just the reverse of conflict of interest or is it a broader notion? Should we understand Article 32.2 as referring to independence from parties *not mentioned* in Article 31 OClin (i.e., someone other than the investigator and the sponsor)? Or is Article 32.2 necessary because Article 31 makes no reference to the REC members' relatives? It is difficult to find a satisfying answer to these queries. It seems that Article 32.2 was established as a sort of "safety net" for cases where Article 31.b would not not operate properly. Indeed, Article 31.b does not explicitly state what is to happen when a REC member is not independent from the investigator or the sponsor? Should he not be appointed to the REC? How can this be decided in advance when the identity of the investigator and that of the sponsor change with every protocol? Thus, Article 32.2 could be understood as the "penalty" for Article 31.b. This clearly does not make for elegant draftsmanship.

Because the notion of independence is "frail," particularly with respect to institutional independence (see subsection 7.1.1.4.2. above), the appraisal of conflicts of interest should be particularly stringent. If colleagues are allowed to judge each other's protocols, strict conflict of interest rules are absolutely imperative to offset these ties. There may even be situations where recusal does not suffice to guarantee independence. Although Article 32.2 OClin stipulates that a member must recuse himself when he has interests in the clinical trial,[1932] having *another* REC review the trial sometimes provide better assurance of independence. An ethics committee may hesitate to come down hard on a protocol submitted by a co-member, even though the latter is not participating in the discussion. For this reason, the COREC document recommends that another committee evaluate the application.[1933]

1931 WHO (Operational Guidelines), *supra* note 1379, at p.21.

1932 *See also id.* at point 7.1 (p.14).

1933 *See* COREC, *supra* note 1379, at point 9.20.b (p.28).

As a point of comparison, a review of FDA warning letters suggests that rules about conflicts of interest are not always followed.[1934] A study of U.S. IRBs affiliated with an academic institution found that some 47% of their members had been consultants for the pharmaceutical industry.[1935] This obviously raises the specter of conflict of interest.[1936]

7.1.1.5. External assistance

According to Article 30.4 OClin, RECs can call on external experts.[1937] They have to do so if they lack the internal expertise to assess a trial.[1938] Experts supply information and advice, but do not vote.[1939]

In practice, deciding when expert knowledge is required can be a tough call. Even physician REC members cannot be experts in each and every medical field. However, a general practitioner should still be able to roughly assess the scientific validity of most clinical trials (see further subsection 7.1.2.5.1.). If the contrary were true, the legislator would have specified that RECs must specialize in a given sector of medicine or that there must be as many REC physician members as fields of medicine under review by that REC. On the other hand, it is true that a general practitioner cannot check aspects of the protocol that are outside his own scope of expertise. For example, he may not know whether the clinical study is duplicative because prior research has already answered the question.

Another difficulty with this provision is whether internal expertise of a *single* REC member is enough to spare the REC the duty to summon external experts. In other words, can the REC rely exclusively on the expertise of one member? The fact that Article 30.1&2 OClin emphasizes the different qualifications of REC members speaks in favor of broad reliance: Members should be allowed to trust each others' judgment in their respective area of competence.[1940] This is a practical and efficient way to operate. But this solution is not without danger. Non-physician members may leave the trial's scientific analysis to physician members; the bioethicist, if there is one, could end up evaluating alone the ethical aspects of the protocol; the lawyer would examine insurance and confidentiality clauses without input from others. This is not the goal of the OClin, which rather contemplates that the final decision is taken in a collegial fashion

---

1934 *See* FDA Warning Letter to Dan F. Ausman, *supra* note 1848 ("IRB members did not always exclude themselves from deliberation and voting on projects in which they were involved."); FDA warning letter to Matthias McGuire, *supra* note 1848.

1935 *See* Campbell et al., *supra* note 1893, at 831-36.

1936 *Id. See also* Janice Hopkins Tanne, *Many US faculty members on institutional review boards have ties with industry*, 327 BMJ 414 (Aug. 23, 2003), at http://bmj.com/cgi/content/full/327/7412/414-i ("Industry ties and service on a review board may mean that researchers can sabotage studies by other investigators or "kidnap" pools of patients with rare disorders to serve their own research interests.").

1937 *See also* section 3.2.6 (p.11) of ICH E6. In the United States, see 21 C.F.R. § 56.107(f).

1938 Article 30.4 OClin. In the United States, IRBs retain discretion to decide to call for an external expert.

1939 Article 30.4 last sentence OClin. However, Dr. Ciaroni indicated that in the few cases where the Geneva outpatient REC hired an external expert, the latter issued a recommendation as to the decision the REC should reach. His recommendations were held as strongly persuasive. Interview with Ciaroni, *supra* note 1338.
In the United States, see 21 C.F.R. § 56.107(f).

1940 Dr. Ciaroni confirmed that the Geneva outpatient REC functions on this basis.

with each member participating fully in the discussion. The problem is difficult to solve, all the more so since REC members have other jobs and, as we have seen, receive only modest fees for their participation. This dissuades them from following extensive training to acquire the scientific/ethical/legal education they may lack.

Finally, tight budgets also make it difficult for RECs to hire outside experts as often as they would like to.[1941] Cantonal regulations should state that the maximum fee ceiling can be exceeded when the REC has to remunerate an outside expert. The need for such an expert would have to be discussed first between the REC and the investigator, before the expense is incurred. However, if the investigator cannot address the concerns expressed by the REC, the latter should be allowed to consult an expert at the investigator's (ultimately the sponsor's) expense.

7.1.2. RECs' decision-taking process

In spite of their appellation, RECs have a limited role, which is to approve clinical trials. RECs rarely issue *general ethics opinions*, or are consulted for ethics problems unrelated to clinical trials.[1942] In this, they differ from the Swiss Federal Ethics Commissions, which have consultative voice over a variety of ethical issues.[1943]

7.1.2.1. Choice of REC

The 2002 federal system ensures that there is no gap in the network of RECs.[1944] For every investigator and/or every research site, at least one REC must have jurisdiction. It is the responsibility of the investigator to determine which REC is competent. In cantons with only one REC, the determination is straightforward.[1945] In cantons hosting several RECs, the investigator submits her request to the REC affiliated with her institution.[1946] As observed above, each REC should specify in its internal regulations which kind of clinical trials from which type of investigators and sponsors it reviews – unless this is already made clear by cantonal law.

1941 *See* OIG (Reform), *supra* note 877, at 6: OIG (Reviewing), *supra* note 1187, at 11.

1942 However, some ethics committees may agree to provide consultative opinions on ethics issues. *See* Interview with Ciaroni, *supra* note 1338. See also the results of 1988 SAMS survey, Ummel (1990), *supra* note 74, at 72.

1943 Other ethics commissions are available to provide general ethics advice. See for example the abstract of a research survey prepared by Michelle Salathé et al., *Clinical Ethics Committees in Swiss Hospitals: an Overview*, at http://www.clevelandclinic.org/bioethics/cec/syllabus_nz.htm#Salathe.

1944 In the former intercantonal system, the IOCM had the authority to designate the REC to review over a given research project if none appeared to have jurisdiction. *See* Article 12.3 of the (former) IOCM 1995 Regulation.

1945 The same is valid for cantons which share a single REC.

1946 For instance, when the investigator is a physician employed by a public hospital, she will refer the clinical trial to the REC (or sub-REC) linked with her specialization. It may happen that an investigator is affiliated with more than one institution and/or that she conducts a clinical trial at more than one research site. In this case, if each institution has its own REC, the investigator may need to request more than one favorable opinion, even though the 2002 federal regulations seem to contemplate one favorable opinion per (principal) investigator.

A situation of conflict among RECs could arise when subjects are supposed to be treated by several different medical facilities. For example, subjects may come to a principal hospital for the initial consultation, but then receive follow-up treatments at local clinics. Should the RECs operating for these clinics also issue opinions or does the consultation of the hospital's REC suffice? The OClin does not answer this question. The answer is probably that the investigator's REC (i.e., the one at her principal institution) has jurisdiction. However, depending on the range of responsibilities delegated to the staff of local clinics and on the degree of risks incurred by subjects, it may be appropriate to also submit the trial to the clinics' RECs.

7.1.2.2. Multicentric review

There are other cases where more than one REC appears to have jurisdiction over a study. One such situation arises with multicentric trials, that is clinical trials conducted according the *same protocol* at several *different research sites* (located in one or more countries), each site enrolling its own research subjects.[1947]

Under Swiss law, several RECs have concurrent jurisdiction over a multicentric trial. The first REC to receive the application from the investigator issues a main opinion; the RECs that subsequently receive the file can issue secondary opinions following a simplified procedure.[1948] These other RECs retain however the option of reviewing exhaustively the application, because – disappointingly enough – the simplified procedure is not compulsory.[1949]

The OClin leaves it to the trial participants (the investigator, certainly after discussion with the sponsor) to decide which will be the *first* REC to receive the protocol. In theory, a small REC affiliated to a small institution (e.g., one where only a few subjects are recruited) could be the main REC doing the principal assessment. In my view, it would be preferable to give principal jurisdiction either to the most experienced REC or to the one where most subjects are enrolled.

[1947] In the past, the central ethics committee of the SAMS gave its opinion on multicentric trials. *See* Truniger et al., *supra* note 1337, at 2398.

[1948] Article 10.3 OClin. This provision attracted many remarks during the comment procedure. *See* DHA (Ordinance Comments), *supra* note 522, at 41-42. *See also* Article 9bis of the bylaws of the Lausanne University REC, *supra* note 1898.
In the European Union, a multicentric clinical trial will give rise to only one REC decision per Member State concerned; Article 7.2 of the 2001/20/EC Directive. *See also* E.U. Guidance (Ethics Committee), *supra* note 270, at 3.
In the United States, IRBs have the latitude to organize their review to avoid duplicative efforts. *See* 21 C.F.R. § 56.114.

[1949] *See* Article 10.3 OClin ("*les autres commissions d'éthiques concernées* peuvent *se prononcer selon une procedure simplifiée*," (emphasis added)). See also for example Article 11a.1.a of the Bern Ordinance regarding experimental research on man, (June 17, 1998), 811.05, at http://www.sta.be.ch/belex/f/8/811_05.html [hereinafter Bern Ordinance 811.05].
In the United States where a comparable system was set up for trials sponsored by the National Cancer Institute, most local IRBs decided to perform their own full review despite prior assessment by the central ethics committee. *See* Michaele C. Christian et al., *A Central Institutional Review Board for Multi-Institutional Trials*, 346 NEW ENG. J. MED. 1407-08 (May 2, 2002), at http://content.nejm.org/cgi/reprint/346/18/1405.pdf.

Multiple jurisdiction also prompts debate as to the balance of powers between RECs.[1950] When a small REC is invited to perform a secondary review of a trial, it may lack the power to negotiate protocol amendments. This should come as no surprise: The sponsor wants neither to implement amendments applicable to only one research site, nor to make the changes valid for all sites and having to go back to their RECs (to re-submit the revised version).

Another problem with multiple ethical reviews is the risk of spawning *contradictory decisions* from the different RECs. This risk is not negligible given that RECs (both within and across countries) follow very heterogeneous practices.[1951] The OClin does not tell us how *conflicts* between RECs must be resolved. If two RECs hold opposite views on some aspect of the trial (e.g., eligibility criteria), how is the disagreement solved? It is usually not possible to have two different protocols at two research sites, otherwise the trial would loose its "multicentric" qualification.[1952] Many RECs do not allow appeals against their decisions.[1953] There is no central authority overseeing ethics committees. Swissmedic has no authority to mediate disputes between ethics committees. The investigators are forced to arrange for some kind of compromise. If none is found, one of the trial sites will have to be dropped. This situation is clearly not optimal.

Consequently, multicentric reviews by several RECs are a cause of *delay*. It adds to the work of investigators and multiplies the sponsor's expenses.[1954] Sponsors complain bitterly that current procedures are exceedingly burdensome.

For the reasons just exposed, Switzerland (as well as all other Western countries) struggles to improve REC review for multicentric trials. The proposal made by the SAMS is a good step in the right direction.[1955] It summarizes the local aspects that the secondary RECs should evaluate on an expedited basis after the first REC has performed its full assessment of the investigator's application.

1950 *See* Jennifer Blunt et al., *Meeting the challenges facing research ethics committees: some practical suggestions*, 316 BMJ 58-61 (Jan. 3, 1998), at http://bmj.com/cgi/content/full/316/7124/58.

1951 *See* Hilary Hearnshaw, *Comparison of requirements of research ethics committees in 11 European countries for a non-invasive interventional study*, 328 BMJ 140 (Jan. 17, 2004), at http://bmj.bmjjournals.com/cgi/reprint/328/7432/140.pdf; Paul Glasziou & Iain Chalmers, *Ethics review roulette: what can we learn?*, 328 BMJ 121, at 122 (Jan. 17, 2004), at http://bmj.bmjjournals.com/cgi/reprint/328/7432/121.pdf.

1952 "To ensure the validity of multi-centre research, any change in the protocol should be made at every collaborating centre or institution, or, failing this, explicit inter-centre comparability procedures must be introduced; changes made at some but not all will defeat the purpose of multi-centre research." CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).

1953 See however Article 10b of the Ticino-Lsan, *supra* note 1925.

1954 "For example, a trial involving 51 centres needed over 25,000 pieces of paper, 62 hours of photocopying, and an average of 3.3 hours of investigator time for each centre." Glasziou & Chalmers, *supra* note 1951, at 122.

1955 The proposal was put forward in April 2003 by the GT StaR, which is the abbreviation for "Groupe de travail 'Standardisation des directives et formulaires de travail et Registres des études et des sujets de recherche'." GT StaR is an informal working group whose members come from the SAMS, from ethics committees and from the Swiss federal and cantonal authorities. *See Procédures simplifiées d'évaluation des projets de recherche multicentriques par les Commissions d'éthique de la recherche (CER)* [Simplified evaluation procedures for multicentric research proposals by ethics committees], at http://www.samw.ch/content/Formulare/F_EmpfApril03.pdf.

However, the existing mechanisms are insufficient to fully solve these problems. For a small country like Switzerland, allowing for up to 20 different REC reviews is certainly not efficient.

A better solution would be to have research sites and investigators go through a public accreditation procedure which would establish, once and for all, the kind of trials that they are authorized to perform.[1956] For example, a large university hospital would receive the authorization to perform all types of clinical trials, while the authorization granted to a small clinic would limit the number of subjects who can be enrolled and the types of permissible medical interventions (e.g., only low-risk procedures). Similarly, one could contemplate a system where experienced investigators would receive a license to perform all kinds of clinical trials, where less experienced researchers would be authorized only a more limited range of studies. This licensing process would then facilitate submission of multicentric protocols to a *single central* ethics committee holding jurisdiction over all Swiss sites.[1957] The central REC would then focus its analysis on the scientific and ethical aspects of the protocol. It would briefly verify that the application contains a copy of the necessary licenses/accreditations.

7.1.2.3. The investigator's application

As indicated above, it is the *investigator's responsibility* to obtain the REC's favorable opinion.[1958] Even though the protocol has been prepared by the sponsor, the investigator presents it to the REC.[1959]

The OClin lists the contents of the application submitted by the investigator to the REC.[1960] The file includes the protocol,[1961] the brochure,[1962] and all documents used to recruit the trial's subjects and to obtain their informed consent.[1963] If these documents exist in different languages, the REC should receive all versions.[1964] The advertisements (e.g., newspaper announcements, flyers posted in clinics) used to sign up subjects must also be submitted (see further on this issue subsection 8.1.3.).[1965]

1956 *See generally*, EFGCP, Interview of Peter Stonier, The EFGCP News, at 4 (Spring 2001).

1957 Switzerland had, until 2001, an optional central REC. It was terminated in the wake of the enactment of the 2002 federal system.

1958 Article 9.2 OClin.

1959 At the time the protocol is submitted to the REC, the investigator must have fully endorsed it.

1960 *See* Article 9.2 OClin.
See also section 3.1.2 (p.10) of ICH E6 itemizing a similar file content.
Compare with the checklist of the information that must be appended to the E.U. request for clinical trial authorization, see E.U. Guidance (Request), *supra* note 270, at 32 (Annex 1); *see also* module 2, *in* E.U. Guidance (Ethics Committee), *supra* note 270, at 18. Compare also with the very detailed list set forth by the Council of Europe in the Appendix to the COE Research Protocol.

1961 Article 9.2a OClin. See subsection 8.3.3.3. below. See subsection 6.2.1. above.

1962 Article 9.2.c OClin. *See* section 4.4.2 (p.13) ICH E6. See subsection 6.2.2. above.

1963 Article 9.2.b OClin. See subsection 8.3.3.3. below.

1964 *See* VanTx Report, *supra* note 148, at 19.

1965 Article 9.2.b OClin. The French text uses the word "*annonces*" which could be misleading in that it suggests a narrow reading. The ICH E6 Guideline refers to "subject recruitment procedures (e.g. advertisements)." Section 3.1.2 (p.10) ICH E6.

If subjects are paid or indemnified for their participation, the investigator must justify in writing the amounts given as well as the schedule and conditions of payments.[1966] The REC must also receive written information on the insurance coverage in case subjects suffer damage due to the trial.[1967] If an insurance contract is signed between an insurance company and – usually – the sponsor, the policy or at least its main provisions must be handed out. [1968] The REC should scrutinize the payments offered to subjects to make sure that they do not constitute an irresistible inducement to enroll (see for further development, subsection 8.6.4.2. below).[1969]

The application also describes the payments that the investigator is set to receive from the sponsor.[1970] As we saw in subsection 5.3. above, these payments have come under fierce criticism, especially if calculated on a per capita basis.[1971]

Since the REC has to make sure that the investigator holds the *appropriate qualifications* to run the trial,[1972] it must receive her detailed curriculum vitae.[1973] The investigator must hold a cantonal authorization to practice as a physician.[1974] (see subsection 5.2.5. above). Key members of the trial team under the supervision of the investigator must be listed in the application;[1975] they may have to provide their curriculum vitae too.

The ethics committee must be told where the *research facilities* are located.[1976] When the REC is directly attached to these research facilities, it can be assumed that it is familiar with them. On the contrary, when a REC operates for many different research facilities (e.g., the Geneva REC for private practice), it may ask for a more comprehensive description (e.g., number of beds, of nurses, medical equipment available, etc.). The extent of the information required depends on the risks triggered by the trial and on the need for subjects' hospitalization.[1977]

In the European Union, see E.U. Guidance (Ethics Committee), *supra* note 270, at 6 (requiring the investigator to also submit "procedures proposed for handling the responses to the advertisement(s)") and also at 21.

1966 Article 9.2.d OClin. See subsection 8.6.4. below.

1967 Articles 9.2.f OClin, and also its Article 10.2.l. *See also* WHO (Operational Guidelines), *supra* note 1379, at points 5.3.13&14 (p.9).

1968 See subsection 8.6.5.2.2. below.

1969 *See* Article 10.2.m OClin. The provision uses the French term "*indemnisation*" which could be misleading, since subjects often receive more than indemnification for their expenses or revenue losses. *See also* Article 6.3.(j) of E.U. Directive 2001/20/EC; WHO (Operational Guidelines), *supra* note 1379, at points 5.3.12 (p.8) and 6.2.3.10 (p.12).

1970 Article 9.2.d OClin. *See also* section 5.9 (p.23) of ICH E6.

1971 *See* Rao & Sant Cassia, *supra* note 960, at 36. *See generally* DuVal, *supra* note 1096, at 32.

1972 Article 10.2.d OClin. See *also* section 3.1.3 (p.10) of ICH E6.

1973 Article 9.2.g OClin. See WHO (Operational Guidelines), *supra* note 1379, at point 5.3.7 (p.7). *See also* VanTx report, *supra* note 148, at 22 (stressing the importance of having the investigator submit her curriculum vitae confirming that the investigator is indeed a licensed physician).

1974 Articles 8 and 9.2.g OClin.

1975 Article 9.2.g OClin.

1976 Article 9.2.h OClin.

1977 Certain multicentric trials are wholly decentralized in that each treating physician acts as investigator for his own group of usual patients; these patients may never go the hospital, but only visit from time to time the private office of their doctor.

The investigator will indicate in writing when the trial is supposed to *start* and when it should end.[1978] If the timing for the various procedures that will be performed on subjects is not already described in the protocol, the investigator will submit a draft calendar to the REC.

A comparison between Article 10.2 OClin (listing the documents reviewed by the REC) and Article 9.2 OClin (listing the documents submitted to the REC) reveals that some documents have been inadvertently omitted from the list of Article 9.2. This was, for example, the case of the contract between the sponsor and the investigator and between the sponsor and the CRO, which, until the 2004 revision, [1979] were only mentioned in Article 10.2.n OClin. [1980] Also not listed in Article 9.2 OClin, but in Article 10.2.k OClin, is the description of the medical follow-up offered to subjects once the clinical trial has been completed (e.g., with what drug they will then be treated, to whom they should direct health-related inquiries). [1981]

The investigator must tell the REC if the protocol or the study has already been submitted to another REC, and with which outcome.[1982] This information should be given whether this other REC received the protocol from the same investigator or from another party. Minor changes made to the protocol should not affect this obligation, since one of the goals of this Article 9.2.i OClin is to avoid forum shopping. Preferably, the investigator should also tell the REC if other protocols for the same compound – for example a phase II that preceded the actual phase III – were ever rejected by a REC. The investigator must reveal the conclusions reached by these other RECs (i.e., favorable or negative opinion); she should not hide the fact that a protocol was withdrawn before

---

1978 Article 9.2.h OClin. See further subsection 10.1.1. below. According to Swissmedic's basic form for submission of a clinical trial protocol (http://www.swissmedic.ch/files/pdf/Basisformular_F.dot), a trial starts with the recruitment of the first human subjects and ends with the last medical treatment or visit of the last human subject.

1979 *See, e.g.,* Sprumont & Béguin, supra note 134, at 899. *See also* section 4.9.6 (p.18) ICH E6.
However, a survey of clinical trials conducted by U.S. academic institutions on behalf of commercial sponsors found that the institutions' ethics committees (IRBs) often do not review agreements passed between sponsors and investigators. *See* Schulman et al., *supra* note 907, at 1335-1341. *See also* DuVal, *supra* note 1096, at 30-34.

1980 The same should hold if there is a data monitoring committee (DSMB): its contract should be provided, although Article 10.2.n OClin does not specifically refer to such committees. Contracts between the investigator's institution and the sponsor should also have been mentioned. Under the 2004 OClin revision, a new letter k at Article 9.2. now obliges the investigator to provide to her REC all agreements between the sponsor, the investigator and a CRO. Under the 2004 OClin revision, a new letter k at Article 9.2. now obliges the investigator to provide to her REC all agreements between the sponsor, the investigator and a CRO.

1981 On this topic, see subsection 8.6.2. below.

1982 Article 9.2.i OClin. *See also* WHO (Operational Guidelines), *supra* note 1379, at point 5.3.16 (p.9) (requiring submission of "all significant previous decisions" pertaining to the proposed study). See also point v. of the Appendix to the COE Research Protocol.
Although the necessity of such a rule seems obvious, for a long time, it was not mandatory under U.S. law. In 2002, proposals by the FDA to compel sponsors and investigators to provide such information to IRBs met with opposition from the pharmaceutical industry. *See* FDA (FAQ-IRB), *supra* note 1814, at question 26; FDA, Institutional Review Board: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews, Advance notice of proposed rulemaking, 67 Fed. Reg. 10,115 (Mar. 6, 2002), at http://www.fda.gov/OHRMS/DOCKETS/98fr/103102a.pdf; Letter of PhRMA to FDA (June 3, 2002) (Docket N° 01N-0322), at http://www.fda.gov/ohrms/dockets/dailys/02/Jun02/060402/80047a2e.pdf; Thompson Publishing Group, Drug, Device Groups Oppose Disclosure of IRB Decisions (Sept. 2002), at http://www.thompson.com/libraries/fooddrug/clin/samplenews/clin0209.html; letter of the Consortium of Independent Review Boards to the FDA (May 23, 2002), at http://www.fda.gov/ohrms/dockets/dailys/02/May02/052402/80046f06.pdf; OIG (Reform), *supra* note 877, at 7; OIG (Status), *supra* note 987, at 12.

decision by a REC. The OClin ought to compel investigators to report to RECs if the investigational compound or a related compound has ever been withdrawn from any market for safety reasons.[1983]

7.1.2.4. Information gathering process by the REC

RECs are not limited as to the range of information or documents they can request from the investigator.[1984] They can ask for information that is not held by the investigator (for example, information held by the sponsor or by a third party, such as the CROs or the insurance company).

According to Article 9.3 OClin, the REC may request an *external expert report.* How exactly this prerogative ties in with the possibility of inviting outside experts to assist committee members is not made clear in the OClin.[1985] A possible difference is that the external report must be paid for by the investigator (to be passed on to the sponsor), while the costs of the expert is borne directly by the REC (which may or may not pass it on to the investigator as part of the REC's fees). However, nothing seems to prevent both experts to perform essentially the same tasks.

The REC may – in accordance with its own internal regulations – decide to *hear the investigator* so as to obtain additional explanations.[1986] Seldom will it hear the sponsor, as the legal system is designed with lines of communication going from the investigator – not the sponsor – to the ethics committee.[1987] However, nothing forbids the REC from hearing a representative of the sponsor.

RECs should not just review the documents submitted by the investigator. Rather, they should assume an active role. It is a pity that the OClin does not encourage RECs to do so. For example, one or two REC members ought to be present when investigators inform subjects and seek their consent.[1988] If not, the REC should at least conduct sample audits of the consent process.[1989] The tangible presence of REC members is beneficial to all parties. Investigators are spurred to abide closely by the protocol and to comply with the commitments made before the REC. Subjects benefit from this additional protection as REC members may direct the investigator to improve the consent process, for example by providing more detailed information to subjects. Finally, the REC itself,

---

1983 In the United States, this information must be provided to the FDA as part of the IND. 21 C.F.R. § 312.23(a)(3)(iii) and (9)(iii) and also § 312.33(f).

1984 Article 9.3 OClin. *See also* Article 6.6 of E.U. Directive 2001/20/EC (admitting only a single request for additional information).

1985 See subsection 7.1.1.5. above.

1986 *See* section 3.2.5 (p.11) of ICH E6, which adds that the investigator must not participate in the deliberations of the ethics committee.

1987 *See* FDA, Sponsor-Investigator-IRB Interrelationship, Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators (1998 Update), at http://www.fda.gov/oc/ohrt/irbs/toc4.html [hereinafter FDA (Interrelationship)]; FDA (FAQ-IRB), *supra* note 1814, a question 30 ("FDA does not prohibit direct communication between the sponsor and the IRB, and recognizes that doing so could result in more efficient resolution of some problems.").

1988 In the United States, the right to attend the informed consent process is explicitly stated. *See* 21 C.F.R. § 56.109(f).

1989 See, for example, in the United States, UCSD-SOPP, *supra* note 485, at 108-109 (on the procedures governing protocol audits by IRBs).

by assuming a more active role, obtains a much needed practical feedback. REC members may for example realize that what seemed clear to them is simply not understood by subjects.

7.1.2.5. Assessment criteria

Once the REC has received a duly complete file, it reviews its contents. RECs are assigned the primary duty of protecting subjects participating in clinical trials.[1990] A second but closely related duty is to assess, chiefly on the basis of the protocol and the brochure, the scientific validity of the trial.[1991] The two responsibilities are linked since a scientifically flawed trial would pointlessly endanger the health of subjects;[1992] even if the trial were to entail strictly no health risks for subjects, the inconvenience borne by subjects would still be inadmissible. The system of essentially altruistic participation in research would be jeopardized if subjects were not protected against scientific fraud which they are not in the position to detect themselves. In other words, the reputation of research must be protected if the motivation of subjects to enroll in studies is to be preserved.

While the law gives ethics committees the responsibility of judging clinical trials, this does not obliterate the sponsor's and the investigator's primary responsibility to protect subjects. The failure of a REC to detect a flaw in the protocol does not excuse the sponsor and the investigator. Provided that the mistake was intentional or the result of negligence, the investigator will be held liable, in spite of the REC's endorsement (see further subsection 8.6.5. below). Hence, the investigator is well advised to conduct her own assessment of the trial according to criteria equivalent to those applied by the REC.

Although the REC's mission could be fairly encapsulated as an assessment of (probable and duly minimized) risks versus (anticipated and duly maximized) benefits (see subsection 7.1.2.5.5. below),[1993] the OClin appends a long list of tasks which are just variations on this main criterion.[1994] For example, Article 10.2.c OClin states that "the REC [should] verify … in particular the protocol." This control over the protocol is plainly part of the risks versus benefits assessment.[1995] What is more, Article 10.2 OClin mostly replicates the list of Article 9.2 OClin (the list of documents to be included in the file submitted by the investigator to the REC). It adds practically no guidelines as to how these documents must be evaluated. It would have been simpler and more logical to write in Article 10 OClin that the REC must verify each and every document of the file described in Article 9.

1990 Article 57.1 LPTh and Article 10 OClin.

1991 Article 57.1 LPTh and Article 10.1 OClin. *See also* Article 2 of the Nuremberg Code.

1992 Scientifically flawed research is forbidden even if the subject incurs absolutely no risk. *See* Principle 11 of the Council of Europe's R(90)3 Recommendation, *supra* note 115; CIOMS 2002 Guidelines, *supra* note 105, at Guidelines 1 and 2; CCNE N°2, *supra* note 57, at 9.

1993 *See* Part C.2 of the (U.S.) Belmont report, *supra* note 61.
See also in the European Union, Article 3.2.a of the Directive 2001/20/EC.

1994 *See* Article 10.2 OClin. This provision is almost identical to Article 6.3 of the European Directive 2001/20/EC. For a more detailed list of criteria recommended by the WHO, see WHO (Operational Guidelines), *supra* note 1379, at chapter 6.2 (p.10-13). *See also* COREC, *supra* note 1379, points 9.13 to 9.18 (p.24-27).

1995 For example, the protocol describes the study's objective, the expected benefits, the precautions taken to minimize health hazards, as well as the residual risks for subjects.

7.1.2.5.1. Scientific validity

As just mentioned, RECs must verify that the submitted study (as described in its protocol and other documents) is *scientifically legitimate*. Scientific flaws in a clinical trial make it unethical. Such a trial cannot be endorsed by the REC,[1996] unless and until its defects are corrected.

A study can be scientifically flawed in several ways: The hypothesis underlying the study may be absurd; the selected intervention may be absurd; the outcome measurements may be inappropriate (e.g., blood pressure is measured before meals, when it should be taken after); the care given to subjects may be unsuitable (e.g., only drug D is administered to cancer patients but no pain relievers). The REC should also verify that the study is designed so as to yield statistically reliable and significant results (e.g., the sample has exactly the right size to yield statistically significant conclusions).[1997]

Unfortunately, RECs often lack the necessary technical expertise to do a comprehensive review of the trial's scientific validity.[1998] Given that clinical research aims to build on the most advanced knowledge, it is unrealistic to expect that REC members truly master the underlying science. Moreover, REC members will only read short summaries (probably prepared by the sponsor and/or the investigator without any peer review) of prior studies on animal or human models. Few of them will take the time to go through all the relevant medical literature. The result is that many RECs review the trial with significantly less knowledge of the underlying science than the investigator.

7.1.2.5.2. Relevance

For a trial to be scientifically sound, it must be more than just scientifically correct, it must also be *relevant* and, to a certain extent, warranted. A typical case of irrelevance is where the same study has already been done and confirmed and there is no reason to repeat it.

Regrettably, an ethics committee cannot go much further than this (i.e., rejecting duplicative studies). It will not reject a trial simply because it feels that the research is uninteresting or ought to be given low priority compared to other more important studies. For instance, a REC cannot rebuff a hair loss drug study on the ground that the sponsor should spend its money in pursuit of worthier objectives. For an analogous reason, RECs struggle with phase IV trials because their purpose may have more to do with marketing than science (see subsection 6.1.4.2. above).[1999] The best that RECs can do in such circumstances is to insist that the risks faced by subjects be truly minimal.[2000]

1996 *See* SPRUMONT, *supra* note 16, at 90.

1997 *See* subsection 6.3.10.1. above.

1998 *See* SPRUMONT, *supra* note 16, at 91.

1999 *See* Peter Wise & Michael Drury, *Pharmaceutical trials in general practice: the first 100 protocols*, 313 BMJ 1245-48 (Nov. 16, 1996), at http://bmj.com/cgi/content/full/313/7067/1245 (the study analyzed the first 100 protocols received by the ethics committee of the Royal College of General Practitioners).

2000 *See* paragraph 18 Helsinki Declaration.

7.1.2.5.3. Assessment of risks

The REC must evaluate the risks in a three-step process: first, verify that risks that can be *removed or minimized* have indeed been eliminated and reined in; then, understand the *residual* risks; finally, grade them. This evaluation is based on safety information provided by the investigator. The investigator is supposed to conduct a thorough evaluation of safety for all products used and all procedures performed. She cannot rely simply on assurances provided by the sponsor, but must complete her own independent inquiry. This entails accessing and reading the available literature, including in some circumstances articles dating back several years or published in foreign countries.[2001] The depth of her probe depends on the circumstances, but the less apparent the safety profile of the drug, the more detailed her investigation should be. While the REC is not expected to independently verify whether the investigator duly cited all available references, it should nonetheless make sure that it has enough data to assess the risks. In some situations, the REC may decide that the available information is insufficient to initiate trials on humans, and that additional animal testing should be conducted first.

The term "risks" here includes both those that are known to occur with certainty (e.g., known side effects) and possible threats. The REC must evaluate the odds of the risk materializing. Risks also encompass inconveniences (e.g., pain, tiredness). Risks may pertain to the investigational drug, the control product, or the procedures carried out (e.g., biopsy).

Each risk should be examined separately. Most clinical trials involve many different components (e.g., a succession of medical procedures), each with a different degree of risk. While the risk attached to one procedure may be acceptable, this may not be the case for another procedure.[2002]

Risks to be weighed are normally those that *befall subjects*. Whether risks that affect wholly different groups should be considered is subject to debate (e.g., social risks of an AIDS trial that would affect all seropositive homosexuals). Of course, studies that involve contagious compounds must weigh the risk for people of incurring secondary infections. For example, in a proposed pediatric clinical trial of a smallpox vaccine, exclusion criteria included pregnancy, immune system diseases, eczema in any member of the subject's family.[2003] More controversial is genetic research. A study may discover a relationship between a gene and a given condition (e.g., schizophrenia). That finding may not only affect the subject himself, but all people, in particular family members, having that same gene. Some commentators hold that RECs should be mindful of risks that could affect the community.[2004] Others consider that RECs' role is to protect research subjects only. FDA regulations state that an "IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the pos-

---

2001 In the Ellen Roche case, relevant safety risks were only disclosed in publications that dated back to the 1950s. *See* John Hopkins Internal Committee Report, *supra* note 378.

2002 *See* NBAC (Issues in Research), *supra* note 244, at 3.

2003 *See* the Dryvax protocol, *supra* note 1379, at 18; Human Sujects Consent Form for the Dryvax clinical trial (Permission by parents), at http://www.hhs.gov/ohrp/dpanel/parent.pdf.

2004 For example, according to guidelines of the University of California at San Diego, "[t]he IRB will not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility." UCSD-SOPP, *supra* note 485, at 34.

sible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility."[2005] I tend to agree.

Finally, RECs must evaluate the seriousness of the risk. Various laws attempt to grade the risks according to their severity. "Minimal risk"* is a commonly encountered notion, although different countries define it differently.[2006] The Council of Europe's draft protocol on biomedical research introduces the additional notion of "acceptable risk."[2007] The United States also uses the concept of "minor increase over minimal risk."[2008] U.S. practice tends to ascribe a risk category to each and every procedure (e.g., PEN scans, venupuncture); this is done in the hope to simplify the work of IRBs and accelerate the submission and review of protocols.[2009]

7.1.2.5.4. Assessment of benefits

In parallel with the risk assessment, the REC must conduct a review of the *anticipated benefits* associated with the trial. These benefits can consist in a personal therapeutic gain for the individual subject or in the progress of scientific knowledge for the whole patient community.

In nontherapeutic clinical trials (e.g., a phase I trial on healthy volunteers), the benefits to be assessed are – by definition – those that accrue to society through future medical advances.[2010] Payments made to volunteers do not qualify as "benefits" to be taken into account by the REC.[2011] Similarly, ordinary health services extended to healthy or sick subjects (for example, a medical check-up) do not constitute a "benefit."[2012] *Follow-up* medical care after the completion of the trial, including follow-up supplies of the investigational drug, is not deemed "benefit."[2013] Finally, should not be held as benefits ambiguous advantages such as "diversion from routine, the opportunity to meet with other people and to feel useful and helpful";[2014] there should be other, less risky, ways to achieve these pleasant feelings.

In therapeutic trials, both individual and societal gains are taken into consideration. The likelihood of each type of benefit must be assessed. The need to treat ten subjects to

---

2005 21 C.F.R. 56.111(a)(2).

2006 The Swiss LPTh refers to minimal risk at Article 55.2.b LPTh. For a Swiss definition of "minimal risks" see Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 315.
For the U.S. definition, *see infra* note 2062.

2007 Under Article 6.2 of the COE Research Protocol, nontherapeutic research should entail "no more than acceptable risk and acceptable burden for the research participant"; see also its Article 23.3 on the use of placebos and its Article 17 on "minimal risk."

2008 For instance, nontherapeutic pediatric clinical trials are admissible only if the level of risk does not exceed this threshold (i.e., minor increase over minimal risk). *See further* NBAC (Mental), *supra* note 1250, at chapter IV (criticizing the tripartite distinction).

2009 *See* however NBAC (Mental), *supra* note 1250, at chapter IV.

2010 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 8 (commentary).

2011 American IRB sometimes forget this. A survey of IRB chairpersons found that 10% of them consider payments to parents of pediatric subjects to constitute a direct benefit! *See* Seema Shah et al., *How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research?*, 291 JAMA 476, at 478 and at 480 (Jan. 28, 2004), at http://jama.ama-assn.org/cgi/reprint/291/4/476.pdf.

2012 *See id.* at 480.

2013 *See* NBAC (Developing), *supra* note 254, at 60.

2014 NBAC (Mental), *supra* note 1250, at chapter IV.

achieve a positive response in one of them is a fact that must be duly taken into account. In trials testing preventive drugs, the likelihood of suffering one day from the disease must also be considered. Indeed, administering a (presumably) effective vaccine to 1000 subjects when the odds of a natural infection is only 1 in 1000 carries less benefits than if the odds were 10 in 1000.

RECs must appreciate the magnitude of the expected benefit. Similarly, the duration of the benefit (e.g., improvement during one week or during six months) is a relevant factor. Relevant therapeutic benefits are the ones that *exceed* those available from alternative or standard treatments.[2015] If the investigational drug only claims to do as well as an existing drug, there is no personal benefit for the patient; moreover, knowledge (a social benefit) is not much advanced.[2016]

7.1.2.5.5. The balancing of risks and benefits

Once duly maximized benefits and duly minimized risks have been assessed, the REC must weigh one against the other.[2017] The risk/benefit assessment is made essentially from a *scientific* perspective. At this stage, ethical analysis has little to add. Generally, if the risk/benefit ratio is medically acceptable, this ratio is also ethically acceptable.

Obviously, there are no mathematical tools for weighing risks against benefits.[2018] Even the basis on which a decision is reached is almost always incomplete: Neither the investigator, nor the REC can know all the risks at this stage.[2019] The knowledge of adverse side effects may be sketchy or based only on animal studies; new serious but utterly unexpected risks may emerge. The benefits also are difficult to anticipate; they may be so low as to become fully unreliable (e.g., what is the actual probability of a compound turning into a marketable drug?).[2020].

Even though there are no mathematical formula for balancing the risks and benefits, there are principles to lead the REC's judgment. The most important ethical rule is that subjects' interests must always take *precedence* over the interests of science, medical

---

2015 Even more broadly, the benefits and risks taken into consideration should be those that go beyond those that would exist regardless of participation in the research. See, in the United States, 21 C.F.R. § 565.111(a)(2).

2016 The question that arises is whether benefits can be purely economic. If the me-too drug does not improve treatment options, it may, in order to compete with the already approved product, be sold at a lower price. The incumbent drug manufacturer may in turn lower its own price so as not to lose market shares. Thus, the community gains by spending less for health care. Is that a benefit that RECs can take into consideration? Although this would stretch a bit the notion of benefits, one must be realistic. Given the number of me-too drugs that are approved each year after going through clinical trials, it is manifest that RECs are not stopping these trials due to lack of benefits. It would be disingenuous to pretend that a potential health benefit has been each time credibly demonstrated (i.e., the sponsor pretends nonetheless that its me-too drug will be more effective in certain patient groups). It is true however that research sometimes yields unexpected results (e.g., the Viagra case). Therefore, it can never be totally excluded that a drug, including a me-too, will show startling activity and therapeutic benefits. Yet, ethics committees should not simply rely on this remote expectation to gauge anticipated benefits.

2017 This risk-benefit analysis is abbreviated RBA. *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 199.

2018 *See* NBAC (Issues in Research), *supra* note 244, at 13; BEAUCHAMP & CHILDRESS, *supra* note 16, at 194.

2019 To see how ethics committees reason in sensitive cases, see for example the meeting minutes of the IRB asked to approve the Dryvax smallpox pediatric clinical trial. IRB Meeting on July 16, 2002 and on July 30, 2002, at http://www.hhs.gov/ohrp/dpanel/min716.pdf and http://www.hhs.gov/ohrp/dpanel/min716.pdf.

2020 The odds for a phase I trial are estimated at one chance in 10. *See, e.g., supra* note 708.

progress and society in general.[2021] Even a study which is vital for humanity cannot be justified if the subjects incur undue risks. In other words, the ends do not justify the means;[2022] research subjects should be treated as persons, and not as objects.[2023] This entails that RECs should primarily balance *personal* risks and *personal* benefits. Significant personal risk cannot be offset only by purely societal benefits. This principle also entails that an unethical experiment does not become ethical just because its results are to save thousands of lives; on the contrary, if the risks for the subjects are excessive, an unethical experiment remains unethical.[2024]

While this principle is appealing on paper, physicians have sometimes had trouble overcoming their desire to act for the greater good of humanity and to accept what they view as patients' egoism. They simply see clinical trials as a way to save future lives.[2025] Nontherapeutic trials on healthy volunteers illustrate the dilemma caused by the divergent interests of science, society and subjects.

While scientific value cannot excuse overly risky research, *unexciting* scientific objectives can be taken into consideration in the risk/benefit assessment. For instance, the level of risk (e.g., nausea) acceptable for a hair loss study is much lower than the one permissible for a cancer study, even if in both cases the trial is conducted on healthy volunteers. Ethics committees should also take into account the number of subjects exposed to a risk. While it may be acceptable to expose 10 AIDS patients to a severe risk in the hope that the investigational vaccine will show efficacy against AIDS, it would be unthinkable to expose hundreds of subjects right away.

Finally, RECs need to take into consideration the "last-chance" factor. When an investigational compound represents the last hope of dying patients, it may be unfair to deny them this hope, even if the benefits appear very slight and the risks are undoubtedly significant.[2026] Yet, the REC must also make sure that these desperate and vulnerable subjects are not exploited in faulty studies (see subsection 8.5.3. below). The REC will have to strike the "right" balance – a very thorny assignment.

7.1.2.5.6. Appropriate information given to subjects

While the REC makes a primary assessment of the risk/benefit ratio, it must further verify that subjects too are in a position to make their own assessment. Hence, the REC must make sure that subjects are given sufficient information to evaluate the entire trial.

2021 *See* subsection 6.3.5.1.1. above.

2022 *See* Beecher (Myth), *supra* note 103, at 34-35; Beecher (Guiding), *supra* note 103, at 158; Angell (Publication), *supra* note 898, at 277 and 278; SPRUMONT, *supra* note 16, at 20-21 and at 50.

2023 On the philosophical underpinning, see BEAUCHAMP & CHILDRESS, *supra* note 16, at 350-51. *See also* NBAC (Issues in Research), *supra* note 244, at 2.

2024 The lead experiment conducted by the John Hopkins University is a good example of unethical research conducted "for the greater good" of society, but not to the benefit of the enrolled subjects, in that case healthy children. *Grimes*, 782 A.2d at 815.

2025 *See, e.g.*, Jeffrey S. Tobias, *BMJ's present policy* (*sometimes approving research in which patients have not given fully informed consent) is wholly correct*, 314 BMJ 111-14 (1997), at http://bmj.com/archive/7087ed2.htm.

2026 For S. J. L. Edwards et al., "RECs should not generally be protective or paternalistic by rejecting research that poses risk to people who are competent to decide for themselves." *Research ethics committees and paternalism*, 30 J. MED. ETHICS 88, at 88 (2004), at http://jme.bmjjournals.com/cgi/reprint/30/1/88.pdf. *See also* SPRUMONT, *supra* note 16, at 87.

Arguably, REC's ethical review consists in the evaluation of a clinical trial from the point of view of a hypothetical subject, but with the added insight provided by full access to all the details of the study as a REC member. Ethics can thus be equated with *fairness* (from the point of view of subjects).[2027] A trial is ethically legitimate if subjects find it fair. Fairness should only yield to the most pressing scientific necessity (e.g., it is imperative to conduct a double-blinded trial in order to avert bias and to distinguish placebo reactions[2028]).

Each REC member should imagine himself in the position of the subject: He should ask himself "what would I want to know before deciding whether or not to participate?" REC members should also compare the information they received and found relevant to appraise the trial with that given to subjects for this purpose. Imagining oneself in the position of a subject also helps identifying other ethical qualms. For instance, if the protocol says that subjects who start taking other medications are automatically excluded, a subject may feel this is an unfair punishment for having taken a single aspirin against a headache. Similarly, "role-playing" exercises can suggest *improvements* to the trial design.

RECs should also act as a *spokesperson* for subjects. Since prospective subjects are too dispersed to successfully negotiate with sponsors and investigators improvements to study design, the REC ought to conduct this negotiation on their behalf. To find out what improvements the subjects would want to see in clinical trials, REC members should take the time to meet with either prospective or former subjects.[2029]

7.1.2.5.7. Financial relationship between the sponsor and the investigator

According to Articles 9.2.d and 10.2.m and n OClin, RECs should review payments ("*indemnisation,*" "*finanziellen Entschädigungen,*" "*indennità*") made by the sponsor to the investigator (see also subsection 8.6.4.1. below). The first two provisions place the focus on the sponsor-investigator relationship, potentially omitting conflicts of interest involving the investigator's *institution* (e.g., an academic hospital). The provisions also leave out conflicts related to equity ownership, which may precede the clinical trial at issue; for example, the investigator may have invested in securities issued by the pharmaceutical sponsor. The conflict may relate to patent or other rights in the tested product that the investigator holds independently from any sponsor's action.

The OClin provisions do not invite RECs to inquire about the source of funding for each aspect of the trial.[2030] Even in clinical trials where the investigator herself receives no payment, a pharmaceutical company may be offering other forms of support, such as free supply of all treatments administered in the trial.

2027 I prefer here the word "fairness" to "ethics," as the former has a more clearly accepted signification that the second.

2028 On the choice of control treatment, see subsections 6.3.3. and 6.3.5. above. However, a trial is not fair to subjects if it is known in advance that one treatment arm is better than the other.

2029 "Although many IRBs would like to, very few oversee the consent process or solicit feedback from subjects. … Seldom, we found, do the IRBs seek out feedback from human subjects or their families, examine the few complaints that they do receive to determine if they reflect broader, systemic problems, or initiate probing inquiries – for example, to determine how the informed consent process is actually working." *See* OIG (Reform), *supra* note 877, at 6, respectively at 8-9.

2030 *See* HHS Interim Guidance, *supra* note 938, at 4.2.

Consequently, a general provision instructing REC to review *all* conflicts of interest would be more appropriate. Furthermore, guidelines articulating the principles presiding over this review would be helpful. In their absence, reference to foreign guidelines, in particular U.S. ones, is helpful.[2031]

RECs must make sure that the financial aspects of the sponsor-investigator relationship cannot result in harm for the subjects.[2032] Ideally, RECs should go one step further and take the necessary measures to preserve the good reputation of clinical research.

It should go without saying that REC minutes must record both the conflicts of interest that were identified and the solution found by the REC. If the REC has advocated some specific measures to address the conflict (e.g., a lower payment to the investigator), it should verify that its instructions were indeed carried out before giving its final "green light."

Swiss ethics committees affiliated with academic research centers may want to further review payments by sponsors to make sure that they suffice to cover the costs of the trial borne by the centers.[2033] For clinical trials conducted at the Geneva University Hospitals (HUG) on behalf of pharmaceutical sponsors, the REC verifies that all related costs are borne by the pharmaceutical sponsor. The only exception is for costs of standard care that would be provided to subjects anyway: These costs are borne by the HUG and then passed on to the subject's social insurance company. On the contrary, costs that are made necessary by the trial cannot be charged to the HUG's general expense funds.[2034] Interestingly, sums paid by the sponsor for clinical trials conducted at the HUG do not go to the investigator herself,[2035] but to the investigator's service.[2036] Conflicts of interest are thus minimized.

7.1.2.5.8. Review of recruitment procedures

RECs should scrutinize the recruitment procedures. They should make sure that the selection criteria are fair (see further on this issue, subsection 8.1.6. below). No groups should be excluded from enrollment unless there is an imperious scientific reason. Safeguards should be set up to protect vulnerable groups rather than excluding them outright.[2037]

RECs must review the advertising material used for recruitment purposes.[2038] This review is parallel to that conducted by Swissmedic[2039]. There are presently no prohibi-

---

2031 *See id.* at chapters 3 and 4.

2032 *See, e.g.*, paragraph 13 Helsinki Declaration.

2033 *See* VanTx Report, *supra* note 148, at 21.

2034 See Article 49.1 of the Federal law on sickness insurance of Mar. 18, 1994; in French: "*Loi fédérale sur l'assurance-maladie*"; abbreviated (from the French): LAMal; RS 832.10; at http://www.admin.ch/ch/f/rs/8/832.10.fr.pdf. *See also* VanTx Report, *supra* note 148, at 20.

2035 Interview with Bounameaux, *supra* note 1718.

2036 *Id.*

2037 On the participation of vulnerable subject populations, see subsection 8.5. below.

2038 Article 9.2.b OClin. The VanTx Working Group insisted that this requirement be specified in the Swiss legislation. *See* VanTx Report, *supra* note 148, at 19.
See also WHO (Operational Guidelines), *supra* note 1379, at point 5.3.8 (p.8).

tion or restriction against advertisements for clinical trials. However, advertisements that promote the drug itself are subject to severe limitations;[2040] sponsors must therefore stay clear of advertising the drug itself.[2041] Moreover, *public* advertising to recruit research subjects (e.g. TV spots) is frowned upon.[2042] Many would like to restrict its use to last resort situations, in particular when recruitment through classic channels is not possible.[2043] This would, for example, be the case of studies for rare or self-medicated diseases;[2044] phase I studies with healthy volunteers could also be advertised.[2045]

While the law itself does not regulate the contents of the ads, ethics committees can control them and even ban them.[2046] The REC's review aims first at verifying that the ad is truthful and in no way misleading.[2047] Advertisements should clearly indicate that the study involves first *scientific* research and not therapeutic treatment, and that the tested product has not been approved by the authority because it is at an investigational stage.[2048] In other words, potential subjects should not be led into believing that they will receive an individualized and riskless therapy. Ads that stress payments made to the subjects or free health care can also be deemed misleading or coercive.[2049] The ad may mention that it was approved by an ethics committee.[2050] A Swiss working group

---

In the United States, although IRBs have the authority to review recruitment methods, they are often uneasy about exercising this power. *See* OIG (Recruiting), *supra* note 815, at 4 and 27. The FDA has issued an Information Sheet to guide IRBs in their review of advertising material. *See* FDA, Recruiting Study Subjects, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators (1998 Update), at http://www.fda.gov/oc/ohrt/irbs/toc4.html [hereinafter FDA (Recruiting)].

2039 Under the intercantonal system, see Kleist (23), *supra* note 798, at 657.

2040 Drugs that lack a marketing authorization cannot be advertised at all. Approved prescription drugs can be advertised only to health care professionals, but not to the public.

2041 Ads used to recruit research subjects should preferably not mention the name of the drug and its manufacturer, especially if it is already available on the market. *See also* Kleist (23), *supra* note 798, at 656. In the United States, see 21 C.F.R. § 312.7(a); FDA (Recruiting), *supra* note 2038.

2042 *See, e.g.,* question by Geneva Parliament Member Christian de Saussure (Nov. 18, 1999), and the answer provided by the Geneva government Council member Guy-Olivier Segond, (Nov. 19, 1999), at http://www.geneve.ch/grandconseil/memorial/data/540301/52/540301_52_partie7.asp and http://www.geneve.ch/grandconseil/memorial/data/540301/55/540301_55_partie7.asp.

2043 *See, e.g.,* Amstad (Suche), *supra* note 425, at 2218.

2044 *See, e.g.,* GT StaR, *Rekrutierung von Versuchspersonen mit Inseraten, Vorschlag für Empfehlungen*, 83(42) BULLETIN DES MÉDECINS SUISSES 2219 (2002), at http://www.saez.ch/pdf/2002/2002-42/2002-42-1030.PDF (page 4) [hereinafter GT StaR (Inserat)].

2045 *Id.*

2046 In the United States, see for instance, FDA (Recruiting), *supra* note 2038 ("No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic, or device."); OIG (Recruiting), *supra* note 815, at 21; UCSD-SOPP, *supra* note 485, at 100.

2047 A U.S. agency warned that recruitment ads are often misleading as they stress the benefits over the risks. Advertisements portray the study (the word clinical trial is rarely used) as a promising new treatment. They invite interest with expressions such as: "are you tired of suffering from condition XYZ." They may highlight the fact that the "treatment" is provided free of charge. *See* OIG (Reform), *supra* note 877, at 4; OIG (Reviewing), *supra* note 1187, at C-1 to C-3.

2048 "Advertising … should not use terms such as 'new treatment,' 'new medication' or 'new drug' witout explaining that the test article is investigational. A phrase such as 'receive new treatments' leads study subjects to believe they will be receiving newly improved products of proven worth." FDA (Recruiting), *supra* note 2038.

2049 *See* FDA (Recruiting), *supra* note 2038 ("Advertisements may state that the subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type."). *See also* GT StaR (Inserat), *supra* note 2044, at 2219.

2050 The HUG-REC asks that advertisements mention the fact that the research has been approved by an ethics committee. Interview with Bounameaux, *supra* note 1718.

composed of authorities and pharmaceutical firms ("AG StaR") has listed the minimal content of advertisements.[2051] Aside from what has already been mentioned above, the ads should indicate the main inclusion and exclusion criteria. There should be a reference to the fact that collected data will be kept confidential.[2052] Initial contact should preferably be made by telephone and not by mail. There should be no reference to the firm manufacturing the therapeutic products under study. If initial contact with prospective subject is made through a call center, the AG StaR asks that RECs review the center's procedures.[2053] In particular, RECs should have the list of questions that subjects will be asked.

7.1.2.5.9. Review of publication policies

It has been proposed that ethics committees should secure commitments from the sponsor and the investigator to fully publish the study results, even if negative or adverse to the sponsor's drug candidate (see also subsection 10.4.1. below).[2054] This is not explicitly mandated by the OClin; however, publication is one of the issues mentioned by the checklist used by RECs and Swissmedic to assess clinical trials.[2055]

Publication policies are extremely important: If the study's findings are not divulged, another group of researchers could initiate a similar trial, not knowing that the scientific question has already been answered. This would needlessly endanger another group of research subjects. The expectations of the initial subjects to contribute to medical progress would be deceived. Moreover, medical science would be stalled since researchers would be unable to build upon the success or the failure of that study.

Hence, the REC should ask when the trial will give rise to publications. It should make sure that the investigator retains freedom to publish her results and the sponsor will not hamper her ambition. The REC should review possible limitations to the investigator's freedom (e.g., a delay to allow the sponsor to file for additional patents). To encourage publication, ethics committees could insist that all new studies be listed on a public register.[2056]

2051 *See, e.g.,* GT StaR (Inserat), *supra* note 2044, at 2219.

2052 When a prospective subject is not enrolled in the study, the data already collected about him is to be destroyed. *See, e.g.,* GT StaR (Inserat), *supra* note 2044, at 2219.

2053 *See id.*

2054 *See* Howard Mann, *Research ethics committees and public dissemination of clinical trial results*, 360 LANCET 406 (Aug. 3, 2002) (underscoring that publication of study abstracts is not sufficient to disseminate knowledge). See *also* WHO (Operational Guidelines), *supra* note 1379, at point 6.2.1.8 (p.10). In Switzerland, see also the results of 1988 survey commented by Ummel (1990), *supra* note 74, at 55 (whereby only a minority of RECs controlled whether clinical trial results were ultimately published).

2055 See point 3.8 of the checklist. This checklist is not a legally binding document, but appears to have the support of Swissmedic; it is available at http://www.samw.ch/content/Dokumente/f_Checkliste%2012_11_03.pdf.

2056 *See* Drummond Rennie, *Fair Conduct and Fair Reporting of Clinical Trials*, 282 JAMA 1766 (Nov. 10, 1999), at http://jama.ama-assn.org/cgi/reprint/282/18/1766.pdf [hereinafter Rennie (Fair Conduct)].

7.1.2.6. The vote

Once all members have completed and discussed their analysis of the application, the REC votes. RECs have only 30 days to reach a decision once they have received the complete file from the investigator[2057]. Although this deadline is postponed while the REC is waiting for complementary information, including as the case may be the external expertise report,[2058] it remains quite short.[2059]

For the REC's vote to be valid, at least five of its members must take part in it.[2060] Proxy votes are not permitted, at least not to meet the quorum.[2061] The OClin does not contemplate expedited reviews with more lenient quorum requirements.[2062] Additionally, for the quorum to be met, Article 32 OClin requires that the REC's composition (at the time of the vote) be balanced under Article 30 OClin.[2063] How strictly this requirement must be construed is subject of discussion, as we saw before. Should there be the exact same number of physician/non physician, health professionals/lay members, men/women? If absolute parity is not imperative, how far away from it can the REC go? Will a decision taken by four men and just two women be held invalid for failure to reach the quorum? Moreover, Article 32 OClin refers to Article 30 in general, whereas only paragraph 3 of Article 30 contains an explicit "balancing" requirement. Hence, it is unclear whether the quorum would be met if the biometry expert or the unaffiliated

---

2057 Article 11.1 OClin.
In the European Union, ethics committees have 60 days; Article 6.5 of the Directive 2001/20/EC. In the United States, the deadline is also of 30 days. The ICH E6 Guideline includes no deadline, referring only to a "reasonable time." Section 3.1.2 (p.10) of ICH E6.

2058 Article 11.2 OClin.

2059 *See generally* Truniger et al., *supra* note 1337, at 2401.

2060 Article 32.1 OClin. *See* DHA (Ordinance Comments), *supra* note 522, at 48.
The rules about the quorum seem not always to be followed. *See* in the United States, FDA Warning Letter to Dan F. Ausman, *supra* note 1848; FDA warning letter to Terry Fredeking, *supra* note 1848; FDA warning letter to Matthias McGuire, *supra* note 1848.

2061 According to Article 32.1 OClin, the five members must be "present." Although meetings through videoconferences or other similar technical means should be allowed, REC decisions taken without prior oral discussions (e.g., proxy votes or telephone polling) among REC members should not be valid. *See however* Article 11b Bern Ordinance 811.05, *supra* note 1949 (allowing the cantonal REC to reach its decision by way of circulation if the decision is unanimous and no members oppose this procedure).

2062 In the United States, expedited reviews are permitted when the research involves no more than minimal risks and belongs to a category of studies for which the FDA has approved such accelerated process. *See* 21 C.F.R. § 56.110(b). *See also* 46 Fed. Reg. 8,392 (Jan. 26, 1981). "Minimal risk" is defined as a situation where "the probability and magnitude of harm or discomfort anticipated in the research are no greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 21 C.F.R. § 50.3(k); 45 C.F.R. § 46.102(i). When the level of risk is unknown, it is never minimal. *See also* UCSD-SOPP, *supra* note 485, at 76-81.
Compare with the essentially similar Swiss definition in the glossary (under risk) of the GCPs accompanying the (former) IOCM 1995 Regulation. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 9 (commentary).

2063 Article 32.1 OClin ("*et que la composition des membres est équilibrée conformément à l'art.30*" "*und die Zusammensetzung im Sinne von Artikel 30 ausgewogen ist*," "*e la composizione è equilibrata ai sensi dell'articolo 30*"). The Swissmedic's form that RECs must use to report their decision asks for information about the composition of the REC, including the profession and sex of each member having taken part in the vote.
Under the former IOCM regulations, the quorum requirements were less severe since the presence of just one non-physician was enough; Article 8.1 of the former IOCM regulation on pharmaceuticals at the stage of clinical trial.
In the United States, see 21 C.F.R. § 56.108(c).

member is absent.[2064] Unmistakably, the rule is treacherous. However, as we will see in the next subsection, there is little or no prospect for challenging a given REC decision on the ground that the quorum was not met.

The OClin does not prescribe any *majority threshold* by which RECs must reach their decisions, and neither does the Geneva Regulation. Ideally, decisions should be adopted unanimously.[2065] The fact that one or more REC member want to reject the application can be a warning sign that there are unaddressed ethical issues. However, since Swiss law does not impose consensus decisions, decisions adopted by a majority of the members are acceptable.[2066]

The minutes of the meetings should at least briefly relate the discussions that preceded the vote.[2067] These minutes prove that the IRB truly evaluated the submitted file.[2068] There have been proposals in the United States to make minutes of IRB meetings accessible to the public.[2069] This is a good idea.

Presently deliberations and decisions of ethics committees are kept confidential,[2070] although the OClin does not explicitly impose this confidentiality. Article 321bis of the Swiss Penal Code ("CP") hardly constitutes a sufficient legal basis to enforce confidentiality, given that RECs are *not* learning protected secrets in connection with their own research activity (see subsection 8.6.3. below).[2071] It is doubtful that Article 61 LPTh *alone* suffices to establish RECs' confidentiality obligation. Rather, there should be a provision in the OClin stipulating that REC members and their staff must protect the con-

---

2064 In the United States, see FDA (FAQ-IRB), *supra* note 1814, at question 16.

2065 *See* SAMS 1997 Guideline, *supra* note 110, at point C.4. at 8; Truniger et al., *supra* note 1337, at 2401. See also the results of 1988 survey commented by Ummel (1990), *supra* note 74, at 52 (whereby a majority of RECs took their decision by unanimous vote).

2066 *See, e.g.,* Article 9.1. of the Regulation of the Canton of Ticino on the ethics committee of July 2, 2002, (Regolamento del Comitato etico), at
http://www.ti.ch/DSS/DSP/SezS/ComEC/PDF/RegolamentoCdS_CE.pdf.
In the United States, a positive vote by the majority of members present is sufficient. 21 C.F.R. § 56.108(c); 45 C.F.R. § 46.108.b. However, some U.S. IRBs have imposed a higher threshold; for example, IRBs at the University of California at San Diego must turn down research projects if there is "more than one dissenting vote among committee members present." *See* UCSD-SOPP, *supra* note 485, at 27.
See WHO (Operational Guidelines), *supra* note 1379, at point 7.6 (p.14); COREC, *supra* note 1379, at point 9.20.g (p.28).

2067 *See* SAMS 1997 Guideline, *supra* note 110, at point C.4 at 8 (adding that minutes should be communicated to REC members).
In the United States, FDA regulations specify that minutes must be sufficiently complete to "show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution." 21 C.F.R. § 56.115(a)(2). For an example of information that must be appear in the IRB's minutes, see UCSD-SOPP, *supra* note 485, at 10.

2068 In the action filed by the U.S. firm SSKR&P in the case of Robertson v. McGee, the plaintiff criticized the IRB for not documenting its review process. It also charged the IRB with limiting its review to the protocol and the consent forms, with other documents not being given proper consideration. The complaint can be viewed at http://www.sskrplaw.com/gene/robertson/complaint-new.html.

2069 *See* OHRP (Children), *supra* note 1636, at 15.

2070 *See* SAMS 1997 Guideline, *supra* note 110, at point C.4. at 8.

2071 According to Article 321bis.1 CP, the secret must have been learned in the context of the person's research activity in the field of medicine or public health.

fidentiality of data identifying research subjects or containing commercial trade secrets.[2072]

7.1.2.7. The form of the decision

Ethics committees' decisions should be recorded in writing.[2073] RECs should provide grounds for their decisions, at least when they are negative.[2074] This allows the investigator to submit a new revised application that will meet the REC's standards.

According to the form prepared by Swissmedic, RECs can choose one of five options.[2075] Approval can take three forms: the REC can give a straightforward approval (option A.); it can issue a favorable opinion along with its recommendations (option B.); it can give a conditional opinion, with the investigator having either to go through a subsequent REC evaluation or to submit additional written information to the REC (option C.).[2076] Positive decisions are accompanied by a statement reminding the investigator of her main obligations.[2077] There are two kinds of negative opinion. There is the negative opinion based on the substantive issues raised by the application (option D.). Finally, there is the decision not to consider the file, usually because it is incomplete (option E.).

Once the investigator is notified of the REC's decision, she communicates it to the sponsor. The sponsor must know which REC reviewed the trial; it receives copy of the decision.[2078] The ICH Guideline asks ethics committees to issue a statement to the attention of the sponsor confirming that they are organized and operated according to GCP.[2079]

RECs should have procedures in place to make sure that the instructions it gave to the investigator are followed.[2080] For example, they should be able to verify that protocols that did not receive the "green light" are not launched. Similarly, when RECs ask the investigator to implement some improvements before starting the trial (e.g., addition to the consent forms), they should make sure that these changes are indeed implemented; to do so, they will typically ask the investigator to issue a written confirmation accompanied by a copy of all altered documents.

2072 *See, e.g.,* Council of Europe (Riis), *supra* note 1847, at 12. See further the new Article 26a OClin, which entered into force in September 2004. This provision belongs to Section 6 of the OClin which deals primarily with adverse event reporting. A general provision at the end of the OClin would have been more appropriate.

2073 *See also* section 3.1.2 (p.10) of ICH E6.

2074 *See* WHO (Operational Guidelines), *supra* note 1379, at points 7.9 and 8.13 (p.15 and 16). *See* Article 9.3 COE Research Protocol. In the United States, see 21 C.F.R. § 56.109(e).

2075 *See* Swissmedic, Formulaire d'avis de la Commission d'éthique de la recherche, [Form for the REC's opinion], (June 2004), at http://www.swissmedic.ch/files/pdf/Beschlussmitteilung_F.dot.

2076 While Article 54.4 LPTh allows Swissmedic to release a clinical trial only under the conditions it sees fit to impose, there is no equivalent provision for ethics committees. However, if a REC can reject a protocol, it is only logical that it be allowed to accept it under conditions. *See also* ICH E6 Guideline in section 3.1.2.

2077 *See also* WHO (Operational Guidelines), *supra* note 1379, at point 8.11 (p.16).

2078 *See* point 5.11.1(a)&(c) (p.23) of ICH E6.

2079 *See* section 5.11.1(b) (p.23) of ICH E6.

2080 A review of FDA warning letters show that RECs/IRBs do not always comply with this requirement. See*, e.g.*, FDA warning letter to Matthias McGuire, *supra* note 1848.

7.1.3. Information about the operation of RECs

7.1.3.1. In Switzerland

Finding information about Swiss RECs is not easy. Most committees do not publish annual reports, although such information would be tremendously helpful to evaluate their work. Switzerland still does not properly appreciate the benefits of transparency – whether in politics or in health care. One often has to rely on fragmented or old (and possibly outdated) information. This certainly does not encourage the public in taking interest in RECs' operations. The information I have been able to glean is detailed below.

According to a survey of Swiss RECs, only 2.5% of all protocols (2.5% of 1580 protocols in 2002) are definitively refused.[2081] However, most cantonal RECs ask for modifications before approving the protocols.[2082] The majority of outright refusals came from the canton Geneva.[2083] Another survey found wide variations among RECs' practices; a handful of RECs handle a great number of protocols (more than 200), while the majority of RECs only review a few.[2084] Talking with the presidents of two very different Geneva RECs (Prof. Bounameaux of the HUG-REC and Dr. Ciaroni of the outpatient REC), I obtained confirmation of the above remarks as well more detailed figures for these two RECs.

All in all, the HUG-REC receives – and dispatches to one of its seven sub-RECs – some 200 applications a year. The number increases slightly every year.[2085] Only a quarter of all these applications falls under Swissmedic's jurisdiction.[2086] The other protocols do not involve therapeutic products or are retrospective studies currently considered to be outside the scope of the federal system.[2087] Most clinical trials performed at the HUG are phase II and phase III studies. There are significantly fewer phase I studies, in part because this would require dedicated facilities.[2088]

The Geneva outpatient REC receives far fewer protocols, about 10 a year.[2089] This number has stayed constant over the last few years.[2090] Most protocols governed by the 2002 Federal Regulation (some 80% of the total) are phase IV studies, sometimes late phase III studies.[2091]

2081 *See* Amstad (Reden), *supra* note 794, at 1735; Amstad (Association), *supra* note 1860, at 5.

2082 *See* Amstad (Reden), *supra* note 794, at 1735 (table 3).

2083 *See id.* at 1734 (table 2).

2084 *See* Amstad (Association), *supra* note 1860, at 5. See also interview with Ciaroni, *supra* note 1338. Variability in RECs' approaches has also been found in other countries. *See* McWilliams et al., *supra* note 1832.

2085 Interview with Bounameaux, *supra* note 1718.

2086 *Id.*

2087 Even though these protocols are not governed by the LPTh and the OClin, they must, under HUG regulations, be submitted to the HUG's ethics committee. *Id.*

2088 *Id.*

2089 Interview with Ciaroni, *supra* note 1338.

2090 *Id.*

2091 Among protocols not governed by the LPTh and the OClin are studies not involving the use of a therapeutic product.

Investigators' applications are usually some 100 pages long.[2092] REC members receive the file about a week in advance.[2093] The time necessary for REC members to read a protocol and prepare for the meeting is between 2 and 4 hours, depending on the complexity of the study and the preparatory work done by the "rapporteur-en-chef" (also called primary reviewer).[2094] The HUG-REC organizes their review so as to have a "rapporteur-in-chief" who performs an in-depth review of the application and then assists his colleagues in their own assessment.[2095] The review of each protocol during a REC meeting takes between 20 and 45 minutes, depending, once again, on the difficulties associated with the proposed study.[2096]

In both the HUG-REC and the outpatient-REC, approvals granted without request(s) for changes are rare.[2097] Outright refusals are also infrequent.[2098] The norm is for the REC to ask for modifications.[2099] When changes are requested, the REC does not give its final approval before the investigator returns its revised application to the REC and the latter has seen the changes implemented.[2100]

These two RECs declare meeting their deadlines. The outpatient REC issues its first response within 20 days following receipt of the full application.[2101] The HUG-REC takes only slightly longer.[2102] Both indicate that, at the other end, investigators (and as the case may be sponsors) take significantly more time to revert to the REC with responses to its queries.

7.1.3.2. In other countries

In England, researchers conducted an analysis of protocols that had been submitted in the 1980s to a British REC.[2103] They found that out of 100 protocols, 82 were finally accepted, albeit with modifications for 45 of them. The most common concerns related to the safety of subjects and the incentives given to investigators for successful recruitment. The information provided to subjects, including the consent forms, was often found deficient. According to another study, consent form shortcomings constitute the

---

2092 Interview with Ciaroni, *supra* note 1338.

2093 According to the HUG's guidelines, the investigator must send her application at least 15 days in advance. See HUG guidelines on the submission of research protocol to the HUG REC, at http://www.hug-ge.ch/QuickPlace/ethiquerecherche/Main.nsf/h_E24BF9D98AEF9A72412569AB0050D3BC/7d80c633c83ab1fbc12569ca002d139c/?OpenDocument.

2094 In the United States, see for example UCSD-SOPP, *supra* note 485, at 102-103 (explaining how an IRB meeting is organized).

2095 Interview with Bounameaux, *supra* note 1718. *See also* SAMS 1997 Guideline, *supra* note 110, at point C.4 at 8.

2096 Interview with Bounameaux, *supra* note 1718, and interview with Ciaroni, *supra* note 1338.

2097 *Id.*

2098 *Id.*

2099 *Id.*

2100 *Id.*

2101 Interview with Ciaroni, *supra* note 1338.

2102 Interview with Bounameaux, *supra* note 1718.

2103 *See* Wise & Drury, *supra* note 1999, at 1245-48 (the study analyzed the first 100 protocols received by the ethics committee of the Royal College of General Practitioners).

most frequent reasons for rejection (54%);[2104] they are followed by poor study design (44%) and problems with the underlying scientific rationale for the trial (14%). These findings are similar to those reached by the former Swiss central ethics committee.[2105]

A survey of ethics committees in three European countries – Denmark, Germany and Spain – has shown several functional deficiencies and significant geographic disparities.[2106] Spanish RECs are slow in granting approval, regularly asking sponsors for additional information. This study also found that RECs pay insufficient attention to the review of local conditions, in particular the fit between the planned clinical study and the research sites.[2107] It remarked that RECs should do a better job at following reports of incidents occurring during the trial.[2108]

Another English study observed that, between 1995 and 1996, the Salford ethics committee had approved 230 new applications.[2109] Only 3 were ultimately refused and 44% were approved with only one review. The time devoted during meetings for each protocol was about 15 minutes. However, the workload for each ethics committee member was seven to eight hours per week. Members were not remunerated for their work.

Between 1998 and 2002, the U.S. Office of Inspector General (OIG) conducted an extensive review of ethics committees (IRBs). It pointed out that the IRBs were established at a time when trials were significantly less numerous and less complex.[2110] Between 1992 and 1997, the number of protocols that IRBs reviewed increased significantly (42% in initial reviews).[2111] High-volume IRBs can review 2,000 protocols each and receive over 2,000 adverse event reports each year.[2112] "It is not uncommon for the reading materials associated with a single RIB meeting to comprise more than 1000 pages… ."[2113] Yet, reviews are sometimes carried out in a matter of minutes, with only one designated IRB member having scrutinized the entire protocol.[2114] Despite increased workload, IRBs have to make do with the same level of funding and staffing.[2115]

2104 *See* OIG (Promising), *supra* note 1882, at 5 (citing a study by Jeffrey S. Jones et al.).

2105 *See* Truniger, *supra* note 1337, at 2399 and 2400 (the most frequent reasons for non-acceptance were related to the study design, the information given to patients and insurance issues).

2106 Peter O'Donnell, *European Ethics Committees – Still Salad Rather than Soup*, APPLIED CLINICAL TRIALS, at 30 (May 2003), *at* http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/222003/58176/article.pdf, reporting on a study by Javier Revuelta.

2107 *Id.* at 32. The suitability of a trial site will depend upon "the quality of the investigating team, their availability, their resources, and their experience, particularly in relation to the local incidence of the pathology under study." *Id.*

2108 *Id.*

2109 *See* Blunt et al., *supra* note 1950.

2110 OIG (Reform), *supra* note 877, at 4.

2111 *See id.* at 5.

2112 *See id.* at 5. *See also* Michaele C. Christian et al., *supra* note 1949, at 1405.
Low-volume IRBs face additional problems besides those identified by the OIG with regard to high-volume IRBs. One of them is the sense of isolation. See OIG, HHS, Final Report on Low-Volume Institutional Review Boards, (Oct. 23, 1998), at http://oig.hhs.gov/oei/reports/oei-01-97-00194.pdf. *See also* OIG (Reviewing), *supra* note 1187, at 7.

2113 UCSD-SOPP, *supra* note 485, at 92.

2114 *See* OIG (Reform), *supra* note 877, at 6; OIG (Reviewing), *supra* note 1187, at 9.

2115 OIG (Reform), *supra* note 877, at 6.

To maintain such a rhythm, committee members are forced to specialize in their given area of expertise,[2116] even though this is not what the legislator had in mind when setting up ethics committees.[2117] The OIG draws stark conclusions: although staffed with dedicated personnel, most IRBs are not able to perform their responsibilities to protect human research subjects.[2118] Broad reforms were called for. The IRB system has lagged behind the pace of scientific progress.[2119]

7.1.3.3. Limits of the REC's assessment

Discussions with REC members left me with the impression that RECs have to navigate in difficult waters. On the one hand, they want to do everything to protect and even help subjects. On the other hand, they do not want to exasperate investigators and discourage potentially useful research. RECs are well aware of the cost of research. They know that the improvements they suggest add to these costs.

As a result, they may prefer to steer a middle-course. Insisting on "perfection" would get them nothing. Provided that subjects are not in danger, they may prefer to assert positions that they expect to be palatable to investigators and sponsors. REC members do not want to judge or arbitrate medical disputes. They are loath to obstruct research carried out by their colleagues, even when they would have chosen to conduct it otherwise. The line between proper assessment by a REC and personal opinions or preferences is hard to draw. Provided that subjects' safety is not at risk, RECs may allow research whose scientific underpinning is debatable provided a divergence of opinion does not seem unreasonable.

On account of these difficulties, it has been pointed out that the term "favorable opinion" can be misleading.[2120] Both protocols that are good and those that are merely acceptable (because they do not entail risks for subjects) are given the REC's "green light." Yet, "favorable opinion" suggests a more affirmative endorsement. Subjects who are typically informed of the REC's approval may interpret this opinion as a safety guarantee to their benefit.[2121]

RECs choose to remain in a too passive role. Many commentators have called for a closer involvement of ethics committee during the recruitment phase. Often, there is no one to witness the interaction between the investigator (or her delegate) and the prospective subject. The subject may feel too intimated to ask questions; he may be embarrassed by his lack of understanding of the information provided; he may fear that not signing the consent form will be detrimental to him in some way. As long as ethics

---

2116 Physician members will examine the scientific-medical aspects, the biometrician will do the statistical computation, the non-physician members will review the legal or ethical features, and so on.

2117 Ideally, each REC member should fully contribute to the discussion, whether it has to do with scientific, legal or fairness-ethical aspects.

2118 *See* OIG (Reform), *supra* note 877.

2119 The OIG lists six principal changes: "expansion of managed care," "increased commercialization of research," "proliferation of multi-center trials," "new types of research," "increased number of proposals," and "rise of patient consumerism." *Id.* at 5 and also at 7.

2120 *See* Anne Langlois, *L'avis du CCPPRB: à qui est-il destiné? Une responsabilité morale*, 5(4) INTERN. J. OF BIOETH. 341-342 (Dec. 1994).

2121 *Id.* at 342.

committees fail to attend the recruitment stage of a clinical trial, they risk overlooking its dire "realities." REC members may act upon idealized notions of research, investigators and patients (e.g., subjects are all smart and investigators are all dedicated). REC members need to leave their scientific "ivory tower" to meet potential subjects and discuss their experiences. Having at least one REC member witness key aspects of the recruitment process would be one positive measure.

7.1.4. Proposals for improving RECs

7.1.4.1. Continuing education

The above mentioned OIG report observed that REC members would benefit from continuing education programs.[2122] However, "[a] 1995 survey of 182 university-based IRBs found that one-quarter offered no training at all to their members. At the vast majority of institutions, training was limited to less than four hours."[2123] The same remarks can be made for Switzerland. Although the importance of educative programs is always highlighted, the concrete results are still not satisfactory.[2124] Private and public-sector efforts continue to expand training options. For instance, the Swiss Society for Biomedical Ethics offers classes for REC members.[2125]

Training programs are certainly a step in the right direction, since they help REC members acquire basic knowledge in areas outside their individual specialty.[2126] Making available fully motivated assessments of previous clinical trials as well as the minutes of REC meetings would be even more helpful. By retaining applications, meetings' minutes, and correspondence,[2127] RECs can also transmit accumulated experience to their new members; RECs ought to put these documents on an intranet so that REC members would have easy and permanent access to prior "cases."

7.1.4.2. Longer deadlines

Given RECs' complex assignment, the 30-day deadline they must respect under Swiss law is disturbing. As a comparison, courts are far from achieving such deadlines. Even in the European Union, RECs have more time (60 days).[2128] This begs the question of

---

2122 *See* OIG (Reform), *supra* note 877, at 15-17.

2123 *See id.* at 8.

2124 *See, e.g.,* Trutmann, *supra* note 929, at 863.

2125 *See, e.g.*, Swiss Society for Biomedical Ethics, Agenda, at http://www.bioethics.ch/content/page_1.aspx?Nid=26&Aid=14&ID=10.

2126 *See, e.g.,* OIG (Promising), *supra* note 1882, at 8-11.

2127 These documents should be kept for ten years starting with the completion or the premature ending of the corresponding clinical trial. Article 33.1 OClin. By contrast, ICH E6 guideline at section 3.4 (p.12) only provides for a three-year conservation period. A three-year period is also stipulated by the WHO (Operational Guidelines), *supra* note 1379, at chapter 10 (p.18). A three-year period also applies in the United States. *See* 21 C.F.R. § 56.115(b).

2128 Article 6.5 of E.U. Directive 2001/20/EC. This deadline is extended to a total of 90 days for investigational products containing genetically modified micro-organisms ("GMMOs") or involving gene or somatic cell therapy. Article 6.7 of this Directive. There is no deadline for products involving xenogenic cell therapy. *Id.* Article 6.6 of this Directive, RECs can make only one request for supplementary information.

whether this deadline allows for a proper review.[2129] REC members have other professional responsibilities beside their commitments to the REC. They meet sometimes once a week but more usually only once a month. The meeting then lasts a day or less, while the file they have to review can be hundreds of pages long. Hence, if every month committee members must review dozens of protocols and if they must reach a decision within 30 days, they are either extraordinarily talented or completely overwhelmed.

The solution is either to diminish their workload or to extend the deadline. Diminishing the workload would require adding REC members and creating subdivisions within RECs. Multiplying subRECs may impair the development of uniform practices. Extending deadlines, at least for initial review of complex trials, therefore seems necessary.

7.1.4.3. Funding RECs properly

Research assessment by RECs is viewed in most countries as a *pro bono* work that REC members should do for the love of science and humanity. The result is that REC members are paid nothing or next to nothing to do a work that is far from easy. This is not to imply that, for this reason, REC members will not perform their tasks with care and dedication. On the contrary, individuals asked to sit as REC members are proud to be offered such a position.

Nevertheless, these members are faced with conflicting demands on their time. When the REC member is a physician, she has to see her own patients, fill out administrative paperwork, manage her practice, in addition to her obligations as a REC member. Obviously, her time is not infinitely extendable. If, at the end of the day, she is given a pile of clinical trial adverse events reports to review, chances are she will rally to the investigator's opinion that "nothing is wrong with the subjects and the investigational drug."

By paying REC members fairly (e.g., based on the Swiss Tarmed hourly fee) and by allocating sufficient time for them to do their work, one would encourage REC members' sense of responsibility.[2130]

7.1.4.4. "Private" RECs?

Switzerland presently has no "private for-profit" REC. Some Swiss RECs are *private* in the sense that they were not set up by a *public* institution such as a canton or a public university. For example, the Geneva outpatient REC is the creation of a *private* physician association. However, to my knowledge, there are no RECs incorporated as private structures (e.g., a corporation) and operating on a for-profit basis.[2131]

[2129] *See also* WHO (Operational Guidelines), *supra* note 1379, at point 6.1.2 (p.9) ("REC members should be given enough time in advance of the meeting to review the relevant documents.").

[2130] *See generally* Savulescu (Two deaths), *supra* note 987, at 2.

[2131] One should also note that a private for-profit REC would still have to be approved by the canton and registered by Swissmedic.

Private for-profit RECs would be frowned upon in Switzerland.[2132] When the OClin was being drafted, the administration even considered a total ban on private RECs. Private RECs give rise to two main concerns.

First, if sponsors and investigators have a choice as to which REC to go to, their choice may be motivated by considerations other than the best interests of research subjects. For instance, they could pick a private REC known for acquiescing to more risky research. This conduct, referred to as *forum shopping*, is viewed as particularly threatening.[2133] The legislator prefers that each investigator resort only to one predetermined REC.[2134] However, cantons remain free to approve private RECs, although none have yet done so.[2135]

The second and related concern is that the decisions of private RECs can be unduly swayed by *financial considerations*. Because these RECs depend on the fees paid by researchers, they need to maintain good relationships with their patrons. The more "popular" they are with their patrons, the more fees they will collect.

Private review boards operating on a for-profit basis exist in the United States, but are not widespread. In 2003, there were some 28 of these so-called private, commercial or independent boards.[2136] Despite – or perhaps owing to – the fact that they oversee a large number of clinical trials, they have attracted criticism. The complaints being raised resemble those set forth above (i.e., forum shopping[2137] and excessively agreeable attitude[2138]). Furthermore, private IRBs may not be sufficiently knowledgeable about characteristics of the research site.[2139]

Yet, no study has demonstrated that decisions of private IRBs are not as scientifically and ethically valid as those of not-for-profit IRBs (e.g., IRB affiliated with a medical institution). On the contrary, a 2000 study by the OIG showed that these independent IRBs can contribute positively. Because they are composed of full-time specialists,

---

2132 The VanTx Working Group expressed strong doubts as to the adequacy of private RECs. See VanTx Report, *supra* note 148, at 27.

2133 *See* VanTx Report, *supra* note 148, at 28. See also, in the United States, OIG (Reform), *supra* note 877, at 7-8 and 14.

2134 The OClin was prepared by the Federal Office for Public Health (FOPH), with the assistance of outside experts such as Prof. Dominique Sprumont.

2135 A private REC does not have a *right* to receive the canton's approval. The Swiss Federal Tribunal confirmed that cantons can decide, on whatever grounds they see fit, which entities are to be entrusted with the delicate and highly important mission of preserving research subjects' health. *See* Decision of the Swiss Supreme Court of July 4, 2003, 2A.430/2002 (yet unpublished), at point 3.2, text at http://www.polyreg.ch/bgeunpubliziert/Jahr_2002/Entscheide_2A_2002/2A.450_2002.html [hereinafter 2A.430 Decision]. See also the comment by Alfred Jost, 1 RSDS 13-14 (Sept. 2003). The Court ruled that a (here private) ethics committee cannot invoke freedom of trade. Similarly, it cannot call upon the freedom to provide services. *See* 2A.430 Decision, at point 5 (in the context of the agreements between Switzerland and the European Union).

2136 See the list established by AdvaMed, at http://www.advamed.org/solutions/reviewboards.shtml (updated Apr. 23, 2003). See for example PPD which undertakes to give its opinion on submitted protocols in less than 10 days. PPD, Independent Review Board (IRB) / Frequently Asked Questions, at http://www.ppdi.com/products/product_development/irb_ethical_review/faq.htm#8.

2137 *See* Erica Heath, *The History, Function, and Future of Independent Institutional Review Boards*, in NBAC BIOLOGICAL REPORT VOLUME II, at E-3 and E-15, (NBAC, 2001), at http://www.georgetown.edu/research/nrcbl/nbac/human/overvol2.pdf.

2138 *See* OIG, HHS, Institutional Review Boards: The Emergence of Independent Boards (June 1988), at iii and 6-7, at http://oig.hhs.gov/oei/reports/oei-01-97-00192.pdf.

2139 *See id.* at ii-iii and 6.

they review protocols faster.[2140] They do not experience problems related to limited time and resources that academic IRBs face. Moreover, the lack of affiliation with the institution hosting the trial promotes independence.[2141] The FDA endorses private IRBs provided they abide by certain additional requirements regarding, for example, the assessment of local factors.[2142]

7.1.4.5. Public RECs

The legal status of Swiss RECs is not self-evident: RECs are appointed by the canton which also designates their members. The canton has the right to receive RECs' internal regulations and, in all likelihood, to approve or reject them.[2143] RECs clearly perform tasks that are in the public interest.[2144] Yet, RECs are not necessarily public authorities;[2145] their members are usually not civil servants; they are not – and must not be – under the direct supervision of public authorities. In many cantons, their decisions cannot be appealed.[2146]

This choice – made in Switzerland[2147] as well as in many other industrialized countries – is most probably rooted in *historical* circumstances, and is therefore not the result of an advantage/disadvantage comparison.[2148] As mentioned earlier, RECs existed well before the inception of the LPTh; many of them predate the IOCM's 1995 Regulation. Institutions have felt a need for ethics committees before the subject matter became the subject of governmental regulations.[2149]

Furthermore, research has historically been viewed as an area where governments should not interfere too much. Researchers, scientists, and especially doctors, have defended their "right" to conduct research without governmental constraints. According to this historical perspective, governments can certainly supply the funds, but are to

---

2140 "On average, those [private independent IRBs] we interviewed reported that they could provide initial research protocol decisions in about 11 days. For the academic health centers we reviewed, the average was about 37 days." *Id.* at ii and also at 5.

2141 Private RECs feel less pressure to please the institution and its investigators. *See id.* at 5.

2142 *See* FDA, Non-Local IRB Review, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators, (1998 update), at http://www.fda.gov/oc/ohrt/irbs/nonlocalreview.html; Office for Protection from Research Risks, Knowledge of Local Research Context, (Aug. 27, 1998), at http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm.

2143 Article 34.2 OClin also mentions a right of inspection (in French: "*droit de regard*"), but this right would make little sense if the canton was forced to tolerate evidently unsatisfying internal REC regulations.

2144 *See* Swiss Supreme Court 2A.430 Decision, *supra* note 2135, at point 3.2.

2145 *See however* Articles 5, 21 and 23 Bern Ordinance 811.05, *supra* note 1949.

2146 *See however* Article 22 Bern Ordinance 811.05.

2147 See in this respect National Council, sixth session, March 13, 2000, BO 2000 N 167-68, at http://www.parlament.ch/ab/frameset/d/n/4602/9085/d_n_4602_9085_9204.htm (discussing whether ethics committees' authority should come as a delegation from the cantonal authority).

2148 *See* Goldner, *supra* note 62, at 100 ("At first blush, this decentralization may appear to be extraordinary, in that non-governmentally appointed bodies, appointed by organizations within the private sector, are given significant control."). *See also* Council of Europe (Riis), *supra* note 1847, at 3.

2149 Review of protocols by ethics committees was made an ethical requirement with the 1975 version Helsinki Declaration. Although the Declaration was not immediately integrated in national legislations, it had an enormous influence and a large majority of research institutions fully obeyed it. Since the Declaration was enacted by a private body, the World Medical Association, it could not directly force governments to create ethics committees.

leave as much latitude as possible to scientists. Only scientists should judge other scientists (e.g., the peer review system[2150]). The freedom of research is cherished,[2151] even though it has been significantly curtailed in the past ten years.[2152].

In this context, it is virtually impossible to set up public/administrative RECs to replace the committees previously established through self-regulation. Only if RECs were to fail in their mission would such a change become politically viable. This does not preclude a trend toward a diminution in the number of institution-related RECs.[2153]

I do not believe that public RECs would necessarily function better. One of the disadvantages of public RECs would be their dependence on public funding. From year to year, they would have to fight to retain their budgets. Another hazard would be deference to political parties or to cantonal economic interests. For example, a public REC may be reluctant to turn down a protocol sponsored by the largest pharmaceutical company based on its territory. Finally, public RECs staffed with public servants are also likely to be more risk averse. If they reach a "bad" decision, their choice may implicate their entire hierarchy. Professional REC members could also lose track of practical considerations, since they would be full-time trial assessors and no longer exercise their medical profession.[2154]

Nonetheless, given the key role of RECs – they are after all entrusted with the health and lives of research subjects – their action should fall under greater public scrutiny than it does today. The VanTx scandal illustrated the very tangible risk of RECs running afoul of their duties, without the canton noticing it in time. Yet, at the time (2000), this scandal received relatively little media coverage. The REC system was challenged to some extent, but its abolition was not considered. Since the LPTh project was already underway, it was felt that RECs could be improved so that abuses would not recur. But if a similar scandal were to surface now, the present REC system would probably be jeopardized. In particular, the issue of REC's independence and supervision are likely to cause problems in the future.

2150 "Peer review is the critical assessment of manuscripts submitted to journals by experts who are not part of the editorial staff." ICMJE, *supra* note 945, at II.C. *See further* Christine Laine & Cynthia Mulrow, *Peer Review: Integral to Science and Indispensable to Annals*, 139 ANN. INTERN. MED. 1038- (Dec. 16, 2003).

2151 This freedom is now acknowledged in Article 20 of the Swiss Constitution. See also its Article 64.1 on encouraging scientific research. See also the decisions of the Swiss Federal Tribunal reached before the enactment of Article 20: ATF 119 Ia 460, at cons.12, at p.499 = JdT 1995 p.586, at cons.12, at 598; ATF 115 Ia 234, at point 10, (p.268-71) = JdT 1991 I 194, at point 10 (p.208-211) (research on sperm and ova). See also, after the enactment of Article 20 Cst, ATF 127 I 145 (freedom of research of a journalist).

2152 See for example the Federal Council's Message regarding the LRCS, FF 2003 1065, at 1090-91 and 1109-22; Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 310.
If the COE instrument on the use of archived biological materials (see subsection 3.4.6.4. above and notes 492 and 493 *supra*) were to be adopted, few research projects would escape prior evaluation by government appointed bodies.

2153 *See, e.g.,* Sprumont & Béguin, *supra* note 134, at 903.

2154 Interview with Bounameaux, *supra* note 1718.

7.1.5. Supervision of ethics committees

The supervision of ethics committees represents a weak point in the system of protection of research subjects. No country has yet succeeded in implementing an effective oversight system for ethics committees.[2155] Almost always ethics committees decide in only – and thus necessarily last – resort. Although RECs reach appropriate decisions most of the time, the lack of any oversight (or even the absence of a reasonable threat of control) represents an obvious risk; we saw it materialize in the Swiss VanTx affair.

7.1.5.1. Cantonal oversight in Switzerland

It was initially contemplated that REC supervision would be shared between the federal government and the cantons,[2156] but the Federal Council's project was modified to diminish the canton's authority to regulate its RECs. Paragraph 4 of Article 57 LPTh was added, and paragraphs 3 and 5 were altered.[2157]

A contradiction, however, remains between paragraphs 3 and 4 of Article 57 LPTh. While cantons are supposed to appoint and oversee RECs (paragraph 4), it is up to the Federal Council to set the corresponding procedures (paragrph 3). Are we to understand that the Federal Council can impose to cantons the procedures of its choice? This is rather unlikely and the OClin contains very few provisions on the suject. In all probability, this contradiction stems from the change made by the Parliament in Article 57 LPTh.

7.1.5.1.1 Sovereignty of each canton

As we saw in subsection 7.1.1.2., cantons appoint their RECs.[2158] Cantons also receive copy of RECs' internal regulations;[2159] they have access to RECs' archives.[2160] Cantons may even have to finance the operations of RECs, if the fees charged by the RECs are not set so as to fully support these operations.[2161] According to Article 57.4 LPTh, cantons are supposed to supervise the activities of their RECs. However, this provision is not further spelled out in the OClin. The OClin contains no provision stipulating how

---

2155 In Europe, see EFGCP (Auditing IECs), *supra* note 163, at 4.

2156 See the Message of the Federal Council accompanying the project of LPTh, FF 1999, 3151, at 3232.

2157 According to the previous versions of Article 57.3 LPTh (at the time Article 56.3) and of Article 57.5 LPTh (at the time Article 56.5), the Federal Council could delegate its powers (as per this provision) to the cantons and Swissmedic was responsible for coordinating the activities of RECs. These two clauses were eliminated.

2158 Article 29.1 OClin.

2159 Article 34.2 OClin.

2160 Article 33.2 OClin. In the United States, see 21 C.F.R. § 56.115(b).

2161 Article 29.2 OClin. The OClin compels cantons to set up and maintain RECs; it lets them however free to decide how their RECs will be funded. Theoretically, a REC could be fully financed either by fees paid by the investigator or by the canton. A third possibility is that the institution(s) to which it is affiliated shoulders the REC's costs. In practice, when a canton has only one REC, it bears a large proportion of its costs. When the REC is set up by a private institution, such as an association of private practitioners, the canton rarely subsidize this REC directly. When the REC is affiliated to a public hospital, a portion of its costs is indirectly assumed by the canton, through the general costs of the hospital.

this supervision is to take place. As a result, cantons can decide freely how and to which extent they supervise ethics committees.[2162]

This autonomy is perplexing since RECs are endowed with significant powers over research and entrusted with an important public health mission. If the only cantonal control over a REC is the receipt of its annual report, this clearly will not do. Rather the canton should conduct periodic inspections and perform sample audits of the applications reviewed by its RECs. In Geneva, the Cantonal Pharmacist, the authority responsible for overseeing RECs, has not – or at least not yet – inspected either the HUG-REC or the outpatient REC.[2163] Relationships between these RECs and the Cantonal Pharmacist are reported to be good and based on trust.[2164] This trust is both an advantage and a risk. It renders aggressive enforcement of federal and cantonal standards unlikely. The Cantonal Pharmacist does not reconsider, on appeal or on request, applications submitted to Geneva RECs.[2165]

7.1.5.1.2. Problems with cantonal oversight

The Federal Office for Public Health touched upon the problem of cantonal oversight; in its December 2000 explicative report on the draft OClin, it underlined the fact that the appeal possibilities against RECs' decision differ between cantons.[2166] According to a survey, 17 RECs allow for some form of appeal against their decisions, while 10 do not.[2167] Even in cantons which have adopted some form of review, the procedures vary significantly.

Organizing some form of material review or appeal of REC pronouncements is envisaged.[2168] Most RECs agree that such a mechanism could be helpful.[2169] However, selecting the proper appellate authority is difficult since RECs' assessments are not bound by strictly legal criteria.[2170] An appellate ethics committee could be the solution. This would also meet the terms of Article 31.c OClin requiring that RECs remain independent from authorities. However, since most cantons have only one REC working with part-time members, setting up an additional appellate committee might be exces-

---

2162 In Geneva, the Cantonal Pharmacist exercises its control based on RECs' annual reports. The first control shall take place this year (2004), with the first annual reports due in the spring. The reports must describe the REC's activities, such as the number of protocols submitted, the number of meetings held. As to the scope of controls, Swiss cantons plan to agree on a common supervision method. To my knowledge, no intercantonal agreement has yet been found on this issue. *See* Telephone Interview with C. Robert (Apr. 2004), *supra* note 1829.

2163 Interview with Bounameaux, *supra* note 1718; Interview with Ciaroni, *supra* note 1338. *See* Telephone Interview with C. Robert (April 2004), *supra* note 1829.

2164 Interview with Bounameaux, *supra* note 1718.

2165 Interview with Ciaroni, *supra* note 1338.

2166 *See* remark on 2000 draft Article 30 OClin, *supra* note 8, at 19.

2167 *See* Amstad (Reden), *supra* note 794, at 1736. There are 15 ethics committees that also have appeal procedures against a decision to request modifications. See also the results of 1988 survey commented by Ummel (1990), *supra* note 74, at 49-50.
In Geneva, there is no review of RECs' decisions. At the HUG, there is an appeal procedure limited to certain procedural issues. Interview with Bounameaux, *supra* note 1718.

2168 Interview with Bounameaux, *supra* note 1718. *See also* Amstad (Reden), *supra* note 794, at 1733-36.

2169 *See* Amstad (Reden), *supra* note 794, at 1736.

2170 RECs must not only make sure that the existing regulations are followed, they must also verify the *scientific* and *ethical* legitimacy of the proposed clinical trial. *Id.*

sively cumbersome; the alternative would be to set up a *federal or intercantonal* appellate body.

Another suggestion is to enhance transparency. The canton should send civil servants to attend REC meetings once in a while. Patients' representatives or associations should be invited to participate in the discussions – of course without taking part in the vote. RECs should publish a yearly report on the Internet (see also subsection 7.1.4. above). The same should go for the negative and positive opinions they have reached – of course while safeguarding sponsors' and investigators' trade secrets. Finally, REC members should have to face administrative or criminal sanctions if they have grossly breached their obligations. Presently, the LPTh contains no such clause punishing negligent REC members. Cantons are free to introduce penalties in their legislation, but few, if any, have done so.

Under Swiss law, it is unclear to which body ethics committees can report breaches of law they have detected.[2171] Of course, a REC can turn up evidence of illegal behavior to the general attorney (i.e., the cantonal prosecutor). Institutional RECs should also report such evidence to the head of their institution. Unfortunately, there is no established communication channel between RECs and Swissmedic,[2172] with the result that violations discovered by RECs may not be communicated immediatly to Swissmedic. To put the matter in perspective, it is only in 2004 that Swissmedic decided to pass its own inspection findings on to RECs. The same problem has been identified in other countries.[2173] In the United States, the FDA has tackled it by intensifying its exchange with IRBs regarding investigator misconduct.[2174]

7.1.5.2. A new role for Swissmedic

Another solution to the oversight problem could be supervision by Swissmedic. In the United States, the FDA supervises IRBs as part of its review of studies submitted to support marketing applications.[2175] Controls consist in IRBs' inspections by FDA officers.[2176] In 1997, the FDA inspected some 200 IRBs.[2177] The FDA can disqualify deficient IRBs and/or their institutions[2178] and its decisions are rendered public.[2179]

By contrast in Switzerland, Swissmedic has practically no authority over RECs.[2180] There are no established communication channels between Swissmedic and RECs.[2181]

2171 *See generally* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).

2172 The same is true in the United States. The U.S. OIG commented that "[w]hen FDA issues a warning letter to a clinical investigator, it typically does not inform the IRB." OIG (Reform), *supra* note 877, at 7.

2173 *See id.* at 14; OIG (Reviewing), *supra* note 1187, at 10-11.

2174 *See* OIG (Status), *supra* note 987, at 2 and 13.

2175 *See* 21 C.F.R. § 56.120 and 121.

2176 *See* FDA (Operations), *supra* note 259 (describing how FDA inspections are conducted).

2177 *See* OIG (Reform), *supra* note 877, at 9 and also at 20 (suggesting how to improve FDA inspections). OIG (Reviewing), *supra* note 1187, at 13. It has steadily increased the number of inspections, reaching 336 in 1999. *See* OIG (Status), *supra* note 987, at 2 and 9.

2178 *See* 21 C.F.R. § 56.121.

2179 *See* 21 C.F.R. § 56.122.

2180 Reinforcing Swissmedic's role in supervising RECs was proposed during the OClin comment period. *See* DHA (Ordinance Comments), *supra* note 522, at 46.

Swissmedic cannot inspect the RECs themselves,[2182] but only their archived records.[2183] If Swissmedic detects something untoward in these records, its recourse is apparently to inform the canton, since the canton, not the agency, has jurisdiction.[2184] However, in practice, Swissmedic does notify ethics committees if serious failings are observed.[2185] Conversely, ethics committees sometimes alert Swissmedic when they are unsatisfied with a trial.[2186] The sometimes strained relationship between RECs and Swissmedic makes it unlikely that the former will welcome the intervention of the latter.[2187] Recent improvements in this relationship may result in a more collaborative interaction.

7.1.5.3. Oversight by the sponsor

Some commentators have proposed that sponsors conduct audits of ethics committees.[2188] This system of private controls can work well in countries where sponsors choose to which REC their protocol is submitted. For instance, in the United States, Wadlund recommends that sponsors pre-screen or "accredit" their IRBs.[2189] In countries like Switzerland where sponsors have little or no choice, letting sponsors audit the semi-private/semi-public RECs (e.g., the single cantonal REC) would certainly not be seen as appropriate.

Besides, the interest that sponsors take in the good functioning of RECs is not aligned with the interests of research subjects, those of the public, or even those of investigators. Sponsors want RECs to systematically follow written procedures and provide properly reasoned opinions within (preferably short) deadlines. Investigators prefer long-term cooperative relationships with RECs, whereas RECs would accept the fact that perfection in the design and conduct of a trial is subject to very practical limitations. Research subjects place the emphasis on the proper evaluation of the health risk-benefit ratio by RECs. Finally, the public and governments want to be reassured that no abuse can ever occur, even if this reassurance comes at the cost of discarding potentially important research.

Nevertheless, it is true that sponsors have the resources to conduct comprehensive audits of RECs. Encouraging such audits would serve a purpose, even if they do not guarantee perfect functioning. I would recommend sponsor-led audits, at least when *large and pivotal* clinical trials are launched on the basis of a specific REC's favorable opinion. Key results of the audit should be communicated to the investigator, to

---

2181 *See* Amstad et al. (Lieux), *supra* note 800, at 2453.

2182 Under the previous intercantonal system, the IOCM could inspect RECs. *See* VanTx Report, *supra* note 148, at 30.

2183 Article 33.2 OClin.

2184 Article 57.4 LPTh.

2185 *See* Interview with Vital-Durand, *supra* note 484.

2186 *Id.*

2187 Interview with Bounameaux, *supra* note 1718; Interview with Ciaroni, *supra* note 1338. See also the revealing questions asked by Parliament member Dunant to the Federal Council and the no less interesting answers received on June 30, 2004, (04.3231), at http://www.parlament.ch/afs/data/f/gesch/2004/f_gesch_20043231.htm.

2188 *See especially* EFGCP (Auditing IECs), *supra* note 163.

2189 *See* Wadlund, *supra* note 680, at 52.

Swissmedic and to the relevant cantons. When the audit findings are critical, they should be made available to the public.

7.2. Drug agency's approval of clinical trials

The 2002 Federal Regulation sets forth two different procedures for the approval of clinical trials: the clearance process for ordinary therapeutic products[2190] (see subsection 3.2.2. above and 7.2.1. below) and the formal authorization process for trials involving genetic somatic therapy or genetically modified organisms (see subsection 3.2.3. above and 7.2.2. below).[2191]

7.2.1. The clearance process

7.2.1.1. In Switzerland

Clinical trials carried out in Switzerland must be notified to Swissmedic before they start.[2192]

The notification is mandatory for all trials. There are no exceptions for emergencies.[2193] This notification differs from an affirmative authorization, or even from the favorable opinion of an ethics committee;[2194] it can be compared to a clearance procedure.[2195] The sponsor submits its application, and if, within 30 days,[2196] Swissmedic has not raised any objection, the sponsor can go ahead with its clinical trial.[2197] As with the REC, the deadline starts running once the agency has received a complete file.[2198] Although Swissmedic can dispense with a formal answer and just let the deadline pass,

---

2190 Article 54.3 LPTh and section 4 of the OClin.

2191 Article 54.5 LPTh and section 5 of the OClin.

2192 *See also* section 5.10 (p.23) of ICH E6.

2193 In the United States, the FDA may allow the use of an experimental product before the IND application has been submitted. Based on a faxed request, the FDA may "authorize shipment of the drug for a specified use in advance of submission of an IND." *See* 21 C.F.R. § 312.36.

2194 See for example in the United States, Kessler (Regulation), *supra* note 447, at 281.

2195 The word "clearance" is not commonly used in Switzerland, Europe or the United States, but the CIOMS Guidelines do refer to it. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 1.
The "clearance" mechanism has also been referred to as a "tell and wait" notification. *See* European Federation of Pharmaceutical Industries and Associations ("EFPIA"), Clinical Trials, (Sept. 1999), at http://www.efpia.org/2_indust/topic_3.pdf.
The German text of the OClin uses the word "*Freigabe*," while the Italian version refers to "*nullaosta*." The LPTh at its Article 54.3 refers to a "*Meldepflicht*."

2196 This deadline is extended to 60 days for radiopharmaceuticals. Article 15.1 OClin. Radiopharmaceuticals are drugs that are tagged with a radioisotope.
In the European Union, the period to notify "grounds for non-acceptance" for a normal clinical trial is a maximum of 60 days; Article 9.4 of Directive 2001/20/EC. In the United States, the period is 30 days: see 21 C.F.R. § 312.40(b)(1).

2197 Article 15.1 OClin. *See also* Federal Council's Message on the LPTh, at FF 1999 3151, at 3230.

2198 Article 15.3 OClin for Swissmedic; Article 11.2 for RECs.

Article 15.2 OClin asks that Swissmedic allow the trial *before* the deadline if it has no objections.[2199]

While the investigator handles relationships with the REC, it is the sponsor that is in contact with Swissmedic.[2200] The sponsor's application to Swissmedic follows the receipt by the investigator of the REC's favorable opinion.[2201] Swissmedic's clearance encompasses all investigators listed by the sponsor in its application.[2202] If other investigators need to be added, the sponsor must amend its application.[2203] Similarly, each research site must be announced and "cleared."[2204]

7.2.1.2. In the United States

The procedure in the United States is mostly similar to that of Switzerland. The U.S. equivalent of "clearance" is called the Investigational New Drug ("IND").[2205] Following receipt of the sponsor's application, the FDA has 30 days to raise objections.[2206] Objections may relate to subject safety or to the scientific design of the study. In particular, the FDA verifies that the planned trial is likely to yield satisfactory data for the purpose of a future marketing application.[2207] If the FDA does not raise objections within the deadline, the IND is said to be "opened" or "in effect."[2208] If there are objections, the trial is placed on "clinical hold," until the FDA's concerns or questions have received satisfactory answers.[2209]

The main difference between the Swiss and the U.S. procedure is that the latter allows for greater interaction between the sponsor and the FDA.[2210] Prior to the submission of the IND application, the sponsor usually meets with FDA officials.[2211] This ex-

---

2199 See in the E.U. Article 9.4 of Directive 2001/20/EC. In the United States, 21 C.F.R. § 312.40(b)(2).

2200 Article 13.1 OClin. *See also* Kessler (Regulation), *supra* note 447, at 283.

2201 In the United States and in the European Union, the sponsor can ask for the drug agency's clearance either before or after the IRB has issued its decision. *See* 21 C.F.R. § 312.30(a), respectively European Union E.U. Guidance (Ethics Committee), *supra* note 270, at 3.

2202 See for example in the United States, Kessler (Regulation), *supra* note 447, at 282.

2203 Article 19.1 OClin.

2204 *See* Swissmedic, Notification form for drug clinical trials, at point 2a, *see supra* note 1636.

2205 *See* 21 C.F.R. § 312.20(a)&(b). The sponsor submits its application using FDA-Form 1571 (*see supra* note 1164). The sponsor's application includes a confirmatory statement by the investigator (using FDA form 1572, at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf). By signing the form, the investigator commits to abide by applicable regulations. *See also* 21 C.F.R. § 312.53(c)(1).

2206 *See* 21 C.F.R. § 312.40(b)(1).

2207 *See* 21 C.F.R. § 312.22(a).

2208 *See, e.g.*, 21 C.F.R. § 312.40(a)(1).

2209 *See* 21 C.F.R. § 312.42. Clinical holds are also used to suspend a trial that is already ongoing. Clinical holds can be complete, in which case all the trial has to stop, or partial, in which case only certain procedures of the trial are discontinued. If a clinical hold (i.e., a suspension) is not sufficient, the FDA can terminate the IND, and thus the clinical trial. *See* 21 C.F.R. § 312.44. *See also* FDA Submitting and Reviewing Complete Responses to Clinical Holds, Guidance, (Oct. 2000) at http://www.fda.gov/cder/guidance/3082fnl.pdf; FDA, The Use of Clinical Holds Following Clinical Investigator Misconduct, Guidance, (Sep. 2004) at http://www.fda.gov/cber/gdlns/clinholdinvest.pdf.

2210 In the United States, INDs can be very long. For clinical trials involving xenotransplantation, a risky procedure, the average IND was 7,000 page long. *See* Campaign for Responsible Transplantation v. Food and Drug Administration, 219 F. Supp. 2d 106, at 109, n.4, and at 111 (D.C.C. 2002).

2211 *See* 21 C.F.R. § 312.41(b). The FDA may also spontaneously volunteer comments about the appropriateness of the study design. *See* 21 C.F.R. § 312.41(a). For a description of the practical consequences of this close

change is an opportunity to discuss the strengths and weaknesses of the upcoming marketing application. The pharmaceutical industry views this opportunity to receive advice from the FDA as highly beneficial. It enables the sponsor to correct mistakes in the trial design early on, thus facilitating the subsequent approval of its application.

7.2.2. Contents of the application

To get clearance from Swissmedic, the sponsor submits an application file in accordance with Article 14.1 OClin.[2212] However, instead of listing the mandatory content as in Article 9.2 OClin, Article 14.1.a OClin refers to the list at paragraph 4 of ICH E6 Guideline.[2213] This reference is regrettably vague, since paragraph 4 contains 13 sub-paragraphs over some 7 pages which all have to do with the investigator's obligations. The only sub-paragraph that concerns documentation is paragraph 4.4 that deals with communication between the investigator and the ethics committee. These clauses are not helpful to determine what exactly must be submitted to *Swissmedic* by the *sponsor*!

Article 14.1.c OClin further stipulates that the sponsor must supply Swissmedic with the REC's favorable opinion as well as all additional documents that the REC approved.[2214] It is not clear which are the documents "approved" by the REC, since the OClin does not explicitly mandate the *approval* by RECs of specific documents.[2215] Article 14.1.c could be interpreted to require that the sponsor hand over the same file as that received by the REC.

Article 14.2 OClin adds that Swissmedic must also receive a copy of the agreement between the sponsor (or the investigator) and the contract research organization when one has been hired.[2216] As we saw in subsection 7.1.2.3., the REC also reviews these con

cooperation, see the explanation provided by Novartis' CEO regarding the approval of Gleevec, see VASELLA, *supra* note 127, at 146-47.

2212 In the United States, see 21 C.F.R.§ 312.23.

2213 ICH E6, in its paragraph 3.1, lists the documents and information that ethics committees must receive to reach their decision. It would have perhaps made more sense to refer to this paragraph at Article 14.1.a OClin, instead of referring broadly to paragraph 4. According to the 2004 proposal to amend the OClin, the provision would have been changed, so that the reference would have been to chapter 8 of ICH E6 instead (titled Informed Consent of Trial Subjects). However, this change was finally not implemented for reasons unclear.

2214 According to the French text, "*… les documents supplémentaires qu'elle a approuvés";* according to the German text *"zusätzliche Dokumentationen, die diese gutgeheissen hat";* to the Italian text, *"e la documentazione ulteriore approvata da quest'ultima."*

2215 Article 10.2 OClin lists the aspects that the REC must verify, but does not use the term "approve." Hence, the REC does not formally approve each and every document, but just gives its opinion in favor of the entire clinical trial. This does imply that all documents were found satisfying, but that does not mean they were specifically approved.

2216 According to the second sentence of Article 14.2 OClin, this contract must clearly state the tasks that are transferred to the CRO. This delegation does not alter the liability faced by the sponsor that remains the person responsible (towards the authority and the human subjects) for the entire conduct of the trial.

tracts.[2217] Pursuant to Article 15.3 OClin, Swissmedic can request additional information as well as an external expert report.[2218]

Swissmedic has prepared a form which sponsors must use when submitting clinical trial applications.[2219] Among the documents that appear on this form, but not in the OClin, is a summary of the protocol in "plain language." Sponsors can choose to include scientific literature to back up the trial's design and scientific objectives. This literature may be very important to evaluate the safety of compounds tested for the first time on human beings.[2220]

The OClin should have contained a clause similar to that of Article 9.2.i OClin (requiring that the REC be informed of applications submitted to other RECs) so as to compel sponsors to submit copies of clearance decisions reached by foreign drug agencies. Thus, Swissmedic would know if the FDA previously turned down an application for the same drug or from the same sponsor. In the European Union, such a rule has been explicitly stated.[2221]

While Swissmedic receives notification of all clinical trials, some are eligible for a lighter version of the clearance process. Phase IV drug trials may receive Swissmedic's clearance following submission of an abridged file.[2222] Requirements are also eased for trials of drugs that contain known (i.e., already approved) active ingredients if their purpose is to gather application data;[2223] this covers generic drugs and well-known alternative/complementary medicines.[2224] Article 14.4 OClin lets Swissmedic decide what documents can be omitted. As of August 2005, Swissmedic had not issued any regulatory guideline on the subject.[2225]

2217 In addition, the REC reviews the contract between the sponsor and the investigator. As Article 14.1.c OClin is interpreted as meaning that all documents received by the REC must also be given to Swissmedic, the latter must also have access to this contract, even though Article 14.2 OClin does not specifically mention it.

2218 The OClin should have contained a clause similar to Article 9.3 OClin (which allows RECs to ask for additional information, including the external expertise report), instead of mentioning these additional documents *indirectly* in Article 15.3 OClin.

2219 The 3-page form can be downloaded at http://www.swissmedic.ch/files/pdf/Anleitung_Basisformular-F.doc and the other 4-page form at http://www.swissmedic.ch/files/formulare/B3.1.121-f.pdf (see also note 1389). Accompanying instructions are available at http://www.swissmedic.ch/files/pdf/Anleitung_Basisformular-F.doc.

2220 See footnote 987 on the Ellen Roche case.

2221 *See* E.U. Guidance (Request), *supra* note 270, at 3.

2222 Article 14.4.b OClin. Phase IV trials are studies where the already authorized drug is administered strictly according to the approved notice of use (see subsection 6.1.4. above). If the sponsor is trying to find a novel therapeutic indication for its approved drug, this is not a Phase IV trial; on the contrary, the sponsor must start from scratch with a Phase I, or perhaps a Phase II clinical trial.
In the European Union, see E.U. Guidance (Request), *supra* note 270, at 6-7.

2223 Article 14.4.a OClin.

2224 E-mail from Méroz (Sept. 2003), *supra* note 517. *See also* DHA (Ordinance Comments), *supra* note 522, at 42.

2225 E-mail from Méroz (Sept. 2003), *supra* note 517.

7.2.3. Assessment of the application

7.2.3.1. In Switzerland

Neither the LPTh nor the OClin says what exactly Swissmedic is supposed to do with the sponsor's application. Does it have to go through the same process as ethics committees? Swissmedic is not bound by provisions comparable to Article 57.1 LPTh and Article 10.1 OClin which describe ethics committees' assignment. The clearance mechanism suggests that Swissmedic's review is not as extensive as that of RECs. However, since Swissmedic receives essentially the same file as RECs (and not simply the latter's favorable opinion), this implies that its role is not just to "log in" new trials. Neither the Federal Council's message nor the FOPH's explicative report addresses the question. The first minimizes Swissmedic's review, highlighting that it is *not* a formal authorization.[2226] The second mentions that Swissmedic is only to verify that the file is complete, without checking that its contents materially comply with applicable legal principles;[2227] only in dubious cases does Swissmedic extend its analysis to the material aspects of the clinical trial. However, it is hard to imagine how Swissmedic can develop doubts if it limits its examination to a formal verification; thus, Swissmedic's officers should at least go over the entire documentation.

In its VanTx Report, the Working Group pointed out that the purely formal review by the IOCM (Swissmedic's predecessor) was inadequate to detect violations of legal or ethical principles. It acknowledged that the IOCM lacked the resources to perform an in-depth review, [2228] yet it criticized this situation as one shifting the entire responsibility for protecting subjects onto ethics committees.[2229] The current state of affairs is not better.[2230] In 2002, the Swiss Federal Audit Office submitted to the Parliament a report that criticized Swissmedic.[2231] In 2003, the Parliament decided to conduct another inquiry. The resulting report concluded that Swissmedic has overcome many, but not all, of its initial problems.[2232]

Swissmedic's department of clinical trials confirmed that its review focuses mainly on formal aspects.[2233] It verifies that the file is complete (e.g., it contains the sponsor's insurance policy). It ensures that the most up-to-date version of the protocol was sub-

---

2226 FF 1999 3151, at 3230. The Federal Council explains its position by pointing out to the fact that sponsors will not have to submit a formal demand satisfying certain conditions and do not have the right to a formal decision subject to appeal. Incidentally, this explanation is not really convincing given that sponsors do need to submit a comprehensive file and to fill in a Swissmedic form.

2227 *See* the administration's remarks on Article 6 of the 2000 draft OClin, *supra* note 8, at 8.

2228 *See* VanTx Report, *supra* note 148, at 7.

2229 *See id.* at 26 and 38.

2230 *See, e.g.,* Dominique Sprumont, *Tout va très bien, Madame la Marquise*, 84(5) BULLETIN DES MÉDECINS SUISSES 183 (2003) (commenting on the aftermath of the VanTx affair and a parliamentary inquiry into Swissmedic's operations).

2231 *See* Swiss Federal Audit Office ("*Contrôle fédéral des finances*"), Annual Report 2003, at 26, at http://www.efk.admin.ch/pdf/jahresbericht_2003_f.pdf. This complete report on Swissmedic was not made public.

2232 *See* Press Release, Swiss Parliament, State Council, (Feb. 4, 2003), at http://www.parlament.ch/f/homepage/mm-medienmitteilung.htm?m_id=2003-02-04_000_02; Commission de gestion du Conseil des Etats, Problèmes lors de la mise en fonction de Swissmedic et évaluation de la situation actuelle (Aug. 25, 2004), at http://www.parlament.ch/e/ed-pa-gpk-swissmedic.pdf.

2233 *See* Interview with Vital-Durand, *supra* note 484.

mitted to the REC. On the other hand, Swissmedic does not assess the scientific merits of the study. It does not determine whether the study will be adequate to support the subsequent marketing application. It gives no advice as to study design, even on request. Only if obvious faults are apparent does the Agency go beyond its formal evaluation;[2234] in such circumstances, Swissmedic oversteps its customary boundaries and engages in a material assessment of clinical trials.

This attitude can be confusing to ethics committees. When Swissmedic requests trial amendments after the REC has given its "green light," the REC finds itself in a situation made even more uncomfortable by the fact that it is not in direct contact with Swissmedic. The REC learns of Swissmedic's requested modifications through the investigator who, in turn, was informed by the sponsor. [2235] RECs resent this meddling by Swissmedic and would prefer to know exactly where the respective sphere of competence lays. They would not necessarily mind an additional assessment of protocols by Swissmedic: What they find problematic is the awkward process whereby lines of communications and areas of expertise remain unclear.[2236] Swissmedic apparently justifies its "transgression" of REC's authority by complaining that some ethics committees lack the expertise to do their job properly.[2237]

To address this problem, a joint group of REC and Swissmedic representatives met in 2003 to lay down recommendations clarifying the jurisdiction of each party in the area of clinical trials.[2238] For instance, the joint group recommended that, when Swissmedic requests that sponsor make a change to the design of its clinical trial, it should send a copy of the letter to the REC. The group prepared a three pages long checklist of issues that Swissmedic and/or RECs must assess before granting their approval; for each topic, the primary responsible party is indicated.[2239]

7.2.3.2. In the United States

In the United States, the role of the FDA in reviewing an IND evolves as the drug development progresses. In phase I, the accent is on the safety of the subjects and not so much on the scientific validity of the trial design.

> By narrowing the focus of the review in Phase 1 to safety, the agency is attempting to reduce "regulatory impediments to scientific creativity" in the early stages of drug development. Since the vast majority of preliminary drug studies do not lead to marketing applications, the agency has argued that it need not focus on study design so long as human subjects are not put at risk.[2240]

2234 *Id.*

2235 *See* Howard Mann, *Clinical trial protocols: agreements between the FDA and industrial sponsors*, 360 LANCET 1345 (Nov. 2, 2002).

2236 Interview with Bounameaux, *supra* note 1718.

2237 *See* Amstad et al. (Lieux), *supra* note 800, at 2453 ("Grâce à l'amélioration de la formulation, les membres des commissions d'éthique devraient éviter à Swissmedic de devoir réexaminer tous les détails des notifications d'essais cliniques.").

2238 Recommandations relatives à la collaboration entre les Commissions d'éthique de la recherche et Swissmedic, (Feb. 4, 2004). Surprisingly, Swissmedic has not published these recommendations on its website, but they are available from http://www.samw.ch/content/Dokumente/f_Checkliste%2012_11_03.pdf.

2239 Several topics are assigned to both Swissmedic and RECs.

2240 Kessler (Regulation), *supra* note 447, at 282.

In later phases, the FDA further verifies the scientific validity of the study design. It makes sure that, provided the study is conducted according to the protocol, it will yield results that will support the sponsor's marketing application.[2241]

At its own discretion, the FDA may review the documents used to obtain subjects' informed consent; such review is based on an assessment of risks.[2242] Risks may pertain to the toxicity of the investigational drug or to the vulnerability of the subject population (e.g., children).[2243] Emergency trials where consent is obtained only after the intervention (see subsection 8.4.4.2. below) usually warrant review by the FDA.[2244] The FDA can also intervene when it notices a serious deficiency that could endanger the subjects' safety.[2245] In particular, the Agency will check that the information provided to the subjects is "medically and scientifically accurate."[2246] However, according to an (admittedly old) 1983 GAO report, FDA reviewers lack the time to do an in-depth review of INDs, with the consequence that this task is given low priority.[2247]

7.2.4. The authorization process

7.2.4.1. Products involved

Pursuant to Article 54.5 LPTh and Articles 16 to 18 OClin, clinical trials involving genetic somatic therapy or genetically modified micro-organisms (GMMOs) do not go through the normal clearance route, but instead require formal authorization.[2248] This rule takes on after the 2001 European Directive.[2249]

2241 "The importance of evaluating the study design during the course of an investigation rather than at its end – at the time of the NDA [New Drug Application] submission – is highlighted by a recent study of 68 NDAs showing that a quarter of them were not approved because of flaws in design." *Id.*

2242 *See* FDA, Center for Drug Evaluation and Research, INDs: Review of Informed Consent Documents, Manual of Policies and Procedures, at 3 (MAPP 6030.2) (Nov. 13, 2002), at http://www.fda.gov/cder/mapp/6030.2.pdf [hereinafter FDA (MAPP 6030.2)].

2243 *Id.*

2244 *Id.* Other situations where the FDA may review the informed consent documents are when "the study design is unusual for the therapeutic class" or when the agency "is in a better position than the IRB to assess whether [the informed consent documents] adequately addresses a particular concern based on proprietary data." *Id.*

2245 *Id.* at 4.

2246 *Id.* at 3.

2247 GAO (Anticancer), *supra* note 1255, at 10.

2248 According to Article 16.1 OClin, the following clinical trials require authorization:
a) the introduction of genetic information into somatic cells (somatic gene therapy) (in French: "*l'introduction d'informations génétiques dans les cellules somatiques (thérapie génique somatique)*"); and
b) clinical trials of therapeutic products that contain genetically modified microorganisms pursuant to the August 25, 1999 Ordinance on confined use (in French: "*microorganismes génétiquement modifiés*"; in German: "*gentechnisch veränderte Mikroorganismen*"; in Italian "*microrganismi geneticamente modificati*").

2249 Article 9.6&4 of the 2001/20/EC Directive require that, within 90 days, Member States issue a written authorization or reject the application to conduct clinical trials involving gene therapy, somatic cell therapy, xenogenic cell therapy, and medicinal products containing genetically modified organisms.

As explained in subsection 3.2.3. above, *somatic gene therapy* is defined as the introduction of genetic information in somatic cells.[2250] The trial must *aim to* introduce such material;[2251] if introduction is only a byproduct or the unwanted result of therapy, the clinical trial does not fall within the ambit of this definition.

Genetically modified micro-organisms are defined by the Federal Council's Ordinance on the use of organisms in confined settings[2252] ("OUC"). A micro-organism is a microbiological entity, such as bacteria, viruses, parasites, prions, protozoa, cell cultures, algae or mushrooms.[2253] A genetic modification is achieved by use of specific techniques mentioned in the OUC's schedule 1, and not by the action of natural conditions (e.g., natural crossbreeding).[2254] According to Article 16.1.b OClin, as soon as a therapeutic product contains a GMMO, it has to go through the authorization procedure. If the therapeutic product does not contain GMMOs, but was produced using a process involving GMMOs, the applicability of Article 16.1 OClin will depend on the risk level.[2255]

7.2.4.2. The application and the authorization process

The sponsor's application for authorization includes, in addition to the documentation required for "ordinary" trials, information as to the risks for human health or for the environment if the GMMOs were to leak into the environment.[2256] The sponsor must also describe the safety measures taken to avoid such leakage.[2257]

Once the file is complete, Swissmedic passes it on to the Swiss Expert Committee for Biosafety,[2258] to the Federal Office for the Environment and to the Federal Office for Public Health. Each authority must issue a favorable opinion for the clinical trial to be authorized.[2259] Each authority, including Swissmedic, checks if the necessary precautions have indeed been taken to protect not only the subjects participating in the trial, but also the population and the environment should GMMOs escape the confined setting.

2250 Between 1989 and 2000, "some 4000 human subjects have participated in over 400 gene therapy trials funded by the National Institutes of Health (NIH), with numerous other subjects enrolled in privately-financed trials approved by the FDA." Baram, *supra* note 253, at 255.

2251 Article 16.1.a OClin.

2252 Ordinance of August 25, 1999; RS 814.912; in French: "*Ordonnance sur l'utilisation des organismes en milieu confiné*"; abbreviated (from the French): OUC; entered into force on Nov. 1, 1999; text in French at http://www.admin.ch/ch/f/rs/8/814.912.fr.pdf.

2253 Article 3.b OUC.

2254 Article 3.c OUC.

2255 Telephone Interview with Yves Chautems (Mar. 2004), *supra* note 170. The Article's wording remains excessively broad. For instance, if a drug's inactive ingredient is made from a variety of yeast that has been genetically modified, there should be no reason to apply Article 16.1. Moreover, when bacteria are genetically modified to produce human proteins, the end-product should not be deemed GMMOs subject to Article 16.1.

2256 Article 16.2.b OClin.

2257 Article 16.2.c OClin.

2258 See webpage at http://www.umwelt-schweiz.ch/buwal/eng/fachgebiete/fg_efbs/index.html.

2259 For example, from 1994 to February 2003, the Swiss Expert Committee for Biosafety had approved some 35 clinical trials involving gene therapy. *See* Swiss Agency for the Environment, Forests and Landscape ("SAEFL"), Gene therapy protocols approved by the Swiss committee for Biosafety, (Feb. 2003), at http://www.umwelt-schweiz.ch/imperia/md/content/efbs/51.pdf.

The above-mentioned authorities, the relevant ethics committee as well as the canton(s) where the trial takes place are informed of Swissmedic's decision.[2260] This decision must be taken within 90 days (once the sponsor's file is complete).[2261] The authorization is only valid for a maximum of five years; the sponsor must request its renewal if its clinical trial is not completed within that period of time[2262].

7.2.5. The opportunities for appeal

Whether Swissmedic delivers a clearance or a formal authorization, the OClin does not describe the possibilities for appeal. It is therefore not immediately clear whether the sponsor can appeal Swissmedic's decision. Similarly, the OClin does not indicate whether other interested parties (e.g., a patient organization) have the right to appeal. However, since the Federal Law on administrative procedure is applicable (Articles 84.1 and 85.1 LPTh), Swissmedic's decisions can be appealed to the federal appeal commission on therapeutic products ("CORE PT").[2263] This commission's decisions can be further appealed before the Federal Tribunal.

In comparison, the European Union apparently has no appeal possibility. In fact, the procedure is quite strict: The sponsor can amend its request for clearance only once.[2264] If the Member State's drug agency still finds the application unsatisfactory, the latter is definitively rejected.[2265]

2260 Article 16.4 OClin.

2261 Article 17.3 OClin.
The European Union has the same 90 days deadline, extendable for an additional 90-day period; Article 6.7 of the 2001/20/EC Directive.

2262 Article 18 OClin.

2263 The name of the Commission in French is "*Commission fédérale de recours en matière de produits thérapeutiques*"; see its webpage at http://www.admin.ch/ch/f/cf/ko/index_10003.html.

2264 Article 9.3 of Directive 2001/20/EC.

2265 See however the advice of the CCNE recommending that appellate procedures be available. CCNE N°79, *supra* note 1251, at 17.

8. Research subjects

Once the investigator has received the REC's favorable opinion and the sponsor has obtained Swissmedic's clearance, the clinical trial can actually start. The first step is to recruit human research subjects;[2266] this marks the formal beginning of the trial. Because recruitment is an integral part of the trial itself, it cannot lawfully commence as long as these two authorities have not given their green light (see section 7 above).[2267]

This section, the single largest in this thesis, is divided in seven subsections. The first subsection deals with the recruitment of subjects. The second tries to identify the type of contract which arises from the relationship between the research subject and the investigator, or between the subject and the sponsor. The third discusses the informed consent process. The fourth and fifth subsections relate to the enrollment of particular classes of subjects. The sixth subsection analyzes specific rights granted to research subjects. The last subsection asks whether subjects have any obligations towards the investigator or the sponsor.

8.1. Recruitment of subjects

8.1.1. Practical and economic issues

Recruiting subjects is typically the responsibility of the investigator, although CROs are more and more involved in this process.[2268] It is one of the most *challenging* aspects of a clinical trial. Only a small percentage of all eligible patients choose to enroll in clinical trials. For instance, despite the large number of well-publicized cancer trials, only 3 to 5% of patients choose to enroll.[2269] This same percentage is believed to hold true for research in other disease areas.[2270] It is reported that less than 50% of potential subjects *approached* by an investigator agree to enroll.[2271] The rise of individualism complicates the search for willing subjects.[2272] Older patients are said to be more receptive to proposals to participate in research.[2273] On the contrary, younger patients (less than 40

2266 No recruitment effort should begin before the approval of the ethics committee. *See* Sprumont & Béguin, *supra* note 134, at 897; VanTx Report, *supra* note 148, at 19.

2267 *See, e.g.,* Amstad (Suche), *supra* note 425, at 2218.

2268 *See, e.g.,* GT StaR (Inserat), *supra* note 2044, at 2219; Amstad (Suche), *supra* note 425, at 2216.

2269 *See* Patty Delaney Klafehn, *A trial for my life*, 273 LANCET 1812 (June 21, 1995). *See also* Mike Mitka, *Help Wanted: Participants for Clinical Trials*, 290 JAMA 1567 (Sept. 24, 2003), at http://jama.ama-assn.org/cgi/reprint/290/12/1567.pdf [hereinafter Mitka (Help)].

2270 Astralis Group, *supra* note 1154.

2271 *See* Colleen Shannon, *NICE annual conference, Better communication is key to recruiting patients to trials*, 327 BMJ 1368 (Dec. 13, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7428/1368.pdf.
See also interview with Bounameaux, *supra* note 1718.

2272 *See also* interview with Bounameaux, *supra* note 1718.

2273 *Id.*

years old) are more cautious;[2274] they may be enthusiastic about the prospect of medical research, but are reluctant to volunteer.[2275]

Once potential subjects have been contacted and enrolled, the problem switches to high attrition rates. "For every twenty patients who respond to a patient recruitment solicitation or referral, only one will complete a clinical trial."[2276] Another study found that about 23% of subjects actually enrolled eventually drop out.[2277] This attrition rate is costly for the sponsor.[2278] Moreover, study results based on a reduced set of observations are not as statistically reliable. Clearly, investing in a clinical trial that ultimately fails to yield practical data is extremely wasteful.

The investigator's standing toward the sponsor hinges in good part on meeting the target accrual rate (see already subsection 5.2.2. above). Tight accrual deadlines set by the sponsor result in considerable pressure on the investigators.[2279] Under ICH E6 Guidelines, investigators have to prove their ability to recruit the required number of subjects.[2280] Sponsors pay close attention to the recruitment performances of each of their investigators. Good recruiters increase their chance of participating in the sponsor's next trials. They may also reap additional benefits, such as bonuses and prominent position on the study authorship list.[2281]

For pharmaceutical sponsors, time is money (see also subsection 4.2.1. above). Delays in subjects' recruitment mean delays in securing marketing approval.[2282] Delays in getting to the market means delayed sales, shorter sales periods,[2283] and the loss of the first-mover advantage.[2284] This translates into market capitalization drop. And managers and officers of drug companies are paid with stock options... With financial analysts closely tracking clinical trials, even in early phases,[2285] pharmaceutical firms need to be wary of each and every delay. According to surveys, clinical trials often fail to achieve their target schedule.[2286]

2274 *Id.*

2275 *Id.*

2276 Centerwatch (Patient), *supra* note 1290, at 138. Moreover, "for every patient enrolled, four to ten must be screened to determine their eligibility." Rowe et al., *supra* note 693.

2277 *See* Wise & Drury, *supra* note 1999.

2278 "[R]ecruitment and enrollment activities consume 22.3% of the clinical development timeline. Assuming clinical trials in the United States cost $8 billion annually, the patient enrollment piece translates into a yearly expenditure of $1.78 billion." Centerwatch (Patient), *supra* note 1290, at 138.

2279 *See, e.g.,* Kleist (dringendst), *supra* note 796, at 2448.

2280 *See* section 4.2.1. of ICH E6. See also under the former intercantonal system, Article 2.5.c) of the Good Clinical Practices accompanying the IOCM 1995 Regulation.

2281 See on the various problems related to choice of authors, Graham Mowatt et al., *Prevalence of Honorary and Ghost Authorship in Cochrane Reviews*, 287 JAMA 2769-71 (June 5, 2001), at http://jama.ama-assn.org/cgi/reprint/287/21/2769.pdf. *See more generally* Philippe Ducor, *Coauthorship and Coinventorship*, 289 SCIENCE MAGAZINE 873-75 (Aug. 11, 2000), at http://watson.fapesp.br/nuplitec/873.html.

2282 The pharma industry speaks of "speed to market."

2283 Since patent protection typically starts running *before* clinical trials are even started, the longer they take, the less patent life remains once the drug finally reaches the market.

2284 *See, e.g.,* Kleist (dringendst), *supra* note 796, at 2448.

2285 See for example a press release by Novartis reporting having met its recruitment target for an important clinical trial: Novartis, Study of aromatase inhibitor Femara in adjuvant breast cancer setting reaches enrollment milestone, (Oct. 3, 2002), at http://www.novartis.de/servlet/novartismedia.pdf?id=5762.

2286 A technical synonym is "target accrual of patients."

> More than half of all US clinical trials from 1993 to 1998 missed their deadlines by at least one month. A failure to get enough patients in time accounts for 85 to 95 percent of all days lost during clinical trials. … Delays can cost pharma companies at least $800,000 a day in lost sales for a niche medication … and as much as $5.4 million for a blockbuster ….[2287]

The sponsor may terminate prematurely studies that fail to achieve their enrollment targets.[2288] The reason is that a study without a sufficient number of subjects cannot disprove the null hypothesis which is being tested by the clinical trial.[2289] In addition, because of this major flaw in the trial's scientific underpinning, subjects are deemed to be exposed to unjustified risks.[2290] Therefore, the decision to terminate a trial can also come from the authorities.[2291]

8.1.2. Factors affecting recruitment

Several factors, reviewed below, affect the speed at which subjects are recruited and enrolled in a clinical trial.

8.1.2.1. Patient pool

Finding healthy volunteers for *phase I trials* might be difficult because few persons are willing to potentially endanger their health only to advance science, without getting any direct therapeutic benefit in exchange. The remuneration received might well be the only inducement to secure their participation. Their consent may not be as disinterested as that contemplated by ethical norms.[2292]

In phase III trials, problems relate to the sheer number of patients-subjects who must be enrolled. As these trials may involve thousands of subjects, they require a huge logistical infrastructure. The studied disease must reach a sufficient prevalence rate in the geographic areas near the research sites.[2293] For rare or orphan diseases, the problem is exacerbated since patients are scarce "resources"; the solution is either to reduce the

---

2287 Rowe et al., *supra* note 693, at 134.
"Another study of 400 sites revealed that 86% of phase II and phase III clinical trials failed to recruit study subjects within the contracted enrollment period. This study also showed that the recruitment period for the typical trial is extended an average of two months." Centerwatch (Patient), *supra* note 1290, at 138.

2288 *See, e.g.*, Duke University, Comprehensive Cancer Center, Institutional Clinical Trial Monitoring procedures and Guidelines, at 5, (Jan. 2001), at http://www.nci.nih.gov/images/Documents/f69ceb.b.b.b.-fe0b-4f89-bee3-1609c2f5197b/DukeDSMPLAN.pdf.

2289 On this notion, see subsection 6.3.10.

2290 Slight overaccrual (10-15%) is relatively frequent but raises only logistic problems (e.g., number of beds, of nurses). Moreover, the investigator can always stop recruiting when the desired number of subjects have been enrolled.

2291 Under Swiss law, the legal basis is not very explicit, but Article 27.2 OClin is sufficiently general to allow for such termination. In the United States, the legal basis is unequivocal. *See* 21 C.F.R. § 312.45(e), § 312.44(b)(1)(x) and (2)(i).

2292 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 13 (commentary).

2293 In other words, there must be enough patients suffering from the disease in the geographic region in order to draw sufficient numbers in the study.

size of the clinical trial (i.e., to recruit less patients) or to conduct a multicentric trial in several regions or countries.[2294] A related factor is the existence of *competing clinical trials*. Since most pharmaceutical companies direct – or at least claim to direct[2295] – their efforts toward serious diseases with unmet medical needs,[2296] there are often many ongoing clinical trials targeting the same condition. The patient population being small, clinical trials compete with each other to enroll them.

A factor which is becoming more important relates to the emerging science of *pharmacogenomics**.[2297] To the extent that drugs are known to differ in safety or efficacy according to the genetic profile of the patient,[2298] a sponsor needs to enroll the *right* subjects, or else it may fail to show efficacy. Pharmacogenomics could result in a reduction in the number of eligible subjects (and subsequently patients). Conversely, the sponsor may find it easier and faster to demonstrate safety and efficacy if, from the start, it excludes subjects who would have suffered adverse drug reactions due to their genotype.

8.1.2.2. Existence of alternative treatments

The existence of *alternative treatments* also affects recruitment. If patients suffering from a disease can avail themselves of many effective remedies, they have less – or no – reasons to take chances with a new investigational drug, even if thought to be possibly more effective.[2299] On the contrary, when no treatment is known for a disease, participating in a clinical trial might appeal to potential subjects as their one and only chance. This occurred with AIDS in the 1980s and early 1990s. Since AIDS patients had no available remedy, they all vied to participate in existing clinical trials. It was thus found

---

2294 For example, "a clinical trial of itraconazole for the prevention of severe fungal infection in children and adults with chronic granulomatous disease … required 10 years to enroll just 39 patients." *See* Stephen W. Lagakos, *Clinical Trials and Rare Diseases*, Editorial, 348 NEW. ENG.J. MED. 2455-2456 (2003), at http://content.nejm.org/cgi/content/full/348/24/2455. *See also* Otesa Middleton, *FDA Panel Partially Backs Serono In Fertility Drug*, YAHOO FINANCE NEWS, (Sept. 30, 2003).

2295 Pfizer announces "94 new compounds in development, along with 68 other projects devoted to expanding the uses of currently available products." However, this R&D investment leads – only ? – to 15 new marketing application over the next five years; Pfizer's Annual Report 2001, Introduction by CEO Hank McKinnel, at 1.

2296 Another common expression is "widespread but highly underserved diseases." *See id.* at 2.

2297 According to the FDA "pharmacogenomics" can be "defined as the use of a pharmacogenomic or pharmacogenetic test in conjunction with drug therapy." FDA, Pharmacogenomic Data Submissions, Draft Guidance for Industry, at 1, (Nov. 2003), at http://www.fda.gov/cber/gdlns/pharmdtasub.pdf [hereinafter FDA (Pharmacogenomic Guidance)].
On the admissibility of genetic tests to decide on the proper therapeutic treatment, see in Switzerland, Federal Council's Message on genetic analysis, *supra* note 353, at 6871 (specifying that such tests do not fall within the scope of the (future) law on genetic analysis).

2298 *See, e.g.,* EMEA, CPMP, Position paper on terminology in pharmacogenetics, EMEA/CPMP/3070/01, at 1, (Nov. 21, 2002), at
http://www.emea.eu.int/pdfs/human/press/pp/307001en.pdf [hereinafter CPMP (3070/01)]; FDA (Pharmacogenomic Guidance), *supra* note 2297, at 2. *See also* the Federal Council's message accompanying the LAGH, FF 2003 I 6841, at 6886-87.

2299 *See also* Allen L. Gifford et al., *Participation in Research and Access to Experimental Treatments by HIV-infected Patients*, 346 NEW. ENG. J. MED. 1373-1382, at 1376 (2002), at
http://content.nejm.org/cgi/reprint/346/18/1373.pdf (indicating that less than 4% of cancer patients enroll in NCI cancer trials).

that 14% of them had taken part in clinical trials, and 24% had received investigational pharmaceuticals.[2300]

Alternatives are not limited to approved treatments and clinical trials. At least in the United States, patients may have the opportunity to access *investigational* drugs in large compassionate access programs (see subsection 3.4.6.2. above). The advantage of these programs is that patients do not face the risk of being assigned to the control arm of the study. On the contrary, they can choose, with the assistance of their physicians, the treatment to be tried.[2301]

A related issue is that of *timing*. Recruitment becomes difficult when physicians and/or patients become convinced of the efficacy of the investigational treatment. The risk of being randomized to the control group deters potential volunteers.[2302] Hence, shared beliefs may ultimately thwart the proof of efficacy.[2303] Furthermore, once insurance companies decide to reimburse a treatment, recruitment becomes more difficult.[2304] U.S. insurance companies occasionally reach this decision even before the treatment receives marketing approval from the drug agency.[2305]

8.1.2.3. Eligibility criteria

Inclusion and exclusion criteria are key factors to anticipate subject recruitment rates. If these criteria are too severe, recruitment of the needed number of subjects is considerably impeded.[2306]

As we have seen in subsection 6.3.7. above, commercial sponsors prefer to enroll a relatively healthy and homogeneous group of subjects (e.g., early-stage cancer instead of late-stage cancer) so as to get results that are easier to interpret.[2307] To increase their chances to prove their drug effective, they want to avoid subjects who suffer from concomitant conditions or who are taking, or have been taking, other drugs.[2308] Patients

---

2300 With more anti-AIDS therapies becoming available as approved pharmaceuticals, the incentive fades away; now, only AIDS patients who are not, or no longer, responding to existing therapies, still insist on being enrolled in clinical trials. Conversely, persons newly diagnosed with AIDS or patients reacting well to their therapy will not gamble their health on an investigational product. This is one of the reasons why sponsors often choose to move their trials to developing countries to recruit more easily so-called treatment-naïve patients, that is patients who have not yet received any anti-AIDS medication.

2301 *See* ARNO & FEIDEN, *supra* note 125, at 100.

2302 Even though there may be a large consensus that the new treatment is efficacious, this may not necessarily be true.

2303 *See* Charles Marwick, *Clinical trial investigators talk about getting the data*, 277 JAMA 1833 (June 18, 1997) [hereinafter Marwick (Talk)].

2304 *See id.*

2305 This occurs generally when there is widespread agreement in the medical community that the treatment is efficacious – whether or not this is truly the case.

2306 Some trials need to have their criteria revised to correct initial mistakes.

2307 *See* GAO (Factors Affect), *supra* note 877, at 13. "A recent study of high-dose chemotherapy for breast cancer showed that, in identifying candidates for a trial, clinicians limited referrals mostly to patients who had the best chance of survival." *Id.* at 13. See BAZELL, *supra* note 673, at 127.
See however the statistical consequences, David L. Sackett, *Why randomized controlled trials fail but needn't: 2. Failure to employ physiological statistics*, 165 CMAJ 1226, at 1230 (Oct. 30, 2001), at http://www.cmaj.ca/cgi/reprint/165/9/1226.pdf.

2308 *See* OIG (Recruiting), *supra* note 815, at 14.

who currently participate in another clinical trial are typically excluded from participation; the protocol may also call for waiting periods for patients who recently terminated participation in another clinical trial.[2309] Conversely, treatment naïve patients are very much sought after as their medical conditions tend to improve significantly with the introduction of a first therapy.

Subjects suffering from psychological disorders are often excluded out of a fear that they will not abide by the protocol and treatment instructions. Similarly, marginalized groups (e.g., drug users,[2310] homeless patients) can be disqualified from participation.[2311] Out of liability concerns, sponsors may also want to avoid subjects who are too young (because the damages awarded would be greater to compensate for a longer period of unemployment) or too old (because health risks are greater). For similar reasons, subjects at risk for suicide are often excluded, even in depression studies.[2312]

Hence, it has been found that "strict trial eligibility criteria are the 'single greatest barrier' to enrolling patients in trials."[2313] They also frustrate physicians who try in vain to refer their patients.[2314]

When eligibility criteria are perceived as exceedingly strict, patients and physicians may elude them. Dishonest investigators have breached eligibility rules of protocols and enrolled subjects who did not meet the eligibility criteria; they falsified records to incorrectly show that the eligibility criteria were satisfied.[2315] Patients who see in a clinical trial their last chance for survival may also cheat or bribe their way into the trial.[2316] Obviously, the data thus generated is less reliable.[2317]

Aware of the scientific limitations of clinical findings arising out of trials with strict eligibility requirements, drug agencies now insist that the recruited sample of subjects be representative of the general patient population.[2318] Furthermore, patient organiza-

---

2309 As Schüklenk and Hogan point out, this may seem to be an undeserved way to "thank" patients who volunteered to advance science. *Supra* note 1618, at 129-29.

2310 "Two explanations were offered for the reluctance to allow drug users to test new drugs … The first explanation was that they were shunned by the medical establishment and disdained by the public at large, making them perhaps the most marginalized members of American society. A second explanation for the absence of drug users in trials was the knee-jerk assumption that they wouldn't comply with the requirements of clinical trials. This was a clear overstatement. The myth lingered that drug users always skip appointments and fail to take their medicines as instructed." ARNO & FEIDEN, *supra* note 125, at 205-6.

2311 *See* Talmadge E. King, *Racial Disparities in Clinical Trials*, Editorial, 346 NEW. ENG. J. MED. 1400-1402 (2002), at 1402, at http://content.nejm.org/cgi/reprint/346/18/1400.pdf. *See* Thomas C. Chalmers, *Ethical implication of rejecting patients for clinical trials*, 263 LANCET 865 (Feb. 9, 1990) (evoking an "ethical double standard" when subjects are excluded, not for their own good, but to facilitate interpretation of the study results).

2312 *See* K. D. Wagner et al., *supra* note 973, at 1034.

2313 *See* GAO (Factors Affect), *supra* note 877, at 13, reporting on a 1999 study by the American Society of Clinical Oncology. *See also* OIG (Recruiting), *supra* note 815, at 14.

2314 *See* BAZELL, *supra* note 673, at 147.

2315 *See* OIG (Recruiting), *supra* note 815, at 25. *See also* FDA warning letter to Leonard J. Caputo, with the Asthma and Allergy Institute, (June 11, 2002), at http://www.fda.gov/foi/warning_letters/g3350d.htm.

2316 Arno and Feiden recount: "Admission into the AZT Phase II trial often reflected political clout more than medical necessity. A telephone call from the White House to the National Cancer Institute got at least one well-connected patient admitted. … … Some AIDS patients offered cash to buy their way into the trial; others extended bribes to BW [Burroughs Wellcome] employees who could supply the drug." *Supra* note 125, at 48, and also at 51.

2317 *See id.* 182.

2318 See for example chapter 2 of ICH E12A.

tions have attacked strict eligibility criteria as constituting unfair discrimination.[2319] AIDS activists fought hard to relax admission criteria in clinical trials.[2320]

8.1.2.4. Lack of information about the trial

Another leading reason for slow recruitment is *lack of knowledge*. Primary care physicians are often unaware of all clinical trials which could benefit their patients.[2321] Doctors lack the time to learn enough about a study and its protocol so as to be able to recommend it to their patients.[2322] Information designed specifically for patients is not sufficiently developed. Therefore, having the primary care physician recommend participation is essential if patients are to consider this option.[2323] The FDA tackled the problem in 2000 by setting up the Clinical Trials Data Bank. This on-line system collects and then publishes information about clinical trials directed against serious diseases (see subsection 10.4.2.2. below). The WHO has followed its example by setting up its own database of trials approved by the WHO.[2324] Unfortunately, no similar database exists in Switzerland.

Competition between sponsors-investigators and primary care physicians can also affect recruitment. The latter may fear "losing" their patients by referring them to another doctor acting as an investigator.[2325] This is especially true when the patient is not in a desperate situation so that the primary care practitioner has a good chance to treat him. On the contrary, when the primary physician wholeheartedly supports his patient's decision to inquire about possible clinical trials, recruitment is considerably facilitated.[2326] Sponsors sometimes address this concern by offering physicians the opportunity to become co-investigators or by paying them a referral fee.[2327] This however triggers conflict of interest problems.[2328]

2319 *See* ARNO AND FEIDEN, *supra* note 125, at 168-171.

2320 One French court has nonetheless upheld the right of the sponsor's to define its inclusion criteria and denied the investigator's right to adapt these criteria to her own liking. The investigator wanted to enroll an AIDS patient who had not yet exhausted all therapeutic alternatives, a requirement under the protocol. With the investigator's support, the patient wanted to bypass available treatments viewed as less effective in order to get immediate access to the investigational treatment. The investigator sued the sponsor for having denied the patient's enrollment. The Court found that the investigator was bound by the strict obligations she undertook when she signed the agreement with the sponsor. See Decision in Leibowitch v. Glaxo of the "Tribunal de Grande Instance" of Paris, (Oct. 4, 1995), reported in 8(3) INTERN. J. OF BIOETH. 141-43 (1997).

2321 *See, e.g.*, Petrelli, *supra* note 3; Chen et al., *supra* note 910, at 669-672; Mitka (Help), *supra* note 2269, at 1567-68.

2322 *See* GAO (Factors Affect), *supra* note 877, at 12. The burden is even greater when the primary physician is recruited as a co-investigator to administer the drug to her patients in an office. "The burden on physicians often includes the need to devote additional time to identifying and enrolling suitable individuals as well as the extra paperwork involved in recording baseline data and screening candidates." *Id.*

2323 *See* Chen et al., *supra* note 910, at 669.

2324 *See* Fiona Fleck, *WHO and science publishers team up on online register of trials*, 328 BMJ 854 (Apr. 10, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7444/854.

2325 *See* BAZELL, *supra* note 673, at 146.

2326 *See* Klafehn, *supra* note 2269.

2327 *See* Herrick, *supra* note 901 (mentioning referral fees of $40-$50 per patient referred).

2328 *See, e.g.*, OIG (Sample Guidelines), *supra* note 945, at 1, 5 and 8-9.

8.1.2.5. Design of the trial

A fifth factor affecting the recruitment of subjects is the *design* and *quality* of the clinical trial. Patients wish to receive the best treatment in the most convenient manner. The location of the research site (e.g., close or far away from home) and even its facilities, such as parking places, might be central in recruiting and retaining patients.[2329] Very sick patients may reasonably privilege quality of life over the prospect of extending their life by just a few months; they would shun clinical trials which have a negative impact on their remaining quality of life.[2330]

Many potential patients are loath to participate in controlled trials, lest they receive the inactive placebo or the (possibly) less effective active comparator.[2331] For the same reason, their primary physicians will be leery of recommending enrollment to their patients.[2332] Thus, trial designs other than the parallel group design (i.e., one group assigned to the test product and the other to the control) are considerably more appealing.[2333]

Investigators' perceptions of a clinical trial also matter. The investigator's enthusiasm can go a long way to convince subjects to enroll. Patients who sense the investigator's excitement about the new treatment get the impression that the trial will benefit them.[2334] Similarly, the way information is communicated to potential volunteers is vital. A study found that consent to inclusion in a randomized study increased significantly once information was conveyed in a more clear, detailed and objective fashion.[2335] Hence, the sponsor should use feedback from investigators and patients representatives to draft its protocol.[2336] The personality of the individual asking for consent can have a significant influence. Obviously, it is easier for pleasant and confident doctors to convince prospective subjects.[2337]

2329 *See e.g.,* Brian Vastag, *Expanded Cancer Trials Access*, Health Agencies Update, 287 JAMA 3070 (June 19, 2002), at http://jama.ama-assn.org/cgi/reprint/287/23/3070-a.pdf (explaining that the U.S. National Cancer Institute now allows all physicians to go through an accreditation process which then allows them to enroll their patients in cancer clinical trials; this facilitates trial access for patients living "in small towns and rural areas."). *See also* GAO (Factors Affect), *supra* note 877, at 13; ECRI (Guide), *supra* note 869, at 54.

2330 *See, e.g.,* ECRI (chemotherapy), *supra* note 316, at 25.

2331 *See* BAZELL, *supra* note 673, at 144; Denise Grady, *For Experimental Treatments: 'Somebody Has to Be First'*, N.Y. TIMES, June 25, 2000, at 15.11. *See* ECRI (Guide), *supra* note 869, at 54.

2332 *See* BAZELL, *supra* note 673, at 147. *See also* Marquis, *supra* note 1602, at 691-693.

2333 For example, in a crossover design, all subjects get the chance to receive the experimental treatment. *See also* note 1682 *supra*.

2334 *See* BAZELL, *supra* note 673, at 155-156.

2335 *See* Jenny Donovan et al., *Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT* (*prostage testing for cancer and treatment) study*, 325 BMJ 766-769 (Oct. 5 2002), at http://bmj.com/cgi/reprint/325/7367/766 (for instance, researchers observed that recruiters must truly believe in equipoise (i.e., equality of all proposed treatments) for the potential subjects to believe it too).

2336 *See* Astralis Group, *supra* note 1154, at 2. "In this environment, it would be a very poor sponsor who did not seek systematically input of academic investigators to the design and conduct of its clinical trial." Michael Bowden (Publish), *supra* note 1168.

2337 I was once told that the best recruiters are pregnant women.

8.1.2.6. Cost issues

A sixth factor is the *cost* of participation in a clinical trial. Costs related to participation in a clinical trial may not be reimbursed by health/sickness insurance policies (see for more details subsection 8.6.4.2. below). Aside from the cost of the drug itself, which is almost never charged to research subjects,[2338] costs may include several other expenses, such as the cost of a longer hospital stay due to the necessity of monitoring the effects of this particular investigational drug.

The issue of cost has led the American Medicare system to start reimbursing part of the costs borne by elderly patients enrolled in clinical trials, provided that they are related to normal care administered within that study.[2339] In Switzerland, only costs which would have been charged had the patient received standard treatment are normally reimbursed by sickness insurance funds.

8.1.3. Recruitment strategies

Various strategies can be implemented to recruit prospective subjects.

First, patients can be recruited through their *usual doctor*.[2340]. When the disease is one for which patients go every once in a while to see their doctors, these are the ideal contact person to approach patients. These doctors can either be invited to participate in the trial as investigators or be asked to refer their patients to the investigator. The doctors determine which of their patients are eligible for participation and try to convince them to enroll. The tradition has long been to pay doctors for their referrals.[2341] Some critics question however whether doctors ought to enroll their own patients, given that the preexisting relationship may induce the latter to acquiesce too easily to any proposal made by the former.[2342] Different approaches have been proposed to ease possible pressure on subjects, full disclosure of conflicts of interest being the most common.[2343]

Second, sponsors may turn to the *media* to hasten their recruitment process. Sponsors now spend significant amounts of money for this purpose.[2344] They place ads in

---

2338 The sponsor must normally pay for the drugs which are administered to the research subjects.

2339 *See* Jane Cys, *Trial and trial again: Matching seniors and clinical trials*, AMERICAN MEDICAL NEWS, (Apr. 1, 2002), at http://www.ama-assn.org/amednews/2002/04/01/gvsa0401.htm. The costs reimbursed include those "required for the provision of the investigational item or service, … for the clinically appropriate monitoring of the effects of the item or service, or for the prevention of complications, [and those] [m]edically necessary for the diagnosis or treatment of complications arising from the trial." *See also* the links from http://www.cms.hhs.gov/medlearn/refctmed.asp.

2340 This is common mainly in Phase IV clinical trials of non-serious disease.

2341 Typical payments to usual doctors acting as investigators are of CHF 300.- per patient visit and an additional CHF 200.- per patient who has completed all his visits. In the United States, several States (e.g., California) have prohibited *paid* referrals.

2342 "Patients may be reluctant to contradict their doctor's wishes by refusing participation in a trial, or may agree to participate because they trust and respect their physician, who they believe is looking out for their best interests. … A Presidential advisory commission went so far as to state that the patients of physician-investigators should be considered a vulnerable population." OIG (Recruiting), *supra* note 815, at 23. *See* also OIG (Reviewing), *supra* note 1187, at 5.

2343 *See* OIG (Sample Guidelines), *supra* note 945, at 11-13.

2344 *See* Diana Anderson, *supra* note 680.

newspapers, buses,[2345] run announcements on the radio or on TV. Newspapers tell the stories of subjects who did well on earlier phases of the trials. Use of the media to recruit subjects is becoming more common, even in Switzerland (see further subsection 8.1.5. below).[2346] When the disease is either self-medicated by patients or not presently treated, placing public ads may be the only way to proceed.[2347] In these circumstances, the patient has no regular contact with a doctor or a health practitioner; he may not even be aware of his medical condition (e.g., depression). The same may be true for health care prevention.[2348] Some have argued that media advertisements are indispensable in a small country like Switzerland; without them, it would be impossible to recruit the number of subjects required for Swiss research sites to participate in international multicentric studies.[2349] However, the SAMS' group on clinical trials, GT StaR, has a more reserved position; it supports the use of the media only to recruit healthy volunteers (phase I trials or preventive medicine) or patients suffering from rare diseases.[2350] It has issued (non-binding) recommendations on the recruitement of subjects using the media; these recommendations explain, for example, what can and what cannot appear in public advertisements.[2351]

Third, the *Internet* can expedite the recruitment of subjects, especially when the disease under study is serious and prominent. Patients can surf the web to find out from others what are the best treatments – whether already approved or still under investigation.[2352] Patient associations serve to relay information about available treatments (see also subsection 8.1.5. below).[2353] They are frequently solicited by pharmaceutical sponsors to help with recruitment efforts.[2354] Pharmaceutical companies post "availabilities" in their ongoing clinical trials on their websites. Private firms sell their services to match subjects and clinical trials.[2355]

Fourth, sponsors also can hold *symposiums* to inform the medical community about ongoing clinical trials.[2356] Institutions and physicians attending these meetings are invited to participate respectively as research sites and investigators. Moreover, these meetings often receive press coverage, amounting to free publicity directed toward

---

2345 *See* OIG (Recruiting), *supra* note 815, at 19.

2346 *See* Amstad (Suche), *supra* note 425, at 2216.

2347 *See, e.g., id.* at 2218; GT StaR (Inserat), *supra* note 2044, at 2219.

2348 If the individual does not know that he is at risk and/or is not aware of the available preventive measures, he will not be in contact with a doctor who could tell him about clinical trial opportunities. See*, e.g.,* GT StaR (Inserat), *supra* note 2044, at 2219.

2349 *See, e.g.,* Kleist (23), *supra* note 798, at 656.

2350 *See* GT StaR, Propositions concernant le projet de directives concernant le recrutement des sujets de recherche par voie d'annonce (Jan. 2002), at http://www.samw.ch/content/Formulare/RL%20Patsuch%20franz.pdf.

2351 *Id.*

2352 In the United States, see for example Laurence Baker et al., *Use of the Internet and E-Mail for Health Care Information*, 289 JAMA 2400-2406 (May 14, 2003), at http://jama.ama-assn.org/cgi/reprint/289/18/2400.pdf (placing the percentage of Internet users drawing on the Internet for health care information at 40%).

2353 *See* BAZELL, *supra* note 673, at 160-161.

2354 *See, e.g.,* Kleist (dringendst), *supra* note 796, at 2449.

2355 *See* ECRI (Guide), *supra* note 869, at 69-70.

2356 *See* BAZELL, *supra* note 673, at 160.

both the general public and patient communities.[2357] Other outreach programs are targeted towards the general public, involving for example patient support groups, religious organizations, or community leaders.[2358]

Fifth, to facilitate prompt recruiting, pharmaceutical firms and investigators can subcontract this task to external partners, notably *contract research organizations* (CROs).[2359] Many such organizations specialize in the recruitment of patients, flaunting impressive claims as to enrollment successes. Their tactics to recruit subjects are typical marketing techniques: The trial and its tested drug must be promoted and sold to patients like a brand name product would be to consumers. In other words, enough patients must be convinced "to buy 'the product'."[2360]

Sixth, when recruitment is difficult, *database mining* may produce a list of potential subjects.[2361] For example, investigators may exploit their hospital's databases of patients. Even more worrisome is the use of "disease registries, school medical records, mailing lists, court records."[2362] In order to protect patients' privacy, U.S. IRBs are starting to enact guidelines to circumscribe or prohibit investigators' use of third party databases.[2363]

8.1.4. Recruitment incentives for investigators

As mentioned in subsection 8.1.1. above, sponsors want to offer incentive payments to investigators that succeed in enrolling subjects. Similarly, physicians or nurses who refer subjects to investigators may receive referral fees.[2364] However, institutions are increasingly alert to the ensuing conflict of interests. Many are prohibiting such payments (see subsection 5.3.2. above), particularly payments made to the investigator based exclusively on the number of subjects enrolled (per capita payments).[2365]

Contracts binding the investigator to the sponsor may stipulate that failure to meet the stipulated rate of subject accrual may result in the termination of the relationship.[2366] Under these circumstances, the pressure on investigators to meet their target accrual rate is intense.

2357 *See* OIG (Recruiting), *supra* note 815, at 22.

2358 *See, e.g.,* NIH (Women Inclusion), *supra* note 55, at sections II.A. and IV.F.

2359 On the role of CROs, see subsection 5.6. above.

2360 *See* Rowe et al., *supra* note 693, at 134.

2361 *See* OIG (Recruiting), *supra* note 815, at 3 and 24.

2362 *See id.* at 24.

2363 *See* OIG (Sample Guidelines), *supra* note 945, at 13-14.

2364 *See* OIG (Recruiting), *supra* note 815, at 18-19 ("For example, one coordinator told us that a site … offered $75 to physicians or nurses for each subjects referred.").

2365 *See id.* at 23 and 17.

2366 *See id.* at 15.

8.1.5. "Self-recruitment"

As noted above (subsection 8.1.3.), the Internet has facilitated recruitment as more and more clinical trials are now listed on websites.[2367] The National Cancer Institute ("NCI") at the NIH has a website for cancer trials.[2368] The NIH has launched its own website, aiming to keep tab on all clinical trials.[2369] Pharmaceutical companies also post their clinical trials on the web; for example, GlaxoSmithKline (GSK) recruits volunteers through its website.[2370] Thus, patients can surf the web to find clinical trials that their primary care physicians do not even know about.[2371]

However, there is no guarantee that web trial lists are exhaustive; in fact, a study found that many trials cannot be found using the most common Internet databases.[2372] Many commentators call for putting all clinical trials on the Internet (see also subsection 10.4.1. below). The information would not only be helpful to patients, it would also allow the medical profession and the public in general to scrutinize the design and the ethics of clinical trials.[2373]

The AIDS epidemic deeply altered recruitment strategies. For the first time, organized groups of patients urged for faster approval of possible cures, while in the meantime (i.e., before the grant of a marketing authorization) lobbying for greater and fairer access to clinical trials. These groups exerted pressure to gain access to clinical trials which they viewed as their only chance to receive at least some kind of treatment. They helped disseminate information about worthy clinical trials open for enrollment. They even pushed for particular study design (e.g., smaller groups assigned to the control arm, crossover study design); they criticized faulty study designs (e.g., continuation of a study long time after the tested drug was shown more effective than the reference/comparator product). They tried to influence selection criteria to open clinical

---

2367 *See id.* at 20.

2368 NCI warns that even though "PDQ is the most comprehensive resource available on cancer clinical trials … [including] information about clinical trials sponsored by the NCI, the pharmaceutical industry, and some international groups … there is no single resource that lists every cancer clinical trial." *See* NCI, cancer.gov, User's Guide for PDQ® Clinical Trials Search, at http://cancer.gov/cancer_information/doc.aspx?viewid=F2AFAEA4-64BD-4E44-B421-56026E252389. See also http://clinicalstudies.info.nih.gov/.

2369 "*ClinicalTrials.gov* contains the most comprehensive central listing of clinical studies sponsored by the NIH, other Federal agencies, the pharmaceutical industry, and non-profit organizations, such as universities." NIH, ClinicalTrials.gov, Help for Searching ClinicalTrials.gov, at http://clinicaltrials.gov/ct/info/help#Finding (July 4, 2003). "As of late June 2004, the registry listed 10,906 trials from about 90 countries; about 40 percent are still recruiting subjects. The NIH and other federal agencies, universities, and other organizations sponsor most of the studies listed. About 2230 are sponsored at least partially by industry, and about 425 companies have registered studies. … The annual budget, including research and development, is about $3.2 million." Robert Steinbrook, *Public Registration of Clinical Trials*, 351 NEW ENGL. J. OF MED. 315, at 315 (July 22, 2004), at http://content.nejm.org/cgi/reprint/351/4/315.pdf?ck=nck [hereinafter Steinbrook (Registration)].

2370 *See* www.findclinicalstudy.com maintained by Veritas Medicine (previously it was GSK's website at http://phillytrials.com).

2371 *See* Judith Newman, *Drug Trials Reach Out for Patients* (*and Vice Versa) on the Web*, N.Y. TIMES, Feb. 27, 2001, at F5 (adding that the wealth of information available to patients on the web can "be perceived as a threat to [doctors'] authority.").

2372 *See* Eric Manheimer & Diana Anderson, *Survey of public information about ongoing clinical trials funded by industry: evaluation of completeness and accessibility*, 325 BMJ 528-531 (Sept. 7, 2002), at http://bmj.com/cgi/content/abstract/325/7363/528.

2373 *See* Richard Horton & Richard Smith, *Time to register randomised trials*, 354 Lancet 1138 (Oct. 2, 1999).

trials to the largest number of patients. They sought to promote the testing of certain combination of drugs, even when the latter were owned by different pharmaceutical companies. On the whole, these associations monitored carefully the activities of sponsors and pharmaceutical companies to defend the interests of their members. In a way, participation in a clinical trial started to be viewed, not as a privilege, but as a right. For these organizations, it was simply wrong to let patients die because of their inability to enter a clinical trial.

The organization of patients in associations has re-equilibrated the forces in presence. At least for some diseases, it is no longer a handful of drug sponsors facing thousands of disorganized individuals. Now the two sides are organized, have access to the medias and to the politicians. They can negotiate together. Patients' organizations act as a check to curb the mighty powers of pharmaceutical companies.

Patient empowerment holds the promise of amplifying this trend. Patients are encouraged to take responsibility over their health. They no longer have to follow blindly and mechanically the instructions of physicians. They are invited to learn more about their diseases, an undertaking made much easier thanks to on-line (and often free) access to medical journals. These "empowered" patients should not have to accept passively invitations to enter a clinical trial; on the contrary, they should actively negotiate their participation with sponsors. By creating and joining associations or support groups, patients facilitate these negotiations.

Imagining the future, PriceWaterhouseCoopers suggested that:

> Through an online older women's organization, [the patient suffering from blood clots] shares experiences with about 1,000 other patients all over the world. Together, they're chipping in to fund and participate in clinical trials for a new gene-based therapy. Through the Internet, they're taking bids from various research organizations, biotech companies and drug makers throughout the world.[2374]

Even though this forecast is overly ambitious, it is true that well-informed patients have the capacity to fashion clinical trials to their advantage.

8.1.6. Fairness in recruitment

In the 1800s and early 1900s, researchers were praised for first trying their treatments on themselves before experimenting on patients.[2375] Good physicians were expected to self-experiment as a proof of their faith in their treatments.[2376] Self-experimentation was invoked as an implicit defense against charges of unethical studies on subjects.[2377] Today, this prerequisite has completely disappeared.

[2374] Healthcare 2010, at 12 and also at 20.

[2375] *See* LEDERER, *supra* note 54, at 76.

[2376] *See* Grodin (Historical Origins), *supra* note 66, at 135 (Dr. Alexander who testified during the Nuremberg Trial felt that an experimenter should believe the studied problem "important enough to risk his own life along with the lives of his non-scientific colleagues."). *See also* BEAUCHAMP & CHILDRESS, *supra* note 16, at 47-48.

[2377] *See* LEDERER, *supra* note 54, at 136-37.

However, the ethical principle of justice requires that the risks and benefits of clinical research be fairly distributed among all classes of individuals.[2378] This principle, also referred to as "distributive justice," is breached if subjects are only selected from one group of people.[2379] This breach occurs whether this group is being discriminated for having to shoulder all the risks of research or favored for receiving early access to new promising treatments. As a consequence, the recruited pool of subjects should have characteristics (e.g., age, sex, ethnic group) that reasonably match those found in the population in general.[2380]

It is debated whether this principle requires that subjects be selected among those better able to shoulder the risks and inconveniences of research. It has been suggested that fully capable adults are less likely to be pressured into giving their consent and should therefore be given priority in recruitment.[2381] Yet, this view can lead to an unfair distribution of the benefits of research, if those adults are the first or the only ones to gain access to promising investigational treatments.

A similar question could be asked with respect to patients whose only therapeutic hope is participation in a clinical trial. Should these patients have priority because the investigational drug represents their last chance? This time, the risk is the opposite: These patients may not be in a position to give a truly free consent.

Ethics committees are usually assigned the responsibility of verifying whether the principle of justice is being respected.[2382] However, Swiss law does not explicitly lay down such an obligation. Besides, RECs find it hard to put this requirement into effect.[2383] First, the inclusion and exclusion criteria contained in the protocol may not be sufficient to foretell what groups of subjects will be recruited. The VanTx Working Group proposed that the investigator or sponsor describe separately the expected target population.[2384] Second, ethics committees are reluctant to object to unfairness in recruitment if the study appears scientifically sound and beneficial to enrolled subjects.

Some have argued that the ethical principle of justice also requires that the *long-term* benefits of clinical trials be fairly distributed.[2385] This implies that sponsors and investigators take steps to ensure that the drugs resulting from clinical trials will be fairly accessible to all patients. In other words, the output of a clinical trial should not be a drug priced so high that it is unaffordable to poor patients; alternatively, sponsors should have an ethical duty to set up "charitable" programs to help these patients afford expensive drugs.

2378 To distribute fairly the burden of research, "age, gender, economic status, culture, and ethnic considerations" should be taken into account. WHO (Operational Guidelines), *supra* note 1379, at 1. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 12.
In the United States, see 21 C.F.R. § 56.111(a)(3).

2379 For example, it would be unfair to target recruitment efforts only toward people living in a poor neighborhood and using the services of a community hospital.

2380 In the United States, see, for example, AAP (Guidelines), *supra* note 385; AMA (E-2.071), *supra* note 1608.

2381 *See* SPRUMONT, *supra* note 16, at 88.

2382 *See* COREC, supra note 1379, at point 2.4, p.6.

2383 Interview with Bounameaux, *supra* note 1718.

2384 *See, e.g.,* VanTx report, *supra* note 148, at 19.

2385 *See indirectly* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 12 (commentary).

8.1.7. Research subjects registers

Because healthy volunteers can earn quite a bit of money by participating in phase I trials, they may be tempted to become so-called "professional subjects." Professional subjects regularly enroll in clinical trials to supplement their income or, in some cases, to live off the revenue generated by this activity. The risks they face are increased: Not only do they take risks with each study, but these risks may be compounded when they participate in one study directly after another.

Financial considerations may also lead subjects to enroll in more than one study at the same time. Although protocols almost always restrict the participation of healthy volunteers in several studies, even introducing "washout" periods between the trials,[2386] these people may cheat for financial reasons. Not only may they lie about their past or current enrollment, but they may also hide medical conditions that would exclude them from the trial. Similarly, they may fake conditions to meet the protocol's inclusion criteria.

To protect these subjects against themselves and to ensure reliable scientific data, Swiss groups have proposed to introduce cantonal registers for healthy volunteers.[2387] These registers would record each participation in a clinical trial. Authorities could thus keep track of volunteers' involvement. Concomitant enrollment or other violations of inclusion/exclusion criteria would be both deterred and more easily detected.

The Canton of Ticino, where Italian volunteers are often recruited in phase I trials,[2388] has implemented such a register, apparently successfully.[2389] Its register uses codes to identify volunteers so as to maintain confidentiality.[2390] To safeguard subjects' health, the Canton also imposes limits on their participation in clinical trials.[2391]

Having Swissmedic establish such a register at the federal level might present some benefits. The main problem is to operate such a register while maintaining a degree of anonymity for the benefit of subjects. However, in the case of healthy volunteers, their interests should – in my opinion – yield before other interests, chiefly the interest in obtaining reliable scientific data as a basis for drugs' marketing approval.

2386 *See, e.g.,* VanTx Report, *supra* note 148, at 11 and 34.

2387 *Id.* at 33 and 35. *See also* ASSM Bulletin 1/2001, *supra* note 1059; Amstad et al. (Lieux), *supra* note 800, at 2452-53; Amstad (Zentrum), *supra* note 1831, at 1976.
See also in the context of gene therapy clinical trials, SAMS (Somatic Gene Therapy), *supra* note 342, at 4.

2388 VanTx Report, *supra* note 148, at 33 and at 11.

2389 *See* Uficio del Farmacista cantonale (Ticino), *Registro cantonale dei volontari sani*, [register of health volunteers], at http://www.ti.ch/DSS/DSP/UffFC/temi/SA/studi-clinici/reg-vol-sani.htm. VanTx Report, *supra* note 148, at 33 and 34-35.

2390 *See id.* at 11.

2391 Uficio del Farmacista cantonale, *supra* note 2389; VanTx Report, *supra* note 148, at 35.

8.2. Legal qualification of the relationship

Swiss lawyers are passionate about legal qualifications; they strive to equate each relationship with one of the few contracts set forth in the Swiss Code of Obligations ("CO"). In marked contrast, the Swiss legislator rarely bothers to spell out legal qualifications in the statutes it enacts.

Lawyers' efforts to identify the "right contract" are often awkward. Not only does the CO define only a handful of contracts, but each of them is plagued by some dreadful compulsory rule. The finest illustration is undoubtedly Article 404 CO on the contract of mandate: According to the current and ill-advised Supreme Court case law, mandates are subject to immediate termination at about any time. This absurd interpretation of Article 404 CO is all the more regrettable since most complex relationship are either labeled as a contract of mandate or as a mixed contract with "elements of mandate." The question then shifts to whether these "elements of mandate" necessarily include Article 404 CO. Unfortunately, the answer given is generally yes. The disappointing result is a legal qualification that is entirely inappropriate to encompass the (unavoidable) subtleties of real life.

8.2.1. Contract between the investigator and the research subject

What has just been said applies in particular to the investigator-subject relationship. The legislator did not bother to classify this relationship. The legal literature is at pains to do so. As always, the contract of *mandate* is the most evident choice, because the relationship between doctor and patient has typically been categorized as a mandate[2392] and because there is little alternative choice in the CO. However, clinical research differs markedly from usual medical care. The investigator's behavior is only partially dictated by the subject's interest; moreover, the subject himself is providing a service to the investigator.

The issue of legal qualification used to have important consequences, for example with respect to the choice of liability system. Taking into account the liability implications, Sprumont held the investigator-subject relationship to create a contract of *mandate* as per Article 394 CO,[2393] whereas Manaï categorizes this relationship as a *mixed* contract, with the contract of mandate being nonetheless predominant.[2394]

[2392] *See, e.g.,* ATF 114 Ia 350, at 358, at point 6. *See also* Manaï (l'éthique et le droit), *supra* note 60, at 306-307.

[2393] *See* SPRUMONT, *supra* note 16, at 324-36.

[2394] *See* MANAÏ (CONTEMPORAINE), *supra* note 16, at 254.

8.2.2. Contract between the sponsor and the research subject?

According to Sprumont, a contract of mandate also binds the sponsor to the research subject. Sprumont does not provide an in-depth analysis to justify his stance. His main argument is that the sponsor is bound by contract with the subject because it benefits from the services provided by the subject (in particular access to, and use of, the data gathered about the subject).[2395] Olivier Guillod and Philippe Schweizer propose other legal theories to establish a contractual link between the sponsor and the subject.[2396]

None of their arguments are entirely convincing. It could be argued as well that there is *no* contract between the sponsor and the subject. First, it appears that the sponsor entrusts the investigator with the entire conduct of the trial. The sponsor is not in direct contact with the subjects, and probably does not even know their identity. Almost all tasks in connection with the clinical trial are carried out by the investigator. Practically all obligations towards subjects are ascribed to the investigator. In other words, the investigator is deliberately interposed between the sponsor and the subjects. Moreover, the investigator does not contract with subjects *on behalf* of the sponsor. Forms signed by the subject mention the sponsor only incidentally, as the party providing the therapeutic products.

The fact that the sponsor is the ultimate beneficiary of the research is not reason enough to accept a direct legal relationship with the research subjects – though it might be a good reason to *want* one. Similarly, the funding of a trial is not a criteria to decide on the existence of such a relationship. For example, if the Swiss National Science Foundation (NSF) were to fund a clinical research project at a university, one would not expect – for this only reason–a direct relationship between the subjects and the SNSF.

One should also verify whether the OClin's definition of the sponsor can be the basis for such a direct contractual link? My answer is no. Although Article 5.b OClin defines the sponsor as the party taking responsibility for the launch, the management *or* the financing of a trial, it does not institute a responsibility *towards the subjects*.[2397]

Article 6.3 OClin could lead to a different interpretation. According to this provision, both the sponsor and the investigator must agree on the measures to ensure subjects' safety. Hence, caring for subjects is not the exclusive province of the investigator. The language of article 6.3 even suggests a third party stipulation ("*stipulation pour autrui*") since the agreement between the sponsor and the investigator relating to safety measures is said to be made "in the interest of research subjects." Nonetheless, the provision remains exceedingly vague to constitute the basis for a contractual link between the sponsor and human research subjects.

Does Article 7.1 OClin clarify the situation? This provision makes the sponsor liable for damages sustained by research subjects. It does create an obligation of the sponsor toward injured subjects. The second sentence of Article 7.2 OClin, especially in its Ger-

---

2395 *See* SPRUMONT, *supra* note 16, at 235-36.

2396 *See* Olivier Guillod & Philippe Schweizer, *Expérimentation des nouveaux médicaments et responsabilité civile*, *in* ASPECTS DU DROIT MÉDICAL, 93, at 97-99 (Editions Universitaires Fribourg 1987).

2397 Compare the definition of Articles 5.b and 5.c OClin, whereby only the investigator has responsibilities towards subjects. See also subsection 5.1. on the role of the sponsor as per Article 5.b OClin.

man and Italian version, suggests that the sponsor bears both a contractual and an extra-contractual (i.e., tort) liability.[2398]

However, Articles 7.1 and 7.2 OClin are insufficient to determine the basis of this contractual liability, most notably whether the sponsor is the principal in a contract of mandate. The contract arising out of these two provisions could be limited to a guarantee of indemnification for injuries sustained. Such contracts would be similar to those existing between insurance companies and insured parties; they do not necessarily give rise to a general mandate with across-the-board effects.

Whatever the qualification is, the legal obligation of the sponsor to cover subjects' damages (see subsection 8.6.5. below) makes this issue of legal qualification significantly less urgent. Before such liability was stipulated, construing a legal contract between the sponsor and the subject was crucial in order to oblige the former to indemnify the latter. Now that the insurance coverage is legally mandated, the lack of a contractual relationship between the sponsor and the subject should rarely harm the latter.[2399]

Yet it would be preferable that this issue be – once and for all – clearly addressed in the law. There has been enough scrambling by commentators. If the sponsor is to be the party ultimately liable for all actions, events and problems arising in the context of a clinical trial, the time has come to state so explicitly. The OClin ought to clearly circumscribe the realms of this liability.

8.3. The informed consent process

Except under certain rare circumstances (described in subsection 8.4. below), a prospective subject cannot be enrolled unless he gives his free, informed and explicit consent.[2400] Before that stage, only general questions can be asked to assess a person's eligibility to participate in a trial.[2401] However, if eligibility is to be decided on the basis of medical tests (e.g., blood analysis), the subject should first give his informed consent.

2398 Article 7.2 OClin ("*pour lui-même et pour l'investigateur une assurance couvrant leur responsibilité civile contractuelle et extra-contractuelle à l'endroit des sujets de recherche*"; "*die seine vertragliche und ausservertragliche Haftpflicht gegenüber der Versuchsperson und jene der Prüferin oder des Prüfers deckt*"; "*la sua responsabilità civile contrattuale ed extracontrattuale nei confronti dei soggetti dello studio nonché quella degli sperimentatori nei loro confronti*.").
On the differences between *ex contractu* and *ex delicto* liability, see GUILLOD, *supra* note 77, at 62.

2399 This is not to say that the subject would not be better off if there was a contractual relationship. For example, if the subject demands to receive follow-up supplies of the investigational drug once the trial is completed (on this topic, see subsection 8.6.2.3. below), he will find it hard to invoke such a claim against the sponsor only on the basis of tort law.

2400 According to Principle 3.1 of the Council of Europe's R(90)3 Recommendation (*supra* note 115), the consent should not only be free and informed, but also express and specific. I use "informed consent" as a short-form. Presupposed in this subsection is that the subject is fully competent (i.e., full decision-making ability). According to the Belmont report, "an autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation." Part B.1 Belmont report, *supra* note 61.

2401 The investigator may discuss the clinical trial and the eligibility tests before obtaining informed consent. However, to perform the screening tests themselves, she must have received the informed consent of the subject. For more details see the detailed guidance by the FDA: FDA (Recruiting), *supra* note 2038.

Although informed consent is not unique to clinical trials – physicians providing care outside of clinical trials must also get their patients' informed consent[2402] – the rules on informed consent for clinical trials are much stricter.[2403] Clinical trials deserve this heightened scrutiny because the scientific study design entails that subjects are not assured to receive the optimum type of care.[2404] For example, they may be receiving a placebo or they may have to give blood more often than necessary (in comparison to classic treatments). While a physician has to do what is best for his patient – and that only –, the investigator must square the subject's interest with the scientific objectives of the trial.

8.3.1. Brief historical overview

Researchers and physicians took a very long time to internalize the concept that they had a legal and moral duty to obtain consent prior to any therapeutic act, including and in particular research.[2405] Although the law has almost always stated the principle that harm done without consent is illegal, the medical profession was inclined to disregard the rule when it impeded medical progress.[2406] It was argued that as long as an intervention had a reasonable therapeutic purpose, consent from the subjects was not an absolute requirement.[2407] Conversely, only nontherapeutic interventions needed some form of consent.

Even in the late 1990s, the medical community remained split on the issue of whether journals may publish reports of studies conducted without the explicit consent of subjects.[2408] Many journals followed a "pragmatic policy" whereby they decided on a case-by-case basis whether or not to publish such reports.[2409] A 1997 study found that

---

2402 However, the rule regarding patients' informed consent (outside clinical trials) is applied strictly only to invasive procedures performed by the physician. When, for example, the latter prescribes classic medications to cure a condition, courts have not insisted on informed consent. *See* Noah, *supra* note 4, at 366.

2403 *See however id.* at 361 ("challeng[ing] the conventional wisdom that special disclosure rules should apply in the experimental context" given that "no distinct line separates standard and experimental treatment." *Id.* at 361 and 362).

2404 *See* Noah, *supra* note 4, at 371.

2405 *See Canterbury*, 464 F.2d at 779-80. A legal duty to obtain consent was acknowledged by the Courts as early as 1914 in the United States, see *Schloendorff*, 211 N.Y. 125 ("Every human being of adult years and sound mind has a right to determine what shall be done with his own body.").
According to Mazur, "[t]he term "informed consent" was first introduced into the judicial lexicon in 1957 in the written opinion of an appellate judge in California." *See supra* note 151, at 731 (referring to the decision of Salgo v. Leland Stanford Junior University Board of Trustees, 154 Cal. App. 2d 560 (1957)); BEAUCHAMP & CHILDRESS, *supra* note 16, at 77.
Today, the principle of consent is the cornerstone of the doctor-patient relationship. See the Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 290.

2406 *See, e.g.,* Annas (Dilemma), *supra* note 70, at 15-16 (about the kind of information that doctors performing early experimental transplantations gave to their patients).

2407 *See id*, at 11 and 19.

2408 *See, e.g.*, Tobias, *supra* note 2025, at 111-14.
The issue also arises in connection with photographs of and stories about patients appearing in books and medical journals. *See* Catherine A. Hood, *Videos, photographs, and patient consent*, 316 BMJ 1009-1011 (Mar. 28, 1998), at http://bmj.com/cgi/content/full/316/7136/1009.

2409 *See* Richard Smith, *Informed consent: edging forwards* (*and backwards)*, Editorial, 316 BMJ 949-951 (Mar. 28. 1998), at http://bmj.com/cgi/content/full/316/7136/949.

few journals had comprehensive ethics policies in connection with articles submitted for publication.[2410] The same year, the British Medical Journal decided, after painstaking reflexion, to publish two studies where the researchers, with the approval of their ethics committees, had decided not to seek informed consent from subjects.[2411] The two articles were accompanied by extensive commentaries.

For a long time, physicians also justified limiting the scope of information provided on the ground that too much information would upset and *distress* the subject.[2412] The upset subject would then refuse to enroll although the study was potentially beneficial.[2413] Researchers argued that patients heal better when they have full trust in their doctors, viewed as all-confident and all-knowing figures. This paternalistic attitude is referred to as the "therapeutic privilege."[2414] It corresponded to a unanimously-held view a few decades ago.[2415] But for surgical interventions,[2416] the therapeutic privilege was the rule, and explicit informed consent the exception.[2417] Instead of informing the

---

2410 "[M]any journals do not give their authors clear ethical guidance. A survey of the published instructions to authors of the 102 major English language biomedical journals showed that a quarter did not give authors any guidance on human research ethics, and only half required approval by an ethics committee or institutional review board before publication. … [in] 53 consecutive research papers published in Annals of Internal Medicine, BMJ, Lancet, JAMA, and New England Journal of Medicine … [t]he authors found that 47% did not record informed consent and 58% did not record approval by an ethics committee or institutional review board." Richard Smith, *Informed consent: the intricacies*, Editorial, 314 BMJ 1059 (Apr. 12, 1997), at http://bmj.com/archive/7087e.htm.

2411 The two studies are: Denis M. O'Rourke et al., *Evaluation of a stroke family care worker: results of a randomized controlled trial*, 314 BMJ 1071-6 (1997) and S. Bhagwanjee, *Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study*, 314 BMJ 1077-81 (1997).

2412 *See, e.g.,* FDA (1981), *supra* note 260 (citing a comment urging to take into account "patient psychology" to dispense with informed consent). In "ordinary medical practice," see *Scott*, 606 P.2d at 558; Manaï (procès), *supra* note 155, at 342 and at 361-63; Manaï (l'éthique et le droit), *supra* note 60, at 310-11. *See also* BEAUCHAMP & CHILDRESS, *supra* note 16, at 61-62 (reporting the results of a survey asking people of different origins whether a patient should be told of a prognosis of terminal illness).

2413 *See* SUSAN E. LEDERER, *supra* note 54, at 14 (also describing a 1903 experiment conducted by Cabot showing that patients are not adversely impacted by truthful disclosure).

2414 The term "therapeutic privilege" is used both in the context of clinical trials and routine medical care as an exception to the general rule of informed consent.
In the United States, see *Canterbury*, 464 F.2d at 789 (stressing that the therapeutic privilege "must be carefully circumscribed … for otherwise it might devour the disclosure rule itself."); FDA (1981), *supra* note 260 (discussing U.S. court cases limiting the therapeutic privilege). See *also* Annas (Dilemma), *supra* note 70, at 21-22.
In Switzerland, see SPRUMONT, *supra* note 16, at 70-71; GUILLOD, *supra* note 77, at 186-97. *See* generally on the obligation to inform and the therapeutic privilege the many articles published in 39(4) CMS 345-445 (1995).

2415 *See, e.g.,* Emile Thilo, *La responsibilité professionnelle du médecin*, JdT 1946 I 105, at 105-106, especially n. 1. *See also* Marina Mandofia Berney et al., *Le partage de l'information médicale dans la relation thérapeutique*, 39(4) CMS 345, at (1995), (reporting major changes of opinion regarding the need to disclose a cancer diagnosis to their patients among American doctors in less than 20 years).

2416 A survey was conducted in Switzerland in 1995 to see how many cantonal hospitals were using explicit written consent documents for surgical interventions. Out of 26 respondents, only 10 had some sort of written text. *See, e.g.,* Alain Thévenaz, Recueil de formules par lesquelles un patient consent à un traitement chirurgical, (1995) (at the Geneva Law School library).

2417 The requirement of informed consent before surgical interventions was justified on the grounds that these procedures are particularly risky. When medical treatment entailed only minor risks of injuries, the fact that the patient did not explicitly object was considered sufficient. Thus, the higher the medical risks faced by the patient, the more complete the information had to be. Thilo, *supra* note 2415, at 109-110. *See also* GUILLOD, *supra* note 77, at 53-54.

patient, the physician would speak to his close relatives who would then support the physician's decision not to inform directly the patient. While the therapeutic privilege was frequently invoked in ordinary medical practice, it was also claimed, albeit more rarely, in research.[2418] Even the 1964 and 1975 versions of the Helsinki Declaration contained therapeutic privilege exceptions.[2419]

It is now recognized that possible distress never justifies withholding information, at least not to research subjects.[2420] The investigator's belief that a potential subject will not be able to withstand full risk disclosure is not reason enough to bypass informed consent.[2421] In such a situation, the investigator has to choose either not to inform the patient and therefore not to enroll him, or to enroll and to inform him despite her concerns.[2422]

8.3.2. Information provided

The investigator and her medical team are in contact with patients, while the sponsor will normally ignore their identity. Thus, the investigator is the person responsible for communicating to subjects the characteristics as well as the risks and benefits of the clinical trial.[2423] Subjects must receive an oral presentation of the clinical trial accompa-

---

Even today in the United States, informed consent outside clinical trials and experimental treatments is an absolute requirement only for surgery. *See* Perkins v. Desipio, 736 A.2d 608, at 610 (Pa. Super. 1999) (having to decide whether a root canal procedure is surgery).

2418 See for example in France, ROUZIOUX, *supra* note 1270, at 81.

2419 The two texts do not explicitly mention the therapeutic privilege, but evoke cases where it is either not feasible to ask consent or essential not to ask it. *See* Helsinki Declaration of 1964, at paragraph II.1; Helsinki Declaration of 1975 (Tokyo amendments), at paragraph II.5.

2420 *See* Len Doyal, *Informed Consent in Medical Research*, 314 BMJ (1997), at http://bmj.com/archive/7087ed1.htm; MANAÏ (CONTEMPORAINE), *supra* note 16, at 249-50. *See however* the policy of the American Medical Association ("AMA"), Clinical Investigation, at E-2.07, at http://www.ama-assn.org/ama/pub/category/8422.html (admitting that "in exceptional circumstances," full disclosure to the subject may be contraindicated); paragraph 57, 72 and 131 of the COE Explanatory Report, *supra* note 417, at 11, 13 and 22 (regarding communication of the study results); Alexandre Mauron, *Recherche et psychogériatrie: quelques réflexions éthiques*, 60 MED. & HYG. 1175-1178 (June 5, 2002), at http://www.revmed.ch/article.php3?sid=22257 [hereinafter Mauron (psychogériatrie)] (pointing out that paternalism is still common in relation with Alzheimer's disease diagnosis).
Invoking the therapeutic privilege in *standard medical care* (i.e., outside research) is today also frowned upon, but still not entirely objectionable. See for example, under Swiss law, this 1980 Supreme Court decision: ATF 105 II 284, at 286-88, at point 6.b) and c); *but see* ATF 114 Ia 350, at 359, at point 6. *See also* GUILLOD, *supra* note 77, at 189-90.

2421 See however the U.S. experimental surgery case of Karp v. Cooley, 349 F. Supp.827 (S.D. Tex. 1972) *aff'd* 493 F.2d 408 (5th Cir. 1974) ("each doctor must use his medical judgment as to whether certain disclosures of risks would have an adverse effect on the patient so as to jeopardize the success of the proposed therapy." at 834).

2422 This issue was raised in the U.S. case of Aden v. Younger, 57 Cal. App. 3d 662 (Cal. Ct. App. 1976). The Court found that the legislator is entitled to impose a prerequisite of informed consent despite the wish of the subject not to be informed. *Id.* at 675. *See also* SPRUMONT, *supra* note 16, at 209; Sprumont, Colloque, Le Consentement Eclairé du Patient, Institut Universitaire Kurt Bösch, Cahier n°4, at 53-54; Sprumont (De l'éthique), *supra* note 159, at 142.

2423 In the United States, see, for example, Kernke v. The Menninger Clinic Inc., 173 F. Supp. 2d 1117, at 1124 (D. Kan. 2001) (confirming that the responsibility for obtaining valid informed consent from research subjects rests with the investigator, and not the sponsor).

nied by a written summary.[2424] Ideally, information should be given in a gracious and gentle manner.[2425]

For the subject to reach a valid decision about participation (i.e., "informed consent"), he must first have received information that is both *adequate in scope* and – it should go without saying – *true*.[2426] For the information to be adequate, it must cover all points that a reasonably curious subject would like to know.[2427]

Swiss law enumerates at Article 53.1 LPTh several points that must be covered. This list is only illustrative. However, the VanTx Working Group insisted that the minimal content of informed consent be stated in the law.[2428] The Federal Council can specify this content,[2429] but the OClin does not do so.[2430]

In contrast, the European Commission has established an illustrative list of points which must be covered during the informed consent process.[2431] The CIOMS has an extremely detailed list with 26 points.[2432] The U.S. OHRP has also adopted a detailed checklist.[2433]

Under U.S. and Swiss law,[2434] the rule is that "a physician is under a legal duty to disclose to the patient *all material information* – that is 'information which the physician knows or should know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject a recommended medical procedure'."[2435] The standard is usually geared toward the patients' objective point of view

---

2424 In the United States, 23% of patients are said to be functionally illiterate; Wick & Zenni, *supra* note 1445, at 526.

2425 *See* CCNE N°58, *supra* note 117, at 16.

2426 *See* GUILLOD, *supra* note 77, at 106-108 (on deceptive practices used to obtain informed consent); paragraph 20 Helsinki Declaration.
"All other factors held equal, the autonomy interest is at its height when information is perfect, because that is the condition under which an individual can exert greatest control over bodily integrity based on personal values." DuBois, *supra* note 118, at 335.

2427 As the (American) Belmont report points out, the standard cannot be the reasonably curious patient, because "the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care." Part C.1 of the Belmont Report, *supra* note 61.
In the past, the United States had set the standard to what the reasonable physician – not the reasonable patient – would find useful to disclose. "With time, this "professional standard" came under criticism for its excessive paternalism and the effective immunity that it granted to defendants in medical malpractice cases." Noah, *supra* note 4, at 367.

2428 *See* VanTx report, *supra* note 148, at 6.

2429 According to Article 54.2 LPTh, the Federal Council can specify the conditions under which subjects' consent must be obtained.

2430 Article 6 OClin mostly refers to the requirement of chapter 4.8 of the ICH E6 Guidance.

2431 *See* E.U. Guidance (Ethics Committee), *supra* note 270, at 7.

2432 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 5.
See also Article 13 COE Research Protocol.

2433 *See, e.g.,* OHRP, Informed Consent Checklist, Basic and Additional Elements, (Sep.30, 1998), at http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm.

2434 Sprumont recommends this standard for Swiss biomedical research. *See* SPRUMONT, *supra* note 16, at 69 and at 209-210. *See also* GUILLOD, *supra* note 77, at 70-71 and at 127-130; section 4.8.2 (p.15) of ICH E6 (requiring the investigator to inform subjects "of all pertinent aspects of the trial").

2435 Daum v. SpineCare Medical Group, 52 Cal. App. 4th 1285 (Cal. Ct. App. 1997), citing to Arato v. Avedon, 5 Cal. 4th 1172, at 1186 (Cal. 1993). *See also Grimes*, 782 A.2d at 844 ("A human subject is entitled to *all* material information."); Bulman v. Myers, 467 A.2d 1353, at 1355 (Pa. Super. 1983); *Canterbury*, 464 F.2d at 786-87.

(i.e., what do they want to know?), and not the physicians (i.e., what do physicians usually tell such patients?).[2436]

In theory, this is easy to say, but in practice, this can be more complex.

The investigator knows that the more she stresses the risks of the study, the lower the odds that the patient will accept to participate.[2437] If the investigator portrays her clinical trial as a succession of major hazards in a stern voice, then few patients of sound mind will ever enroll.[2438] There is so much uncertainty in clinical research that a certain level of trust is indispensable. Even a fully informed subject needs at least implicit reassurance by a figure of authority that he is making the "right choice" by enrolling.

One question is whether materiality (of information) should be appreciated only from the point of view of an *ordinary* subject or vary depending on the characteristics of the individual subject.[2439] For example, should a highly-educated subject be given very detailed information, because not only will he be able to grasp it, but he will be expecting it? In my view, the amount of information should be adapted to the expressed needs of subjects.[2440] If a subject asks to receive very detailed information, then the investigator should gratify the subject's request. However, this should not be an excuse for under-informing the uneducated, dim-witted or indifferent patient. To the extent that such a patient cannot comprehend the trial's basic principles (as summarized in the written information), he should not be enrolled. The rules are equally valid when the patient belongs to a culture which does not value self-determination.

As we saw before, the documentation in relation with a clinical trial (e.g., the protocol and the brochure) is lengthy and sometimes ridden with technical jargon. Subjects cannot be required to go through all these papers. In fact, many subjects do not even read what they are given, preferring to rely on the oral information provided by a doc-

---

See also section 4.8.5 (p.15) of ICH E6 (calling for the information to cover "all pertinent aspects of the trial."); CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6 (commentary).

2436 The first standard is generally called the "reasonable person" standard, while the second is referred to as the "professional practice" standard. In the United States, several States still follow the professional practice standard. However, it is increasingly under attack. The "arguments for 'professional' [i.e., physician-based] standard smack of an anachronistic paternalism that is at odds with any strong conception of a patient's right of self-determination." Largey v. Rothman, 540 A.2d 504, at 509 (N.J. 1988). See *also* Zeleznik v. Jewish Chronic Disease Hospital, 366 N.Y.S.2d 163, at 170 (N.Y. App. Div. 1975) ("a medical standard is largely self-serving"); *see however* Retwka v. Orentreich, 584 N.Y.S.2d 710 (S.Ct.N.Y. 1992). *See also* Jansson, *supra* note 192, at 250; Mello et al., *supra* note 1873, at 40-45; M. Miller, *supra* note 83, at 218; BEAUCHAMP & CHILDRESS, *supra* note 16, at 81-83.
Compare with the situation in the United Kingdom, see Michael Powers, *Commentary: communicating risk in the United Kingdom*, 327 BMJ 735-36 (Sept. 27, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7417/735.pdf.

2437 *See, e.g.,* R. J. Simes et al., *Randomised comparison of procedures for obtaining informed consent in clinical trial of treatment for cancer*, 293 BMJ 1065-68 (1986), abstract at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3094776&dopt=Abstract ("The main effects of total disclosure of all information compared with an individual approach to seeking consent were: a better understanding of treatment and side effects and of research aspects of the treatments; less willingness to agree to randomised treatment; and increased anxiety.").

2438 The way risks are described may even matter more than the extent of the risk. For example, a study found that risks framed in terms of probability of *survival* elicit different responses compared to risks expressed in terms of probability of death. *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 90.

2439 In the United States, most courts have opted for an objective test. *See* Noah, *supra* note 4, at 367-68.

2440 *See also* GUILLOD, *supra* note 77, at 129-30 (in the context of "ordinary medical care") and also at 130-40 (presenting other countries' stance on this issue); Manaï (procès), *supra* note 155, at 347.

tor they trust.[2441] Despite efforts to simplify the documents handed out to prospective subjects, they still require insight in medical science that most people lack.[2442]

> Most patients wouldn't dream of reading medical research. They probably imagine it to be arcane, mystical material full of numbers, formulas, and Greek symbols – the kind of stuff that Merlin used to cast his spells. They aren't far wrong, but it is possible to get to grips with medical research without being as clever as Wittgenstein. If it's any comfort, most doctors don't read or understand medical research either … [2443]

Yet, underestimating patients is not going to help. Investigators should rather try their best to educate subjects so that the latter acquire a basic grasp of medical literature. Once familiar with the terminology, subjects can become more involved in the clinical trial and in their own health care. Since some subjects participate in many successive trials, this instruction will follow and assist them for the rest of their lives. As we live to experience old age and the many medical conditions it entails, the public educational system ought to provide basic medical courses. In the meantime, subjects' requests to receive the protocol and other accompanying documents should be satisfied, and even encouraged.[2444] Confidential clauses in these documents can be edited to protect the sponsor's legitimate interests.

The investigator should provide information to subjects even if she believes or knows for certain that subjects already hold this information. She should not defend herself by saying that the subject needed no information at all on the ground that he was already cognizant of the risks.[2445] However, the amount of information given can be reduced if there is no doubt that the subject is already entirely familiar with the study (e.g., a former study nurse enrolls as subject in the trial).[2446]

It is debatable whether the subject can validly waive his right to receive information prior to enrolling.[2447] This might be admissible in cases where the subject has obtained the information from other sources, for example because the subject is himself a

---

2441 According to a 2002 survey by CenterWatch reported by Stiffler, 14% of subjects sign the written form without having read it. *See* Helen L. Stiffler, *Guidelines for Obtaining Informed Consent for Clinical Research*, APPLIED CLINICAL TRIALS, (Nov. 2003), at http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=77704.
See also Interview with Bounameaux, *supra* note 1718.

2442 *See also* Interview with Bounameaux, *supra* note 1718. *See however* P. R. Ferguson, *Patients' perceptions of information provided in clinical trials*, 28 J. MED. ETHICS 45-48 (2002), at http://jme.bmjjournals.com/cgi/content/full/28/1/45 (finding that a large majority of English research subjects surveyed considered having received the appropriate amount of information and having understood it).

2443 Smith (Read research), *supra* note 51, at 1307.

2444 The National Cancer Institutes already contemplates this possibility. *See* National Cancer Institute ("NCI"), cancer.gov, Simplification of Informed Consent Documents, at http://www.nci.nih.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page2 [hereinafter NCI (Simplification)]. *See also* CCNE N°58, *supra* note 117, at 8-9.

2445 *See however Whitlock*, 637 F. Supp. at 1468 ("Since [the subject] knew of such danger, any reliance upon its concealment [by the investigator] would be patently unreasonable.").

2446 *See also* GUILLOD, *supra* note 77, at 98-99, at 129, and at 174 (admitting such exception to the general rule only very restrictively). *See also* ATF 117 Ib 197, at point 3.b), p.203 = JdT 1992 I 214, at point 3.b), p. 218.

2447 Outside the research setting (i.e., in "ordinary medical care"), such waiver of informed consent was found acceptable under Swiss law if a minimum level of general information has been provided. *See* ATF 105 II 284, at 288, at point 6.c). *See also* GUILLOD, *supra* note 77, at 175-78; Manaï (procès), *supra* note 155, at 360-61.

doctor. But when the patient refuses to receive information because he prefers not to know, the safer – if harsher – rule is that this patient should not be enrolled.[2448] Informing the next of kin is no substitute for informing the subject.

The next subsections go over the key points that the informed consent process must cover. The emphasis here is on the type of information which goes beyond that required in ordinary medical settings.

8.3.2.1. Research versus treatment

First, patients should be aware of what a clinical trial is. They should not falsely believe that the study's objective is to give them individualized therapeutic care, nor that benefits are in any way guaranteed (i.e., "therapeutic misconception").[2449] Instead, they should appreciate that they are participating in a test study to confirm or rebut a given hypothesis, for example whether an experimental (i.e., unapproved) compound is safe and/or effective.[2450] They should know which aspects of their treatment are going to be experimental and which involve standard care.[2451] For example, if the drug has not (yet) been approved by the national agency, this fact should be explicitly disclosed. Since the objective of the trial is first scientific, subjects should understand that the treatments they will receive is to follow preset procedures. The main purpose of some of these procedures might be purely scientific, with no possible therapeutic benefits (e.g., a biopsy or extra blood taking).[2452] Subjects should be told which is which.[2453]

Although these principles seem obvious, evidence shows that subjects – at least in the United States – are still befuddled.

> In a survey of 1,882 randomly selected patients in the waiting rooms of 16 hospitals, … 371 had been research subjects. Yet, almost 20 percent of these research subjects incorrectly stated that they were not and never had been research subjects. Worse yet, about 40 percent of the studies reviewed involving these individuals were experiments that posed greater than minimal risks.[2454]

To buttress this distinction between research and treatment, the consent form should systematically refer to the studied drug as an "investigational agent," a "research drug," or some similar wording.[2455] Similarly, enrolled persons should be re-

---

2448 *See also* CCNE N°58, *supra* note 117, at 14.

2449 This belief is particularly misleading in Phase I trials where the expected benefits are practically nonexistent. *See, e.g.*, Chen et al., *supra* note 910, at 670; Grunberg & Cefalu, *supra* note 1605, at 1386-1388; Miller & Rosenstein, *supra* note 1293 (observing that "[i]nvestigators also may be subject to therapeutic misconception.").

2450 *See* section 4.8.10(b) (p.16) of ICH E6.

2451 *See* sections 4.8.10(a)&(f) (p.16) of ICH E6; paragraph 31 Helsinki Declaration. In the United States, see 21 C.F.R. § 50.25(a)(1).

2452 *See* Miller & Rosenstein, *supra* note 1293.

2453 *See* NCI (Simplification), *supra* note 2444. In the United States, see 21 C.F.R. § 50.25(a)(1).

2454 OIG (Reviewing), *supra* note 1187, at 5 (citing to a study by the 1995 Advisory Commission).

2455 *See* Horng et al., *supra* note 1256. In addition, the consent form document should not refer to the experimental drug as "new" since "the word 'new' often connotes that something is automatically better." UCSF, Consent Guidelines, Part X, CHR Guidelines, (Feb. 2005), from http://www.research.ucsf.edu/chr/Guide/chr10_ConsentGuides.asp and at http://www.research.ucsf.edu/chr/Recruit/ChrconsentBySections.asp [hereinafter UCSF (Part X)].

ferred to as "subjects," and not "patients."[2456] Subjects should be told what the scientific purpose of the study is.[2457] The study's purpose is not to be confused with the description of the study's possible or expected benefits.

If the study is a randomized well-controlled clinical trial ("RCT"), there are at least two groups with one receiving the investigational test product, while the other group receives either an inert placebo or an active drug as point of comparison. Explaining randomization procedures is usually among the hardest tasks for the physician-investigator.[2458] Understandably, patients worry that assignment by the flip of a coin does not ensure as good a treatment as a careful choice by the physician considering all medical circumstances. Even when the two treatment arms are considered equivalent – as they should, given the equipoise principle (see subsection 6.3.5.1. above) –, patients may have trouble accepting the cold logic of randomization. Many people simply do not grasp the explanations they are given regarding randomization and other trial characteristics.[2459] According to a U.S. survey of parents enrolling their children in pediatric trials, only 27% of racial minority parents understood randomization ![2460]

Patients must also understand blinding. They must accept the fact that they will not be told during the trial what kind of treatment they are receiving. Even if they choose to withdraw from the study before its normal completion, they may not learn then in which treatment arm they were randomized. However, potential subjects should be informed of the odds of being assigned to any given arm of the study.[2461]

The investigator must explain in details the *procedures* that subjects will undergo.[2462] These procedures can be medical (e.g., one visit every month to the hospital, blood taking every two months for analyses A and B, etc.) or not (e.g., photographs taken). The investigator will also describe their purposes and duration.[2463] The unforeseen addition of a significant procedure should require a complement to the subject's informed consent.[2464]

2456 *See* Miller & Rosenstein, *supra* note 1293. *See, e.g.*, the complaint filed by U.S. law firm SSKR&P in the case of Scheer v. Burke, July 2003, at http://www.sskrplaw.com/gene/scheer.pdf.

2457 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 5, point 3.

2458 *See, e.g.,* Tobias, *supra* note 2025, at 111-14. *See however* Cicely Kerr et al., *Randomisation in trials: do potential trial participants understand it and find it acceptable?*, 30 J. MED. ETHICS 80-84 (2004) (finding that English respondents to a survey did understand randomization), at http://jme.bmjjournals.com/cgi/reprint/30/1/80.pdf.

2459 *See, e.g.,* Eric Kodish et al., *Communication of Randomization in Childhood Leukemia Trials*, 291 JAMA 470, (Jan. 28, 2004), at http://jama.ama-assn.org/cgi/reprint/291/4/470.pdf (reporting that parents of children enrolled in clinical trials often do not understand the basic design of clinical research and their basic rights as legal representatives of subjects); Jeremy Sugarman, *Determining the Appropriateness of Including Children in Clinical Research*, 291 JAMA 494, at 495 (Jan. 28, 2004), at http://jama.ama-assn.org/cgi/reprint/291/4/494.pdf.

2460 This compares to 69% of parents belonging to the racial majority. "Education level alone demonstrated a significant linear association with understanding, from 7% understanding for those with less than a high school education to 78% for those parents who were college graduates." *See* Kodish et al., *supra* note 2459, at 472.

2461 *See* section 4.8.10(c) (p.16) of ICH E6

2462 *See* section 4.8.10(d) (p.16) of ICH E6. In the United States, see 21 C.F.R. § 50.25(a)(1).

2463 In the United States, see 21 C.F.R. § 50.25(a)(1).

2464 E.U. Guidance (Ethics Committee), *supra* note 270, at 23.

The investigator must tell subjects if, when and how they will be apprised of the results. She will indicate what time commitments the clinical trial entails for subjects.[2465] She will give an estimate of how many subjects are to be enrolled.[2466] The investigator will specify under what circumstances the subject may be dropped from the study without his consent.[2467]

8.3.2.2. Risk disclosure

Once subjects have been duly made aware of the fact that they are not to receive individualized care, but are to participate in a research endeavor, risk disclosure is the second most important topic to be discussed during the informed consent process. Investigators need to highlight the risks because subjects enrolling in therapeutic trials tend to be overly enthusiastic at the idea of receiving a "new" treatment. Desperate patients equate "new" with "better," although many clinical trials have concluded that "old" treatments work as well as – or even better than – new ones.[2468]

Patients should be told about the *risks and discomfort* of the study.[2469] The information is similar to that used by ethics committees in reaching their decisions on whether or not to grant a favorable opinion. Patients should know what pain or inconveniences they are sure or likely to endure.[2470] If there are known side effects, they should be described (e.g., type, gravity and statistical frequency for each side effect).[2471] Of course, risks pertaining to the experimental drug or to additional procedures mandated by the study must be mentioned. However, risks that relate to standard aspects of the treatment should also be described, unless they are entirely minor and self-evident.

This risk overview should be derived from all available information sources, most notably from past clinical trials, whether conducted by the same investigator or by different researchers. Unfavorable results of animal studies are also relevant and should be disclosed in the risk statement.[2472] When the risk profile is derived only from a small number of studies with few subjects, this fact should be specifically disclosed.[2473] Risks

---

2465 *See* section 4.8.10(s) (p.17) of ICH E6.

2466 *See* section 4.8.10(t) (p.17) of ICH E6. In the United States, see 21 C.F.R. § 50.25(b)(6). *See* FDA (1981), *supra* note 260, at comment 48 ("When multi-institutional studies are involved, an indication of the number of institutions and the approximate number of subjects will be sufficient."). See in the United States, FDA Warning Letter to Dan F. Ausman and FDA warning letter to Matthias McGuire, *supra* note 1848.

2467 *See* section 4.8.10(r) (p.17) of ICH E6.

2468 *See* ECRI (Guide), *supra* note 869, at 6.

2469 Article 54.1.a.4 LPTh. *See* sections 4.8.10(g)&(h) (p.16) of ICH E6. In the United States, see 21 C.F.R. § 50.25(a)(2). On the distinction between risks and inconveniences, see for example SPRUMONT, *supra* note 16, at 79.
Subjects should also be told about the risks related to their disease. However, I do not expand on the issue since this disclosure aspect is essentially similar for patients (receiving ordinary medical care) and for subjects (enrolled in clinical trials). *See also* Manaï (procès), *supra* note 155, at 349.

2470 Some U.S. universities have developed standard wording for common medical procedures. *See, e.g.*, UCSF (part X), *supra* note 2455.

2471 "To the extent possible, consent forms should characterize the likelihood of risks using words like 'likely,' 'frequent,' 'occasional,' and 'rare.'"UCSF (part X), *supra* note 2455.

2472 *See, e.g.*, the complained filed by the SSKR & P law firm in the case of Aderman v. the Trustees of the University of Pennsylvania in June 2000, at http://www.sskrplaw.com/gene/aderman.html.

2473 *See, e.g.,* John Hopkins Internal Committee Report, *supra* note 378.

may include hazards to the fetuses of women who are pregnant or become pregnant during or after the study (see further subsection 8.5.2. below).[2474]

Risks should not only be catalogued, they should also be evaluated for *probability and severity*.[2475] In my view, the investigator should be allowed to use a generic formula[2476] to encompass risks that are extremely unlikely to occur (e.g., 1 odd in 1,000[2477]) provided that their consequences would not be more serious than that of specifically disclosed risks. Similarly, the risk disclosure should be more extensive when the expected benefits are tenuous; thus, the highly unlikely risk of death due to cardiac attack should be disclosed in a trial of a hair loss drug, but not necessarily in a terminal stage cancer trial.[2478] Of course, if the subject expresses the wish to be told of improbable risks, the investigator should comply with his request.

Subjects should also be told how the risks they face by participating in the study differ from those they would incur if they opted for standard treatment.[2479] Subjects' attention should be drawn to the fact that not all risks might be known at this stage and that new side effects, serious or minor, may come to light during the study.[2480]

For some studies, the risks might not only relate to subjects' physical health, but may be social, legal or even psychological risks.[2481] For example, if the subject learns that he is predisposed to suffer from a genetic disease, he may have to acknowledge it when filling insurance documents (e.g., to get life or health insurance); these companies may then decline to cover the risk or raise insurance premiums.[2482] "Social risks" are

---

2474 In the United States, see 21 C.F.R. § 50.25(b)(1). *See also* FDA Warning Letter to Dan F. Ausman, *supra* note 1848.

2475 *See generally*, in the ordinary care setting, Manaï (procès), *supra* note 155, at 351.

2476 For example, the form could state "In experimental treatments, the subject may suffer medical problems because of risks that were not initially anticipated or that were believed highly unlikely. These problems can sometimes be very serious (such as death). It is important to understand that this consent form only states risks that could be foreseen and that reach a certain level of likelihood. It does not state risks that are extremely unlikely to occur. By definition, risks that are unknown at this point in time cannot be stated here. If you feel you need more information regarding this uncertainty or these risks, please say so to the investigator before signing this form."

2477 The larger the clinical trial, the more risks should be disclosed. For example, if a trial enrolls 10,000 subjects and the risk of a serious adverse reaction is estimated to be 5 out of 10,000, all subjects should probably be informed of this, because it can be anticipated that five subjects will experience this adverse reaction. On the other hand, if the trial only has 100 subjects, this risk is less relevant, even if the risk borne by each individual subject remains the same.

2478 If the subject has already received a disclosure statement including 20 different serious risks, the marginal value of adding a 21st risk is less than in trials where only 2 risks needed to be disclosed. *See however* GUILLOD, *supra* note 77, at 99 and 149-151.

2479 However, for the NCI:"[t]he risks associated with standard medical therapy that would be delivered regardless of participation in the clinical trial (such as placement of a central venous catheter) should not be included in the research consent document. Information about the risks of standard medical procedure should continue to be provided in separate informed consent documents as part of usual (nonresearch) medical care." NCI (Simplification), *supra* note 2444.

2480 In the United States, see 21 C.F.R. § 50.25(b)(1).

2481 See the Glossary (under risk) of the GCPs accompanying the (former) IOCM 1995 Regulation.
See NCI (Simplification), *supra* note 2444.

2482 Many countries have enacted laws that forbid genetic discrimination in insurance matters.
See McWilliams et al., *supra* note 1832 (remarking that RECs often lack the experience to assess psychosocial risks in genetic studies).

rare in developed countries, but in certain regions, persons can be ostracized simply because their community learns of their diseases (e.g., AIDS).[2483]

Psychological problems may arise if the subject learns, for instance, that he has a serious disease (e.g., HIV[2484])[2485] or if he finds out that his medical conditions does not respond well to treatment. To a certain extent, these risks can be removed if the investigator takes the necessary safety precautions.[2486] Thus, the investigator can propose psychological counseling for depressed subjects. She can launch educative initiatives in the community where subjects live so as to promote tolerance for subjects afflicted with a particular disease. The protocol may authorize subjects to waive their right to be informed of serious and non-treatable diseases if they do not want to or fear the consequences on their "insurability."

Care should be taken not to place an excessive emphasis on social or psychological risks. Subjects unhappy with their experience in a clinical trial could too easily claim that they suffered psychological "injuries" from their participation.[2487] Social and psychological risks must be serious and reasonably foreseeable to require disclosure. Obvious social and psychological risks should not have to be cited (e.g., the emotional pain of having to witness the dying of other subjects during the trial).

8.3.2.3. Benefit disclosure

Very few patients enroll in clinical trials exclusively to further the progress of science. Much more realistically, research subjects participate in clinical trials because they expect to personally gain something out of it.

When sick patients enroll in clinical trials, what they expect is a personal therapeutic benefit.[2488] In phase I trials that recruit healthy individuals, the motivation is usually purely financial. In both cases, the subject's expectation of future benefits may be exaggerated. Very sick patients are especially prone to this tendency (see subsection 6.1.1.3.

[2483] The risk materializes if the medical condition is disclosed, either voluntarily by the patient or accidentally by the medical team (see on confidentiality obligations, subsection 8.6.3. below). In some situations, disclosure may be inevitable, for example if the subject is seen going to a medical clinic associated with AIDS research or treatment.

[2484] In the United States, the University of California at San Francisco proposes that consent forms contain the following language: "Some of the blood taken for laboratory tests will be used to test for HIV (the AIDS test). You will receive the test results in person and will be counseled about the meaning of these results before and after the test. … Being tested for HIV may cause anxiety regardless of the test results. … Receiving positive results may make you very upset. If other people learn about your positive test results, you may have trouble obtaining insurance or employment." UCSF, Consent Guidelines, Part X, *supra* note 2455.

[2485] Since genetic pre-screening of subjects is becoming increasingly common, enrollment in a clinical trial may reveal diseases or pre-dispositions to conditions other than the one for which the trial is specifically intended.

[2486] *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 299.

[2487] Frivolous lawsuits appear likely in sensitive medical fields, such as abortion. *See* City of Akron v. Akron Center for Reproductive Health, 462 U.S. 416, at 447-48 (1983) (stating that informed consent forms do not have to comment on the psychological risk of abortion). *See* Damon Adams, *New Jersey obstetrician-gynecologist wins informed consent case*, AMNEWS, (Jan. 5, 2004), at http://www.ama-assn.org/amednews/2004/01/05/prsc0105.htm.

[2488] *See* ECRI (Guide), *supra* note 869, at 53.

above). They often view participation in a clinical trial as their best or only chance to find a cure.[2489]

Subjects should hence be told what the clinical trial's expected benefits are.[2490] Contrary to the risk disclosure, only the benefits *specific* to the trial's medical aspects should be mentioned.[2491] Benefits that are commonly available to patients receiving standard care should not be confused with benefits related to the study.[2492] Mentioning the two types of benefits together could easily mislead the subject into believing that the benefit is attainable only if he signs the consent form and accepts enrollment.

Consent forms need not focus exclusively on the benefits for the subjects themselves. They can also mention benefits for another group or society at large. Such benefits can derive from a better knowledge of the disease, which may in turn be of use for future patients.[2493]

Investigators should be particularly cautious about the way they present the expected benefits;[2494] in particular, they should explain the basis of their judgment. The investigator, as well as the consent form and all advertising material, should be extremely conservative in the way they state the benefits.[2495] As is the case with the risk disclosure, both the importance of the benefits and their likelihood should be described.

Language that could induce excessive hope in the subjects should be avoided.[2496] Words like "great," "wonderful," "promising," should not be used. Similarly, expressions like "this is your chance" or "this is an opportunity" or "you have been selected to join" can be misleading.[2497] Promises that subjects will receive better care or more attention than that available in standard individualized treatments should not be made (even if true).[2498] The investigational compound should rarely, if ever, be described as "safe," since the objective of any clinical trial is precisely to assess this. Even preliminary evidence of efficacy should be described in guarded terms. To the extent that the investigator is affirming that the investigational product is efficacious, she should give accurate measures of this efficacy, since a blank statement – such as 'this product was

---

2489 *See, e.g.,* OHRP (Children), *supra* note 1636, at 11.

2490 Article 54.1.a.4 LPTh. In the United States, see 21 C.F.R. § 50.25(a)(3).

2491 Sprumont points out that the fact that subjects will enjoy a private room in the hospital (as opposed to a common room shared by "ordinary" patients) should not be mentioned as a benefit. *See* SPRUMONT, *supra* note 16, at 86.

2492 *See id.* at 85.

2493 The U.S. National Cancer Institute suggests the following language: "The information learned from this study should help future patients with" disease X. *See* NCI (Simplification), *supra* note 2444.

2494 SPRUMONT, *supra* note 16, at 85-86.

2495 *See* in the United States, NCI (Simplification), *supra* note 2444. *See also* FDA Warning Letter to Dan F. Ausman, *supra* note 1848; UCSF, Consent Guidelines, Part X, *supra* note 2455; Lawrence K. Altman, *The Doctor's World, Fatal Drug Trial Raises Questions About 'Informed Consent'*, N.Y. TIMES, Oct. 5, 1993, at C3.

2496 See for example, the following clause cited in the U.S. court case of Hendricks v. Central Reserve Life Insurance Co., 39 F.3d 507, at 510 (4th Cir. 1994). "Although it is hoped that this treatment and study will be of benefit and that it will help others, it cannot be said that it will help directly. I may expect to benefit from this project to the extent that any treatment I receive helps to manage my condition. There is no assurance, however, that participating will result in any improvement. I may also receive personal satisfaction from the knowledge that my participation in this project has contributed to the advancement of science."

2497 *See, e.g.* Council of Europe (Riis), *supra* note 1847, at 19.

2498 *See, e.g.*, the complaint filed by the SSKR&P law firm in the case of Scheer v. Burke, July 2003, at http://www.sskrplaw.com/gene/scheer.pdf.

shown effective in the treatment of X' – can be misleading if the evidence is not absolutely clear-cut.

The consent form should not stress that the product has received marketing approval if the clinical trial investigates *another therapeutic indication* (e.g., approved for breast cancer but tested for colon cancer). The favorable opinion of the ethics committee should not be presented deceptively as an assurance of scientific quality.

Payments given to healthy volunteers or indemnities offered to patient-subjects should not be presented as a benefit. Clauses regarding payment and those pertaining to benefits should appear in different sections of the consent form.[2499]

8.3.2.4. Information about available alternatives

It is important that the patient-subject be told what his other *alternatives* are.[2500] He should know for example if there is already an effective drug on the market that he will not be allowed to use if he is enrolled in the clinical trial.[2501] For this information to be really useful, the investigator must explain what are the *comparative* risks and advantages of the investigational treatment versus the other available treatments.[2502] This comparison is made difficult because the advantages and disadvantages of the treatments that are available on the market are well known (based on the notice of use), while the advantages and disadvantages of the investigational treatment are only speculative at this stage.

Should comparisons also be made with treatments not (yet) on the market? Article 54.1.a.3 LPTh only refers to "the existence of treatments other than those proposed within the clinical trial." As many therapies against serious diseases (e.g., AIDS) are accessible as investigational treatments in the context of clinical trials, the question is whether the investigator must inform her potential subjects that other clinical trials are presently enrolling subjects with the given medical condition.[2503] The same question must be answered when an alternative but unapproved treatment is available under some kind of compassionate use program. A similar issue arises – but is easier to resolve – with respect to off-label use.

My answer to these questions would be positive. Subjects have an evident interest in knowing *all* alternatives – approved or not – before deciding to join a given clinical trial. Moreover, since information about the availability of clinical trials and other access programs is not easily available, subjects necessarily depend on the investigator to provide them with such information.

2499 *See* ECRI (Guide), *supra* note 869, at 63.

2500 Article 54.1.a.3 LPTh. Of course, if the subject is a healthy volunteer, this disclosure is not applicable. *See also* section 4.8.10(i) (p.16) of ICH E6. In the United States, see 21 C.F.R. § 50.25(a)(4).

2501 This obligation is sometimes breached. *See, e.g.,* BRODY, *supra* note 447, at 31 (discussing the ethical validity of a clinical trial of two investigational thrombolytic agents).

2502 In the United States, see for example, Steward v. Cleveland Clinic Foundation, 736 N.E.2d 491 (Ohio Ct. App. 1999); Foflygen v. Allegheny General Hospital, 723 A.2d 705, at 708 (Pa. Super. 1999).

2503 In a study on Phase I oncology trials, researchers found that "[informed consent] forms for trials involving subjects with metastatic or advanced cancers included other experimental therapies as alternatives more often (125 of 222 forms [56 percent]) than forms for trials that did not involve subjects with such cancers (17 of 49 [35 percent] …)." Horng et al., *supra* note 1256.

Of course, this obligation of the investigator is contingent on her knowledge. The investigator may not be aware of all clinical trials and expanded access programs. These trials may take place in another region or country. Many drug agencies do not publicize their trials.[2504] Even when the existence of a trial is made public, the amount of information available may be limited to a brief summary of the key facts (e.g., objectives, entry criteria), with no explanation as to the respective advantages and disadvantages. Nearly all sponsors and investigators regard their protocols as highly confidential and will not lend it to third parties, notably potential rivals (see also subsection 10.4.2.). As a result, in many cases, the investigator herself lacks access to information to describe to her prospective subjects the other unapproved alternative treatments.

The U.S. National Cancer Institute ("NCI") insists that cancer patients be informed of the "no treatment" alternative.[2505] Hence, its template consent form mentions among the alternatives: "no therapy at this time [but] care to help you feel more comfortable."[2506]

Conversely, the question arises whether physicians who are not participating as investigators in a clinical trial have a duty to inform their patients of the alternative that consists in enrolling in such a trial. If the existence of ongoing clinical trials were to be better publicized (e.g., an Internet database describing all current trials), physicians too should have the duty to communicate good research opportunities to their patients.

8.3.2.5. Information about conflicts of interest

Swiss law does not state whether human research subjects *must* be informed of actual or potential conflicts of interest affecting people involved in the study (e.g., investigators, sponsors, monitors, REC members). Nevertheless, ethics committees ought to systematically impose this requirement. This assumes of course that RECs have asked to receive the corresponding information from investigators;[2507] information provided to RECs pursuant to Article 9.2.d OClin (i.e., amounts to be paid to the investigator) is not sufficient to ascertain all potential conflicts of interest.

The United States favors extensive disclosure to subjects. The HHS recommends that subjects be told of funding sources for the various aspects of the trial (including payments to investigators and funding of IRB review).[2508] Existing conflicts of interest should be disclosed to subjects, alongside with the corresponding measures undertaken to minimize their consequences.[2509]

2504 On measures to promote transparency, see subsection 10.4.2. below.

2505 *See also* Bouvia v. the Superior Court of Los Angeles County, 179 Cal. App. 3d 1127 (Ct.App. Cal. 1986) (defending, in a "very well reasoned and superbly crafted opinion," the right of a patient to commit suicide by refusing medical intervention).

2506 *See* NCI (Simplification), *supra* note 2444.

2507 *See, e.g.*, paragraph 13 Helsinki Declaration.

2508 *See* HHS Interim Guidance, *supra* note 938, at chapters 5.1 and 5.2. Such disclosure must occur when the source of funding is deemed material information for the subject. The Guidance does not say how this materiality is to be judged. *See also* paragraph 22 of Helsinki Declaration (requiring that "sources of funding" be disclosed to subjects).

2509 *See* HHS Interim Guidance, *supra* note 938, at chapter 5.3; ICMJE, *supra* note 945, at II.D.1.

The U.S. case of *Moore v. Regents of the University of California*[2510] buttressed the importance of conflicts of interest disclosures. In this affair, the Supreme Court of the State of California had to decide whether a patient named John Moore could stop University researchers from using his cells extracted from his spleen to manufacture a product, which was to be sold on a for-profit basis.[2511] Moore had agreed to the *therapeutic* procedure during which part of his spleen was excised. However, he had given no instruction as to how his removed organ and cells were to be used or discarded afterwards. In fact, he was not aware that the researchers had, from the beginning, intended to use his cells for research purposes. Additionally, the researchers tricked Moore into participating in additional medical procedures which were not aimed at improving his condition, but rather were made necessary by the team's research objectives.[2512] These non-therapeutic actions entailed extracting additional samples of biological material. Ultimately, the medical team led by its principal researcher, Dr. David Golde, applied and obtained a patent on a cell line derived from Moore's cells. Later, Golde and the University set up a lucrative collaboration with a commercial firm with a view to developing a commercial product out of the cell line.[2513]

The California Supreme Court agreed with Mr. Moore that the medical team had breached its fiduciary duty by not disclosing "facts material to the patient's consent" and by conducting medical procedures without his informed consent.[2514] Although this case was not decided on the basis that it involved a clinical trial (but rather a medical procedure apparently intended exclusively for the therapeutic benefit of the individual patient), it is highly relevant in the clinical trial setting: Protections bestowed upon patients should *a fortiori* be granted to subjects. The right to be informed of financial conflicts of interest is even more valuable in the clinical research context, because research subjects – as opposed to patients – are accepting to bear increased risks; they must know exactly the underlying reasons for the risky procedures they agree to go through.[2515] Furthermore, in the *Moore* case, the issue was indirectly whether the researchers had honored their duties toward a human research subject.

The Court's first finding was articulated in a straightforward manner: It reiterated the right of patients (and implicitly research subjects) to be informed of all material facts. Financial interests, including ones related to research, are material facts, given the possibility that they "affect the physician's professional judgment."[2516] They should therefore be disclosed. The Court observed that information about researchers' ultimate

---

2510 Moore v. Regents of the University of California, 51 Cal. 3d 120 (Cal. 1990), at http://www.richmond.edu/~wolf/moore.htm. This decision is only valid law in the State of California. However, it has been influential throughout the United States and even in Europe. *See* Henderson & Smith, *supra* note 938, at 453.

2511 The California Supreme Court essentially reviewed whether the plaintiff, Mr. Moore, had validly stated a cause of action against the defendants. It overturned the decision of the lower court which had found that Moore had failed to state such a cause. *See Moore*, 51 Cal.3d at 133-34.

2512 *See id.* at 126.

2513 *See id.* at 127-28.

2514 *Id.* at 129.

2515 On the other hand, the threshold of what constitutes a conflict of interest is somewhat different in research (as compared to ordinary medical care), because subjects already expect that the sponsor has a commercial interest in its product and that the investigator is being paid by the sponsor.

2516 *See id.* at 129.

interests may confuse the patient, but nonetheless insisted that the responsibility for accepting a given medical treatment must ultimately rest on *fully informed* patients.[2517]

Hence, subjects should be given information about all conflicts of interest which may affect the study actors, in particular the investigator and her team.[2518] In more benign cases, the investigator may be moved only by a desire to publish or to explore additional avenues of research beyond those specifically pursued by the sponsor. When those endeavors can interfere with the ordinary conduct of the clinical study, for example because they necessitate additional medical procedures that go beyond the sponsor's needs, the subjects should receive corresponding information.[2519]

Special attention should be paid to *financial* conflicts of interest. Those should be clearly stated and summarized in the consent form. When the amount at issue is relevant, for example because particularly large, it should be mentioned.[2520] Investigators could very well use the disclosure requirements of U.S. medical journals as a guide; what readers may want to know should obviously be of even greater interest to research subjects. The disclosure should not only extend to the investigator and her medical team, but also to all other parties involved in the trial (e.g., the CRO). Even obvious comments, such as the fact that the sponsor is hoping to commercialize a product based on the clinical trial data, should be made. The Draft Additional Protocol on Biological Research of the Convention on Human Rights and Biomedicine states that subjects should be informed of "any foreseen potential further uses, including commercial uses, of the research results, data or biological materials."[2521]

8.3.2.6. Information about costs

As is the case with patients, subjects must be informed of the cost they will have to bear in relation with the clinical trial, including the standard medical treatments they may be receiving too.[2522]

First, they should be informed of any costs they will have to bear themselves. In Switzerland, there are usually none, except for the insurance copay or deductible amount (see subsection 8.6.4.2. below).

2517 *See id.* at 131.

2518 On patients' wish to receive information about conflicts of interest related to clinical trials and the effect on their willingness to participate, see the Internet survey conducted by Scott Y. Kim et al., *Potential research participants' view regarding researcher and institutional financial conflicts of interest*, 30 J. MED. ETHICS 73-79 (2004), at http://jme.bmjjournals.com/cgi/reprint/30/1/73.pdf.

2519 In the Moore case, the obligation to disclose possible conflicts of interest was made to lie with the investigator, and not with other parties involved in the research project (e.g., the sponsor). However, Mr. Moore was not enrolled as a research subject in the trial, but was treated as a "classic" patient. *See* Frank J. Wozniak, *Physician's Use of Patient's Tissues, Cells, or Bodily Substances for Medical Research or Economic Purposes*, 16 A.L.R.5th 143 (1993).

2520 *See* Wadlund, *supra* note 680, at 51.

2521 Article 13.2.vii&viii COE Research Protocol (mandating disclosure of source of funding). *See also* Article 15.2.vi) draft COE Biological Instrument and paragraph 60 draft COE Biological Report, *supra* notes 492 and 493, at 12.

2522 See in relation with "ordinary medical care," the Supreme Court decision of December 23, 1993, ATF 119 II 456, from at http://www.polyreg.ch/begleitentscheide/Band_119_1993/BGE_119_II_456.html (finding that doctors have a duty to warn patients when the costs of their treatment is not (or may not be) covered by sickness insurance).

Second, they should be told about the costs to be borne by their insurance company and the procedures needed to obtain such insurance payments (see subsection 8.6.4.2.3. below). This is necessary when the subject has to initiate himself the steps to secure reimbursement. In cases when the insurance company could refuse reimbursement (e.g., the gray zone between experimental and standard treatment), this obligation matters all the more.

Finally, in my view, the subject should also receive a general and normally brief description of the costs undertaken by the sponsor and/or the investigator. Subjects should be made sensitive to the costs associated with R&D. For example, knowing that the sponsor is investing millions of dollars to test its compounds is relevant information.

8.3.2.7. Information about future research

We saw that clinical trials under the OClin are defined as those involving the administration of a therapeutic product to living subjects to study its properties. Many other types of research do not come under the ambit of the OClin because they do not meet these conditions. In particular, research using already gathered data is not subject to the OClin.

Although Switzerland has not yet enacted a comprehensive set of regulations to govern these other types of research (see subsection 3.2.1. above), this does not mean that the general requirement of informed consent can be entirely avoided. Ethical texts call for such consent. For example, the Council of Europe's draft Instrument on the use of archived human biological materials in biomedical research would compel researchers to obtain the prior consent of the donor before engaging in research making use of already available identifiable biological material.[2523]

Hence, it is good practice to anticipate and solicit the subject's consent in advance for all possible anticipated use in research of "his" data or biological material. Such further use of biological material is increasingly common. Whenever the data are not destroyed but remain stored at a research institution (e.g., a medical school), it can be expected that they will be "recycled" for some future research. Thus, the mention of further research uses should be the rule, not the exception.

Since the subject should provide his consent for these other scientific projects, the consent form should include a corresponding section on these proposed uses. Of course, the information that the investigator can provide at this stage may be considerably less than for a current project. However, the information should be sufficient for the subject to reach some decision, which could also be the postponement of his consent until a precise study has been put forward. The draft COE Instrument stresses that subjects should be offered as many options in order to "adjust" their consent.[2524] According to the Council of Europe, the subject should be allowed to give his consent to a given category of research projects, while refusing it for others. When there is no risk of disclosure to third parties and thus no or little threat to the subject's privacy and confi-

[2523] For example, see draft COE Biological Report, *supra* note 493, at 12.

[2524] *See* draft COE Biological Report, *supra* note 493, at 12, paragraphs 61 and 62.

dentiality interests, one can ask whether the position of the Council of Europe is not excessively strict. Although the general principle is that the interests of subjects should prevail over that of science and that self-determination is of paramount importance, what is left of the research freedom if scientists cannot engage in most research avenues without multiple authorizations?

8.3.2.8. Information about subjects' rights

Prospective subjects must be informed of their rights before, during and after the clinical trial. These rights include, for example, the right to refuse consent, the right to withdraw consent at any time, the right to be compensated in case of injury. These rights are further analyzed in subsection 8.6.

8.3.3. Consent as a process

It has been repeated that research subjects' consent, and especially the signing of the written form, should not be viewed as an isolated event occurring at the beginning of the trial; rather, informed consent is a *process*.[2525]

That informed consent is a process also reveals its somewhat mythical nature. Fully informed consent is an idealized or utopian standard.[2526] Philosophically, it can be argued that no human decision is ever fully informed. Where is the liberty of choice when very sick patients are asked by their doctor to enroll in what could represent their last chance of survival?

8.3.3.1. The main steps of the process

Although the OClin says little about what information must be provided and how, guidelines have elaborated a consent process which is rather formal.

First, subjects must receive information about the study and retain a written summary of this information. The information should be given both orally and in writing, usually in that order. Information given exclusively in writing does not suffice.[2527] Pref-

---

[2525] *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary); FDA (1981), *supra* note 260, at comment 51 ("The consent form, thus, should not be viewed as an end point. Rather, it is the beginning."); NCI (Simplification), *supra* note 2444; Office for Protection from Research Risks ("OPRR"), Tips on Informed Consent, (updated June 23, 2000), http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm [hereinafter OPRR (Tips)]. *See also* Theresa Arnold, *The Informed Consent Doctrine*, *A Defined Responsibility*, 99 NEW JERSEY MEDICINE 24 (Apr. 2002), at http://www.msnj.org/pdfs/NJMApril02/ProfessionalLiability.pdf.

[2526] *See* Beecher (Myth), *supra* note 103, at 34; Beecher (Guiding), *supra* note 103, at 157. *See also* GUILLOD, *supra* note 77, at 165-66; BEAUCHAMP & CHILDRESS, *supra* note 16, at 89.

[2527] Especially when the patient is hospitalized and has to sign various documents, he could too easily overlook the informed consent form and sign it without even having read it. *See, e.g.,* Baird v. American Medical Optics, 713 A.2d 1019 (N.J. 1998) (a case where the patient had signed a four-page consent form but nevertheless contended that she had never read it, had received no oral explanations and had not been aware of having participated in a clinical trial).

erably the *same* information should be given orally and in writing.[2528] To satisfy the oral requirement, new communication techniques are now coming into use; investigators can employ video presentations.[2529] Subjects may also be given a DVD that encapsulates all the key information;[2530] increasingly, subjects are encouraged to tape record their discussions with the investigator (or her delegate) so that they can go back to the tape in order to recollect the entire information.[2531]

Informing subjects and getting their consent is normally the responsibility of the investigator.[2532] Under her responsibility, the investigator is allowed to *delegate* this task, for example, to a sub-investigator or to a study nurse. The person entrusted with this task must be fully knowledgeable about the trial.[2533] He must have received training to familiarize himself with applicable regulatory, ethical and internal guidelines.[2534] Not less importantly, he should have the "social" skills necessary to convey the required information in an appropriate manner.[2535] The subject, if he so choses, may nonetheless ask to speak with the investigator.[2536]

Normally, the information should be supplied during a one-on-one session, that is the dialogue should take place between the potential subject and the investigator or her appointed delegate. A witness may also be present (see subsection 8.3.3.5. below). Group sessions where all potential subjects are present are as a rule not appropriate. The presence of other subjects could easily inhibit questions. Others may feel pressured into following the opinions expressed by the majority.

This dialogue between the prospective subject and the investigator (or her delegate in charge of the informed consent process) should be appropriately documented. Preferably, the length of the conversation should be stated. The file should also indicate that the subject was invited to ask questions, whether he asked any and which answers he received. Such information is important in case of subsequent litigation. Oral information constitutes a key complement to the signed consent form.

2528 In case of subsequent disputes, only the written form is likely to be available as evidence. This speaks in favor of detailed consent forms. However, when the form becomes *too detailed*, it ceases to convey information efficiently.

2529 *See, e.g.*, Arnold, *supra* note 2525, at 26, 27 and 30. *See also* GUILLOD, *supra* note 77, at 58 and 171 (in the context of "ordinary medical care").

2530 *See* paragraph 72 of the COE Explanatory Report, *supra* note 417, at 13.

2531 *See, e.g.,* ECRI (chemotherapy), *supra* note 316, at 27; ECRI (Guide), *supra* note 869, at 2. *See also generally* Martin H. N. Tattersall & Phyllis N. Butow, *Consultation audio tapes: an underused cancer patient information aid and clinical research tool*, 3 LANCET ONCOL. 431-37 (July 2002).

2532 *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6, (commentary).
See in the United States, 21 C.F.R. § 312.60.

2533 In the United States, see for instance Foflygen v. Allegheny General Hospital, 723 A.2d 705, at 710 (Pa. Super. 1999). See also *City of Akron*, 462 U.S. at 447-48 (in the context of surgical abortion).
See however, under Swiss law, in the context of "ordinary medical care," GUILLOD, *supra* note 77, at 119-121. *See also* EFGCP News (Autumn 2000), *supra* note 1145, at 1 and 4.

2534 *See* Stiffler, *supra* note 2441.

2535 *See* Wadlund, *supra* note 680, at 52.

2536 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6, (commentary).

At no point should subjects be coerced into giving consent.[2537] Persuasion used by the medical team must remain within acceptable limits, which may in turn depend on the risk and benefits of the study (see on this issue, subsection 8.3.3.9. below).

Second, subjects' consent must be laid down in writing;[2538] they sign and date the consent form prepared by the sponsor and approved by the ethics committee[2539] (see subsection 7.1.2.5.6. above). When subjects are competent (i.e., capable of judgment/self-determination), only their consent is needed to enroll them in a research. Spouses and other family members cannot object to the subject's wish to participate in research.[2540] Similarly, they do not have a right to receive information.[2541]

Third, investigators should document the whole consent process.[2542] For instance, they should write when they met with potential participants to explain them the purpose and risks of the trial. The signed consent form should be kept in a regulatory file.[2543] In U.S. commercial trials, appointees of the investigator often witness the signing of the informed consent form, in order to protect the investigator and the sponsor in the case of a subject-initiated lawsuit.

8.3.3.2. Right to think it over

Excessive pressure during the enrollment process is unethical (see also subsection 8.3.3.9. below).[2544] The corollary is that subjects must be given an appropriate period of time to ponder what they have been told before reaching and communicating their decision to participate in a proposed clinical trial.[2545] A minimum of 24 hours should elapse between the moment the subject has received all the information and the moment when he signs and dates the consent form. Whenever feasible, the interval should be longer, for example a week,[2546] especially for vulnerable subjects.[2547] During this period, as well

---

2537 BEAUCHAMP & CHILDRESS distinguish three kinds of influence: coercion, persuasion and manipulation. *Supra* note 16, at 84-95. *See also* GUILLOD, *supra* note 77, at 109-113.

2538 On the admissibility of *faxed* consent forms in the United States, ECRI (Guide), *supra* note 869, at 43.

2539 European Union's Directive 2001/20/EC allows to replace signature by oral consent, when the subject cannot write; however, a witness must be present; Article 3.2.(d).

2540 A U.S. Court found that imposing the legal requirement that a relative give his consent (in addition to that of the subject) constitutes "an unconstitutional invasion of the patient's right to privacy." *Aden*, 57 Cal. App. 3d at 681.

2541 *See also* GUILLOD, *supra* note 77, at 124-26 (in the context of "ordinary medical care").

2542 *See, e.g.*, section 4.8.2 (p.15) of ICH E6.

2543 For the contents of this regulatory file, see University of Pittsburgh, Standard Operating Procedure Audit of Investigator Regulatory File(s), at 2-3, (SOP #: I-A-9), at http://www.rcco.pitt.edu/educ/SOPS/Investigator_audits/A_9_reg_file.doc.

2544 For example, the OIG reports that potential subjects have sometimes been recontacted numerous times. See OIG (Recruiting), *supra* note 815, at 8 and 25.

2545 *See* SAMS 1997 Guideline, *supra* note 110, at point D.6. at 10; section 4.8.7 (p.15-16) of ICH E6 (requiring that subjects be given "ample time."); CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary).
See also Sprumont & Béguin, *supra* note 134, at 897; SPRUMONT, *supra* note 16, at 172; GUILLOD, *supra* note 77, at 167-68. *See also* Article 1.11 of the (former) Good Clinical Practices accompanying the IOCM 1995 Regulation.
Compare with Article 14.4 of the future Swiss law on human genetic analysis (LAGH), which requires an appropriate interval of time between the moment information is provided and the decision to undergo a genetic analysis. See also the accompanying message of the Federal Council, FF 2003 I 6841, at 6895.

2546 Compare, for the patient in "ordinary" setting, Manaï (procès), *supra* note 155, at 347-48

as during the entire prior process, subjects can ask investigators any questions that come to their mind.[2548] They should be invited to consult with family and friends as well as with their usual doctor.[2549]

Similarly, there should be a period of time – at least 24 hours, and more for trials entailing significant risks – between signature of the consent form and the beginning of the experimental treatment.[2550] For life-threatening diseases, it is preferable that there be an interval between the very first communication of the diagnosis (e.g., the doctor telling the patient "I'm very sorry but you have cancer") and the presentation of the opportunity to enroll in a clinical trial.[2551] Patients having to face dreadful news may take exception to being immediately confronted with difficult choices.

8.3.3.3. Written consent forms

Signed consent forms were not common until the 1970s. Early accounts of signed forms include an experiment led in 1900 by U.S. scientists but taking place in Cuba whereby subjects were deliberately infected with yellow fever.[2552] Historically, written forms were rather used to release doctors from all liability.[2553]

8.3.3.3.1. Purpose

Nowadays, subjects must receive written informed consent form ("ICF") that mostly repeat, and sometimes complement, the information that they previously[2554] received in oral form.[2555] The form also marks the subject's agreement to take part in the trial. The subject must date and sign the ICF,[2556] and keep one copy for himself.[2557] The person

---

2547 See for example in the United States, NIH, Research Involving Individuals with Questionable Capacity to Consent: Points to Consider (Mar. 11, 1999) http://grants.nih.gov/grants/policy/questionablecapacity.htm [hereinafter NIH (Questionable Capacity)].

2548 *See* section 4.8.7 (p.16) of ICH E6.

2549 *See* SAMS 1997 Guideline, *supra* note 110, at point D.6. at 10; Article 2.5.q) of the (former) Good Clinical Practices accompanying the IOCM 1995 Regulations.

2550 However, in one U.S. court case, the subject was asked to sign the consent form *on the day* of his operation, possibly just minutes before undergoing anesthesia. *Daum*, 52 Cal. App. 4th 1285. A doctor involved in this litigation on the defense side acknowledged that "for years consents were routinely obtained on the morning of the surgery." *Id.* at 1299. *See however* ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH, 142-43 (2d ed. Urban & Schwarzenberg 1986) (citing evidence of very short waiting periods) [hereinafter LEVINE (1986)].

2551 *See, e.g.,* Stiffler, *supra* note 2441.

2552 *See* LEDERER, *supra* note 54, 20-23.

2553 *See* PAUL S. APPELBAUM, CHARLES W. LIDZ & ALAN MEISEL, INFORMED CONSENT, LEGAL THEORY AND CLINICAL PRACTICE 176 (Oxford University Press 1987).

2554 *See however* SPRUMONT, *supra* note 16, at 77 (according to whom information is first provided in writing and then orally).

2555 *See* paragraph 22 Helsinki Declaration. The United States allows the use of short forms (as an alternative to the full forms that repeat all key information). *See* 21 C.F.R. § 50.27(b)(2). The short form essentially confirms that the subject has received complete oral information. A witness must confirm that the subject has indeed received oral information before he signed the short form. Moreover, the subject receives a summary of information regarding the trial, which however he does not sign. *See also* SPRUMONT, *supra* note 16, at 147.

2556 *See* section 4.8.8 (p.15-16) of ICH E6. The requirement is that the subject must personally both sign and date the form. In the United States, see 21 C.F.R. § 50.27(a). Based on FDA warning letters, it appears that investigators sometimes disobey this rule and fill in the date themselves.

who provided the subject with the necessary information during the consent process (whether the investigator or a member of the medical team) must also sign it.[2558]

Frequently, a clinical trial entails more than one consent form.[2559] There may be a general form that describes the study; a second one that authorizes HIV or other sensitive screening tests (e.g., a genetic test);[2560] a third one that covers the use of biological materials (see below subsection 8.6.7.2.). Risky medical procedures dictated by the occurrence of an adverse drug reaction may call for another consent form. At least in the European Union, genetic testing is a special procedure for which subjects must receive specific information.[2561]

The ICF is not meant to substitute oral information. It rather serves to document the informed consent process and remind the subject of his rights. Since the subject retains a copy of the form, he can refer to it whenever helpful. Additionally, the form should be used as an educative instrument.[2562] Given these purposes, it has been suggested that the form should not be titled "informed consent form," since this label implies that the form suffices to render the consent informed.[2563]

The format of explanations contained in the form should be adapted to the reading and understanding skills of the subjects.[2564] Technical scientific words should be avoided or else fully explained.[2565] ICFs should be in a language subjects readily grasp; the sponsor may need to prepare forms in several different languages.[2566] In the United States, researchers are advised to use the second person ("you, the subject") form instead of the first or third person.[2567] The consent form should avoid creating the impres-

---

2557 *See* section 4.8.11 (p.17) of ICH E6. If the consent form or the accompanying documents are changed, the subject must also receive a copy of the new version. In the United States, see 21 C.F.R. § 50.27(a).

2558 *See* section 4.8.8 (p.16) of ICH E6.

2559 In the United States, these forms are also referred to as ICDs (for Informed Consent Documents). *See* FDA (MAPP 6030.2), *supra* note 2242, at 1.

2560 According to Articles 5 and 36 of the future Swiss law on human genetic analysis (LAGH), the prior informed consent of the tested individual is necessary for any genetic analysis. *See however* Article 1.3 LAGH (introducing an exception for genetic analyses performed for research purposes); Federal Council's message regarding the LAGH, FF 2003 I 6841, at 6842 and at 6867-68. The precise scope of this exception (Article 1.3 LAGH) is not clear today since the draft law on research on human beings has not even been made public yet.

2561 According to E.U. Guidance, "[t]he information [provided to subjects] should give the background and purpose of the genetic tests, the planned analyses and whether the samples will be kept to make future analyses possible in conjunction with the planned project. When applicable, the information on the genetic part of the trial might be separate from the information on the other part. Information should be provided on the possibility for the subject to abstain from the genetic testing but still be able to participate in the non-genetic part of the trial, according to national recommendations." E.U. Guidance (Ethics Committee), *supra* note 270, at 23.

2562 *See* OPRR (Tips), *supra* note 2525.

2563 *See, e.g.*, Arnold, *supra* note 2525, at 24.

2564 Point C.1 of the (U.S.) Belmont Report, *supra* note 61. In the U.S., forms should be adapted to the reading skill of an 8th grade child (about 12-year old). *See, e.g.,* Copernicus Group, Subject Information and Consent Form Checklist, at http://www.copernicusgroup.com/irbForms/20040801_SubjectICchecklist.pdf. *See also* Jennifer Fisher Wilson, *The Crucial Link between Literacy and Health*, 139 ANN. INTERN. MED. 875, at 877 (Nov. 18, 2003), at http://www.annals.org/cgi/reprint/139/10/875 (observing that the "average Medicaid recipient reads at as fifth-grade level.").

2565 *See* section 4.8.6 (p.15) of ICH E6.

2566 *See* FDA (FAQ-IRB), *supra* note 1814, at questions 51.

2567 *See* OPRR (Tips), *supra* note 2525.

sion that the national drug agency has a stake in the clinical trial or will take an active role in supervising it.[2568]

U.S. law admits exceptions to the written and signed consent requirement.[2569] However, most of these exceptions do not apply to drug clinical trials. Yet U.S. regulations do contemplate a waiver when a research involves "no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context."[2570] The CIOMS Guidelines has approved this last exception.[2571] In addition, the CIOMS allows waivers when "the existence of a signed consent form would be an unjustified threat to the subject's confidentiality."[2572] This could occur, for example, in an AIDS trial taking place in a country where seropositive people are commonly stigmatized or discriminated against.

8.3.3.3.2. Legal status

The written consent form should not appear as a binding bilateral contract. Because subjects are asked to *sign* the form, they may derive the impression that they are entering into an agreement.[2573] This is not the case. The form does not necessarily *create* obligations on the part of subjects (see subsection 8.2. above), nor on the investigator's side. The subject is bound by no obligation (see subsection 8.7. below), whereas the investigator's obligations exist independently from any written form.

In my view, the subject may have consented to participation even if he did not sign the ICF. However, if no form has been signed, the burden of proof is shifted to the investigator. The latter may, for instance, ask the witness (who was present during the informed consent process) to testify that the subject received full information and gave his verbal consent; similarly, the study nurse could confirm that the subject, even though he did not sign the form, was fully aware of his enrollment and was a willing participant. If the investigator succeeds in proving that the subject had, despite the formal omission of signature, given his informed and free consented, she should not be liable. She may nonetheless be sanctioned for not having complied with her own obligation to have signed forms for all subjects.

An exception to the above-mentioned view that the form does not create a contract is warranted when the consent form states rights not granted by law. For example, a clause may establish the subject's right to a payment for his participation or may describe the insurance coverage which the subject will enjoy. These clauses are contractual in nature.

2568 The FDA has found inappropriate clauses such as "[the FDA may inspect all records from this study due to their interest in and support of this vaccine." FDA warning letter to Terry Fredeking, *supra* note 1848.

2569 Exceptions generally involve emergency situations. *See* 21 C.F.R. § 50.23 and 50.24 and also §56.109(c). *See also* UCSF (Part X), *supra* note 2455.

2570 21 C.F.R. § 56.109(c). For the U.S. definition of "minimal risk," see *supra* note 2062. This exception could, for example, apply to a study that survey the weight of the subjects and where the procedure entails stepping on a scale.

2571 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary).

2572 *Id.*

2573 *See, e.g.,* VanTx Report, *supra* note 148, at 13. On the legal nature of the consent itself, see GUILLOD, *supra* note 77, at 29-30.

At least one U.S. court has held (in the context of a nontherapeutic study[2574]) that the consent process together with the consent form does create a contractual relationship between the subject and the investigator.[2575]

8.3.3.3.3. Frequent problems with consent forms

Written consent forms have attracted considerable attention. Many criticisms have been levied against them.

First, forms have a propensity to increase in length so as to state all rights and obligations of the parties.[2576] The result is a form that resembles a contract replete with "boiler-plate" clauses and undeniably complex for an average research subject. Though meant to protect the latter, such a form gives the impression of shielding the investigator and her institution by managing their legal risk.[2577] Angell, for example, evokes "a legalistic ritual, designed more to obfuscate than to clarify."[2578] True enough, the historical rationale for written forms was to guard the researcher from liability.[2579]

Other commentators have observed that "the demand for written consent forms may have more to do with providing an IRB something concrete and uniform to review in advance of a clinical trial than an assessment of the relative effectiveness of communicating in this fashion."[2580] Indeed, ethics committees' work is – unfortunately – chiefly limited to the review of written documents, in particular the protocol and the informed consent documents (see subsection 7.1.3. above).

Another criticism of consent forms is that they are only adapted to well-educated patients able to take advantage of the information and protection they impart.[2581] Indeed, many subjects do not read, at all or not attentively, consent forms before signing them.[2582] Instead, they trust the physician-investigator to protect them.

2574 The Court of Appeals of Maryland "made no determination as to whether informed consent in a therapeutic medical context can generate contractual obligations." *Grimes*, 782 A.2d at 844.

2575 "By having [the subject's parents] sign [the] Consent Form, both [the investigator and the subjects] expressly made representations, which, in our view, created a bilateral contract between the parties." *Id.* at 844.

2576 See the model consent form provided by the San Francisco University on its website: http://www.research.ucsf.edu/chr/HIPAA/CF-Bio-with-HIPAA-OK.doc; Stanford Sample Consent Form, at http://humansubjects.stanford.edu/medical/SUSampCons.html. Compare with the one-page sample consent form of the Lausanne University, at http://www2.unil.ch/cercfbm/formulaire.html.

2577 *See* George J. Annas, *Reforming informed consent to genetic research*, 286 JAMA 2326-2328 (Nov. 14, 2001), at http://jama.ama-assn.org/cgi/reprint/286/18/2326.pdf; OIG (Reviewing), *supra* note 1187, at 4-5; T. E. King, *supra* note 2311, at 1400-402 ("Many blacks view signing the informed-consent document as relinquishing their autonomy and providing legal protection for the physician or the institution."). *See* also the vivid description of the reaction of a breast cancer patient being given an informed consent form for signature *in* BAZELL, *supra* note 673, at 97. *See also* SPRUMONT, *supra* note 16, at 78. *See also* Kass & Hyder, *supra* note 822; Jeremy Sugarman et al., *International Perspectives on Protecting Human Research Subjects*, NBAC Volume II, *supra* note 103, at E-5.

2578 *See* Angell (Publication), *supra* note 898, at 278. *See also* GUILLOD, *supra* note 77, at 162-64.

2579 *See* LEDERER, *supra* note 54, at 122-23.

2580 *See* Noah, *supra* note 4, at 383-84.

2581 *See* Isabel Wilkerson, *Medical Experiment Still Haunts Blacks*, N.Y. TIMES, June 3, 1991, at A12.

2582 *See* Jacqi Wise, *Patients do not read consent forms*, 313 BMJ 1421 (Dec. 7, 1996). *See also* Interview with Bounameaux, *supra* note 1718.

Surveys have shown that consent forms can be difficult to read.[2583] Even consent forms prepared by IRBs were shown to be hard to understand.[2584] Mackintosh and Molloy have established a list of 39 common mistakes or inaccuracies found in consent forms.[2585] The U.S. National Cancer Institute at the NIH reacted in 1998 by taking steps to improve the quality of consent forms.[2586] It set the minimum standard of readability at the level of a 12-14 year old child.[2587] Patient representatives and consumers have sometimes been asked to review and evaluate consent forms to make sure that they will be understood by subjects.[2588]

8.3.3.4. Testing comprehension

To deal with absentmindedness, comprehension problems and ineffective communication techniques used by the investigator, a solution would be to *systematically test* subjects after they received information, but before they are enrolled.[2589] The test would verify that each subject has really understood what he has been told and remembered it. One much appreciated test consists in asking the subject to repeat "in his own words" the information he was given during the informed consent process. In prolonged trials, subjects should be tested at regular intervals to determine whether the consent process ought to be repeated. These proposals are far from being generally accepted in clinical trial practice, although studies have shown that tests do improve subjects' concentration. True enough, sponsors and investigators may wish to avoid setting the standards too high for fear that too few subjects will finally be eligible for enrollment.

2583 *See* Douglas R. Mackintosh & Vernette J. Molloy, *Opportunities to Improve Informed Consent*, APPLIED CLINICAL TRIALS, at 42 (May 2003), (reporting on studies conducted by Hochhauser and by Lin). Consent forms were found to have "too many uncommon words, too many words per sentence." *Id*. *See also* FDA Warning Letter to Dan F. Ausman, *supra* note 1848.

2584 "Our findings suggest that the sample texts provided to investigators by IRBs of U.S. medical schools generally fail to meet the IRB's own standards for readability." Michael K. Paasche-Orlow et al., *Readability Standards for Informed-Consent Forms as Compared with Actual Readability*, 348 NEW. ENG. J. MED. 721-726 (2003), at http://content.nejm.org/cgi/content/full/348/8/721.

2585 *Id*, at 44-45.

2586 *See* NCI (Simplification), *supra* note 2444.

2587 *See id*. In addition, "[u]se of active voice, short sentences, personal pronouns, clear page layout with "white space" borders, and large fonts make documents easier to read. The use of simple outlines, flow charts, diagrams, study schemas, calendars, and other graphics are encouraged. Consent forms should use the second person because it reflects the conversation between the investigator and potential research participant." *See also* appendix 3 to the NCI recommendations, where, for example, the NCI advises against use of "words containing more than three syllables (where possible)." *See also* UCSF (Part X), *supra* note 2455 (adding that "Legalistic sounding language such as "You hereby agree," "You certify that," "You, the undersigned, do acknowledge that" should not be used.").

2588 *See* Bec Hanley et al., *Involving consumers in designing, conducting, and interpreting randomised controlled trials: questionnaire survey*, 322 BMJ 519-523, at 521 (Mar. 3, 2001), at http://bmj.com/cgi/reprint/322/7285/519.

2589 *See e.g.,* point C.1 of the (U.S.) Belmont Report, *supra* note 61; CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary). *See also* SPRUMONT, *supra* note 16, at 73.

8.3.3.5. Patient advocates and witnesses

When the direct involvement of the investigator in the consent process could intimidate the subject or sway him into giving his consent, the investigator should hand over the task to a neutral party.[2590] For example, a patient may feel uncomfortable refusing his consent if asked by his primary care doctor (acting as investigator); a medical student may fear declining if invited by his professor.

Similarly, when the investigator has a *conflict of interest*, she should not personally seek subjects' consent; she should leave the task to a "non-biased third-party."[2591] For instance, if the investigator holds equity in the company holding the patent right on the investigational compound, she should avoid contact with the subjects at this particularly sensitive juncture.

Ethically sensitive studies should also require the intervention of a neutral third party to explain the protocol.[2592] This is often the case with placebo-controlled studies where an effective treatment is temporarily withheld.

Similarly, trials enrolling *vulnerable or incompetent subjects* may engage the services of a "patient advocate," "uninterested party" or mediator,[2593] whose mission is to give independent advice to potential volunteers.[2594] Her role is akin to that of a primary care/community physician. She must represent and defend the exclusive interests of volunteers. She will help the volunteers to make the decision that suits them best, even if this entails not participating in the clinical trial. These advocates could also act as a go-between between subjects and ethics committees.[2595]

When subjects cannot read, an impartial witness should accompany them during the entire informed consent process.[2596] The form should be read to them, after the oral phase of the process has been performed. Preliminary evidence suggests that a surprisingly high number of patients (possibly as high as 50%) are not able to read and

---

2590 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6 (commentary). *See also* SPRUMONT, *supra* note 16, at 76 (adding that the intervention of a third party does not excuse the investigator from her own responsibility to ensure that consent was validly given).
See generally on the difficulties that a third party intervention could cause, GUILLOD, *supra* note 77, at 57.

2591 *See* HHS Interim Guidance, *supra* note 938, at chapter 5.3.

2592 In the United States, see AMA, Policy, Surgical "Placebo" Controls, E-2.076, at point (2), at http://www.ama-assn.org/ama/pub/category/8425.html (recommending a neutral party for clinical trials involving the use of surgical placebos). *See also* Article 17.2 COE Research Protocol applicable to different types of research where only minimal risks are tolerated.

2593 In France, see CCNE N°79, *supra* note 1251, at 15. In the United States, see NBAC (Mental), *supra* note 1250, at chapter III (highlighting the importance of "independent health care professional advisors" in trials on incompetent subjects "involving greater than minimal risks"); *see also* NIH (Questionable Capacity), *supra* note 2547.

2594 In the United States, *see* OIG (Sample Guidelines), *supra* note 945, at 1. *See also* 45 C.F.R. § 46.409.b. (requiring the appointment of an advocate for wards participating in clinical research).

2595 *See* OIG (Promising), *supra* note 1882, at ii and 12-13.

2596 *See* points 4.8.9 (p.16) cum 1.26 (p.4) of ICH E6.
Under the former intercantonal system, it was either the subject or an independent witness (acting on behalf of the former) who had to sign the informed consent document. *See* Article 1.12 of the (former) Good Clinical Practices accompanying the IOCM 1995 Regulation.
Compare with the U.S. case of *Anderson*, 982 F.2d 1513 (where patients with very little education or none at all were asked to sign consent form which they could not understand).

fully understand written texts.[2597] Investigators should be careful not to take reading skills for granted.[2598] Moreover, people with low literacy skills may require closer supervision during the clinical trial, in particular for correct drug adherence.[2599]

When the investigator and/or her institution propose the services of a patient advocate, they must make sure that the advocate is truly independent and thus able to protect assertively prospective subjects. If they fail to do so, they may face increased liability, because the subject may view the implied promise of the advocate's services as misleading or broken. The subject may file claims not only against the advocate directly, but also against the investigator and her institution.[2600]

Under Swiss law, emergency clinical trials on incapacitated subjects who cannot give their consent are the only ones to require the presence of an independent physician.[2601] The role of this physician is to defend exclusively the interests of subjects. He must not be otherwise involved in the clinical trial.

It should go without saying that subjects can always come accompanied by friends or other acquaintances whom they trust. Subjects find the presence of a friend helpful in many ways.[2602] The friend can ask questions that the subject would feel uncomfortable asking; he may remember bits of information that the subject did not catch. He can take notes while the subject can concentrate on what the investigator is saying.

In pediatric trials, parents are always encouraged to be present during all procedures that their child must undergo. Thus, they can decide if or when to withdraw their child (see also subsection 8.3.3.10. below).[2603]

8.3.3.6. The role of the primary care physician

As mentioned above (subsection 8.3.3.2.), the potential subject should be invited to discuss his enrollment with his usual treating doctor.[2604] Without the subject's authorization, neither the primary care physician in a private practice nor the investigator conducting the clinical trial can communicate information about the patient-subject to each other. In particular, they cannot give each other access to the patient-subject's medical file. Doing so would be a breach of their confidentiality obligations.[2605]

2597 *See* J. F. Wilson, *supra* note 2564, at 875-78. The percentage may be even higher for seniors. *Id.* at 876. *See also* National Center for Education Statistics, Adult Literacy in America, A First Look at the Findings of the National Adult Literacy Survey, (NCES 1993-275), at http://nces.ed.gov/pubs93/93275.pdf.

2598 *See* J. F. Wilson, *supra* note 2564, at 876 ("One study at a women's health clinic found that, among patients considered to have low literacy, physicians identified only 20%.").

2599 *Id.* at 875 (commenting the link between literacy and health outcomes).

2600 *See also* subsection 8.6.5. below.

2601 Article 56.d LPTh.

2602 *See, e.g.,* ECRI (chemotherapy), *supra* note 316, at 27; ECRI (Guide), *supra* note 869, at 2 and 41.

2603 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 14 (commentary).

2604 When this is necessary to coordinate health care, subjects may be *required* to authorize communication between the investigator and the primary care doctors.

2605 *See* ECRI (Guide), *supra* note 869, at 57.

Hence, subjects must take the necessary steps to keep their primary doctor informed. Failing to do so may have adverse consequences.[2606] The primary doctor may hold information that is important to determine whether the subject will benefit from his participation in the study. For example, the subject suffers from a particular allergy or mental condition that speaks against his participation in the trial. Conversely, the primary doctor may need to be told that her patient is participating in a study so as to adapt her medical advice to this new situation (e.g., avoid prescribing drugs that the study forbids).

The primary doctor may also assist his patient in interpreting the information received from the investigator. The doctor may temper the patient's misplaced enthusiasm in the research; she can serve as a "second medical opinion" at the beginning as well as during the trial itself.

8.3.3.7. Right to ask questions

We have seen that the consent phase should be viewed as a process and that subjects have the right to withdraw from the study at all times. Subjects also have the right to ask questions to the investigators at any time throughout the study.[2607] Investigators must provide complete and detailed answers to questions raised by subjects, even if these cover material already discussed during the initial consent process.

While the right to ask questions is fully acknowledged during the initial consent stage, it is rarely brought up after that. The duty that the investigator has to keep subjects informed of significant developments so as to ensure that they are still willing to assume the – presumably – increased risks does not suffice (see subsection 8.6.2. below). The right of subjects to ask questions is at least as important. The consent form should clearly indicate to whom subjects can address their questions.[2608] Questions can pertain to the research itself, the rights of the subjects, indemnification and include other complaints if the subject is unsatisfied with the conduct of the study.[2609] The person identified to answer the questions should not necessarily be the investigator herself, since subjects could hesitate directing their queries to her.[2610]

2606 *See, e.g., id.* at 37; Kleist (23), *supra* note 798, at 658.

2607 *See, e.g.*, ICH E6, at section 4.8.7 (p.15); CIOMS Guideline, *supra* note 105, at commentary to guideline 4.
Novartis has even put on its website a list of questions that subjects are invited to ask the investigator. See Novartis, e-trials, About Informed Consent, http://etrials.novartis.com/patients/at_aboutTheICA.jsp.

2608 *See* section 4.8.10(q) (p.17) of ICH E6. See also Article 10.2.h OClin referring to procedures to claim subjects' rights ("*les procédures en revendication de ces droits*").
In the United States, see 21 C.F.R. § 50.25(a)(7). A review of FDA warning letters suggests that consent forms do not always provide this information. See, in the United States, FDA Warning Letter to Dan F. Ausman, *supra* note 1848; FDA warning letter to Matthias McGuire, *supra* note 1848.
In the European Union, see E.U. Guidance (Ethics Committee), *supra* note 270, at 7.

2609 There is no authority appointed specifically to handle subjects' complaints. During the OClin comment period, this was pointed out as a weakness of the Ordinance. *See* DHA (Ordinance Comments), *supra* note 522, at 40.

2610 "Furthermore, a single person is not likely to be appropriate to answer questions in all areas." *See* OPRR (Tips), *supra* note 2525. *See* FDA (FAQ-IRB), *supra* note 1814, at question 49; FDA (1981), *supra* note 260, at comment 38.

By regularly asking the right questions, a proactive subject can do his own monitoring of the trial. This opportunity is especially valuable when the trial is particularly risky, its outcome uncertain, the procedures cumbersome and lengthy. On the contrary, when the clinical trial is not very different from ordinary treatment of a non-severe medical conditions, for example because it requires no hospitalization, but only sporadic visits to the subjects' own usual doctor, asking questions may not be as useful – although it may relieve natural anxiety. If patient empowerment develops – which is to be hoped –, the right to ask questions is to become a very valuable instrument in the hands of sophisticated subjects.[2611] To a certain extent, subjects are in the best position to notice whether the investigator is in fact complying with all her obligations and treating them fairly. This direct on-site "supervision" cannot simply be replaced by occasional inspections by drug agencies or by even rarer visits from REC members. Yet, subjects today are not taking full advantage of their right to ask questions; a survey has shown that a majority of subjects did not know what questions to ask.[2612]

Finally, the investigator should also set up procedures to address complaints made by research subjects.[2613] Subjects should be told to whom they can address grievances and how these will be processed. It is a good idea to also involve ethics committees. In the United States, it is suggested that one IRB member be designated as a contact person for subjects with questions or complaints.[2614]

8.3.3.8. "Group consent"

When research or clinical trials are conducted on large groups of people that form some sort of community, the *individual* informed consent process has been questioned. Ordinarily, informed consent is obtained only from the individual enrolled in the trial, even if the trial has possible implications for people not enrolled (e.g., members of the family, members of the community).[2615] Because this narrow focus may be unsatisfactory, it has been suggested that the community and/or its appointed representatives should also be invited to participate in the consent process. In tribal cultures, these representatives may be the village chiefs or elders.[2616] Evidently, individual informed consent is not eliminated; group/community consultation is an *additional* measure.[2617]

The issue of group consent arises principally in two kinds of situations: genetic research performed on large ethnic groups (e.g., the DeCode project in Iceland) and research in traditional close-knit, indigenous communities[2618] (e.g., clinical trials in rural

---

2611 *See also* subsection 8.6.3.3. regarding subjects' rights under data protection law.

2612 *See* Wadlund, *supra* note 680, at 52 (citing to a survey by CenterWatch).

2613 COREC, *supra* note 1379, at point 9.17.e (p.27).

2614 *See* ECRI (Guide), *supra* note 869, at 50. U.S. IRBs are often assigned the additional task of investigating violations of the protocol or of regulations. *See* UCSD-SOPP, *supra* note 485, at 91.

2615 An example of research that could affect not only the enrolled subjects, but their community at large, is one that would uncover higher rates of "shameful" diseases or behavior in the community as opposed to average rates in other groups. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 8 (commentary).

2616 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary).

2617 *See generally* Kass & Hyder, *supra* note 822, at B-5.

2618 *See* Annie O. Wu, *Surpassing the Material: the Human Rights Implications of Informed Consent in Bioprospecting Cells Derived from Indigenous People Groups*, 78 WASH. U. L. Q. 979, at 983-984 (2000) (men-

areas of developing countries[2619]). The problem of informed consent is compounded by the perception that these groups or communities are deprived of their fair share of the benefits that should accrue from their participation in research that ultimately results in profitable commercial products (see subsection 8.5.8. below).

The WHO Operational Guidelines contain elaborate guidance regarding community implications of research.[2620] For example, the investigator and sponsor should explain to the REC what steps are taken to consult with the community.[2621] The WHO defines community as:

> a group of people understood as having a certain identity due to the sharing of common interests or to a shared proximity. A community may be identified as a group of people living in the same village, town, or country and, thus, sharing geographical proximity. A community may be otherwise identified as a group of people sharing a common set of values, a common set of interests, or a common disease.[2622]

This definition is obviously very broad. It stems from the desire of the WHO to encompass various cultural viewpoints. Ethical guidelines on individual consent have been criticized as the product of Western mentalities; they are allegedly unadapted to non-Western countries, particularly developing countries. The WHO Guidelines aim to address this concern.[2623] Similarly, the CIOMS Guidelines and the NBAC recommendations were drafted with these same considerations in mind.

They propose that the community where the research is taking place be consulted before the trial is launched. The community, through its approved representatives, is to give its opinion as to design of the trial. It should comment on whether the offered benefits are sufficient to offset the risks. It should advise researchers as to the best way to seek consent from individual subjects. For instance, it should evaluate the way essential information is to be conveyed to subjects,[2624] taking into account the level of literacy and medical fluency as well as local culture and values.[2625]

---

tioning research projects taking place in the native population of Papua New Guinea and in the island of Tristan da Cunha).

2619 "[S]ome commentators have suggested that exporting the doctrine of informed consent to developing countries, many of which have more communitarian outlooks than developed countries and which lack the same concept of 'self' or 'personhood,' amounts to 'ethical imperialism' – an imposition of Western values on non-Western cultures." DuBois, *supra* note 118, at 198-99. *See also* EGE, *supra* note 110, at points 1.28 to 1.33 and at point 2.7; Shapiro & Meslin, *supra* note 245, at 140; Nuffield (Developing), *supra* note 813, at xv.

2620 *See* WHO (Operational Guidelines), *supra* note 1379, at chapter 6.2.6 (p.13). *See also* COREC, *supra* note 1379, at point 9.18 (p.27).

2621 *See also* COREC, *supra* note 1379, at point 9.18.b&c (p.27). *See also* Kass & Hyder, *supra* note 822, at B-7.

2622 *See also* WHO (Operational Guidelines), *supra* note 1379, at p.21.

2623 *See also id.* at p.30.

2624 *See, e.g.,* NBAC (Developing), *supra* note 254, at 42.

2625 *See, e.g.,* Paul Bolton et al., *Group Interpersonal Psychotherapy for Depression in Rural Uganda*, 289 JAMA 3117, at 3119 and 3124 (June 18, 2003), at http://jama.ama-assn.org/cgi/reprint/289/23/3117.pdf. *See also generally* NBAC (Developing), *supra* note 254, at 49-50.

Group/community consultations are not without drawbacks, even if they only supplement individual consent.[2626] They may perpetuate iniquitous hierarchical structures (e.g., the authority of a chief over villagers of a lower social class; the authority of a husband over his wife or over other female members of the family[2627]). They may scare potential subjects away from the available trials out of fear of going against the community consensus. They may leave researchers with more ethical problems than solutions. What happens, for example, if the community is split in its assessment of the trial? Or if the community consensus, for "traditional/cultural" reasons such as distrust of western medicine, results in denying treatment to patients-subjects?

8.3.3.9. Rights to refuse enrollment

Participation in a clinical trial rests on consent which must be both informed and voluntary. In other words, once fully informed, the subject must have unrestrained freedom to choose whether to participate. The subject can refuse to participate in the trial, before it starts as well as at all time during its course.[2628]

Patients should not be coerced, intimidated or deceived into participating in a trial.[2629] If their consent is to be truly free, they must not be influenced by misleading information. Investigators should not influence patients by exalting the merits of the trial. Ideally, patients should be given the objective facts devoid of the investigator's impressions or recommendations. The investigator should not answer patients asking her whether she would participate in the trial if she was herself a patient – although in practice this happens often. The goal is that research subjects reach their decision by themselves.

From a practical point of view, it is nearly impossible to suppress all influences, both those generated consciously or unconsciously by the investigator and her team and those felt consciously or unconsciously by the prospective subject. Naturally, the subject will almost always think that the investigator would not ask him to participate in a trial if she herself as a doctor was not utterly convinced that this is in his own best interest.[2630] Moreover, subjects want and need to be reassured.

The degree of acceptable persuasion vary. For example, in a nontherapeutic trial, practically no urging should be admitted. In a phase III therapeutic trial offering good prospects to a patient with no other alternatives, the investigator can use more pressing arguments. These arguments should – of course – always be entirely truthful; benefits should not be stressed unfairly over disadvantages; alternatives, if any, should be discussed candidly and should be given due consideration. Subjects should not be asked

---

2626 Individual consent can *never be replaced* by permission granted by a father, a husband, a village chief or a community representative. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 16 (commentary); NBAC (Developing), *supra* note 254, at 42-45.

2627 *See* Nuffield (Developing), *supra* note 813, at 43-44.

2628 *See* section 4.8.10(m) (p.16) of ICH E6; paragraph 22 Helsinki Declaration.

2629 *See, e.g.,* section 4.8.3 (p.15) of ICH E6. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary).

2630 However, this is partly wishful thinking. Scientists know that a significant proportion of investigational compounds fails during clinical trials; thus, even if the results of the pre- and clinical trials look good, there can always be negative surprises later on.

repeatedly to give their consent, a conduct which would amount to outright harassment. Investigators are not allowed to "shame" patients into participating in research, for example by passing judgment on the selfishness of those that refuse.

Of course, no threats of adverse consequences can be made to extract consent. For example, the investigator may not lean on the prospective subject by saying that if the latter refuses enrollment, he will have to leave the hospital in order to free his bed for other patients whose conditions are worse than his own.[2631] The principles are the same as those applicable to subject withdrawal: The subject should suffer no penalty for refusing consent (see subsection below).

8.3.3.10. Right to withdraw from the trial

Subjects can withdraw their consent at any time, and thus end immediately their participation in the trial.[2632] Given its central importance, this right must be highlighted during the informed consent process.[2633]

As the right to choose to join a study must be exercised unfettered, the right to revoke consent and withdraw from an ongoing study must also be uninhibited.[2634] Subjects can decide whenever they want and for whichever reason (including no reason at all) to leave a clinical trial. They do not need to notify the investigator in writing.[2635] On the contrary, the investigator should take into account even unspoken clues indicating that the subject no longer wishes to participate. For example, the subject may feel shy toward the doctors and instead confide in the study nurse his doubt about his participation. The nurse should act upon this confession;[2636] for example, she can recommend that the informed consent process be repeated or that the subject be given more time to think it over. The steps taken to ascertain subject's sustained consent should be documented.

Subjects cannot be sanctioned for leaving a study; they cannot be denied medical treatment or be offered only an inferior level of care. This obligation is not mentioned in the OClin, but is based on ethical principles, in particular the Helsinki Declaration,[2637] that ethics committees should uphold.[2638] The investigator must take precautions so that the interruption of treatment by the patient does not harm his health. For instance, some treatments should not be discontinued abruptly lest the disease worsens. There-

---

2631 Compare with *Barrett*, 660 F. Supp. at 1299-1300.

2632 Article 54.1.a.6 LPTh. *See also* paragraph 22 Helsinki Declaration; Article 9 of the Nuremberg Code; Articles 5 and 16.v. of the Biomedicine Convention, *supra* note 107. In the United States, see 21 C.F.R. § 50.25(a)(8).

2633 A survey of parents enrolling their children in pediatric clinical trials found that 20% of parents were not aware of this right ! *See* Kodish et al., *supra* note 2459, at 472.

2634 In the European Union, see Article 3.2.(e) of Directive 2001/20/EC.

2635 The fact that informed consent is provided in writing could imply that withdrawal similarly requires a written form. This is not the case.

2636 Compare with the U.S. cases of *Barrett*, 660 F. Supp. at 1299-1300; Busalacchi v. Vogel, 429 So. 2d 217, at 219 and 222-23 (C.A.Louis. 1983).

2637 *See* paragraph 31 Helsinki Declaration. *See also* Article 14.2 COE Research Protocol.

2638 In the United States, see 21 C.F.R. § 50.25(b)(1) (requiring that subjects be told "the consequences of [their] decision to withdraw from the research and [the] procedures for orderly termination of participation… .").

fore, the investigator should make sure that the subject who dropped out continues to receive adequate health care, whether at the research site or from another physician/hospital. The subject must also be told about the risks of interrupting the treatment, even if this leaves him with no practical choice other than continuing the treatment.

When the subject is also a patient staying at a health facility, forms often add that withdrawal will not impact the quality of care that the patient will continue to receive on site.[2639] It may seem like a straightforward rule, but in practice it is not necessary so. Subjects enrolled in trials do receive first-rate medical attention by renowned specialists. If they choose to leave the trial, they may feel that they have been suddenly "abandoned" to nurses or interns with little interest in their "case." Previously hospitalized subjects-patients may be invited to "surrender" their bed, because they are deemed "well enough" to go back home.

Withdrawals should only have effects for the future. If the investigator collected data from the subject before the latter withdrew his consent, she can use it and communicate it to the sponsor (duly anonymized, of course). In my opinion, the subject should not be allowed to demand that all data pertaining to his participation be destroyed or be left unexploited. The consent form should contain a warning to this effect.

The European Union applies a stricter rule with respect to biological samples. Subjects who withdraw their consent can require the destruction of all identifiable samples obtained during their earlier participation in the trial.[2640] Only *information* gathered while the consent was still in force remains fully exploitable.

From a scientific perspective, the investigator has to *account* for every subject who drops out of the study. The reason is that ignoring such drop-outs can easily distort the study findings. For example, it might be that only subjects who did not tolerate the investigational drug chose to leave.[2641] The final study report should indicate, for each subject who withdrew or was withdrawn, the relevant study arm, "the specific reason for discontinuation, the treatment (drug and dose), cumulative dose (where appropriate), and the duration of treatment before discontinuation."[2642] If possible, the investigator should add other information such as age, sex, concomitant medication, that could be helpful in determining whether the withdrawal can be explained by these other factors. For example, based on the study report, the sponsor may notice that male subjects over 65 were particularly likely to withdraw from the study when they were concurrently taking drug X. While the investigator should inquire in the reason for the subject's withdrawal, the latter is not obliged to answer her,[2643] even though this reason

---

2639 *Id. See also* UCS (Part X), *supra* note 2455.

2640 *See* E.U. Guidance (Ethics Committee), *supra* note 270, at 7 and also at 23.

2641 "A large number of dropouts, however, even if included in an analysis, may introduce bias, particularly if there are more early dropouts in one treatment group or the reasons for dropping out are treatment related or outcome related. Although the effects of early dropouts, and sometimes even the direction of bias, can be difficult to determine, possible effects should be explored as fully as possible." chapter 11.4.2.2 (p.16 and 17) of the ICH E3. See however the British 1996 study by Wise and Drury which found that "only 36 of the 71 final reports on completed projects provided reasons for withdrawal." *Supra* note 1999.

2642 ICH E3, at chapter 10.1 (p.13).

2643 *See* SAMS 1997 Guideline, *supra* note 110, at point D.8. at 10. *See* section 4.3.4 (p.13) ICH E6.

(if there is one) could be scientifically important (e.g., the subject withdraws because he feels unbearable side effects but has not revealed them to the investigator).

8.3.3.11. Renewal of consent

By giving their consent, research subjects mark their agreement with a given set of circumstances, including a specific balance and appreciation of risks and benefits. Whenever these circumstances change, for example because new information is acquired regarding the risks of the investigational compound, consent should be sought and obtained again.[2644] Thus, the investigator should periodically review the data derived from the trial *or from external sources* to decide whether she should communicate new information to research subjects.[2645] If this information could possibly alter subjects' desire to maintain their participation, the investigator should go through the consent process again.[2646] The sponsor should support this process.[2647] Similarly, the REC should be consulted again (see subsection 9.2.1. below).[2648] In some cases, the REC may approve an exception to this rule, for instance, when informing the subjects of new facts would spoil the scientific validity of the trial (e.g., only subjects on the investigational arm of the trial suffer from nausea).[2649]

This requirement is perfectly congruent with the logic behind every medical interventions that entail health risks. However, in practice, the weight is predominantly on the initial consent. Many investigators fail to re-assess periodically the data and, on that basis, to request a "fresh" informed consent. Moreover, as we will see in subsection 9.2.1., ethics committees do not closely supervise the progression of clinical trials and often limit themselves to the review of the documentation to be submitted to subjects at the onset of the trial. Interim reports by DSMB are generally not communicated to subjects out of fear by investigators and sponsors that they would pointlessly alarm subjects.[2650]

Even though existing principles are not strictly followed, there have been suggestions to strengthen the consent process by requiring periodical update of consent, even when the initial circumstances have remained unchanged.[2651] According to this proposal, the investigator should regularly check that subjects still understand the study and agree to participate in it. This proposal has been made, among other reasons, be-

---

2644 *See* sections 4.8.2 (p.15) and 4.8.10(p) (p.17) of ICH E6; CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary); WHO (Operational Guidelines), *supra* note 1379, at point 6.2.5.4&5 (p.12). In the United States, see 21 C.F.R. § 50.25(b)(5).

2645 *See however* SPRUMONT, *supra* note 16, at 173.

2646 According to the ICH E6 Guideline, the investigator should inform subjects of any new information "that may be relevant to the subject's willingness to continue participation in the trial." ICH E5, at section 4.8.2 (p.15).

2647 The right of subjects to be informed of newly uncovered unfavorable information was at issue in the Olivieri case. *See* subsection 5.3.3.1.

2648 Article 20 OClin applies when new facts call into question subjects' safety. This provision does not state whether the REC is supposed to go through the reviewing process again. Article 20 OClin does not apply to new knowledge unrelated to a safety. However, subjects and ethics committees should nonetheless be informed.

2649 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary).

2650 *See* Slutsky & Lavery, *supra* note 1193, at 1145.

2651 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6.

cause it has been noticed that subjects have a tendency to forget that they are participating in research, as opposed to ordinary medical care.[2652] They also forget what they have been told about the risks of the trial.[2653]

Another question is whether subjects have a right to be informed of deficiencies in the conduct of the clinical trial. Monitors and auditors issue written reports listing failings and deviations from GCP, but current practices do not require communicating these reports to subjects. However, it is likely that the information contained herein would impact subjects' willingness to maintain their participation in a trial. Hence, when serious faults have been uncovered, they should be divulged to the subjects.

8.4. Enrollment of incapable subjects

The legislator has opted to place the entire regulation concerning clinical trials on incapable[2654] subjects in the LPTh.[2655] This is justifiable given the constitutional issues that the topic elicits. A medical intervention performed on someone who has not given valid consent impinges on the victim's constitutionally protected personal freedom, human dignity,[2656] and physical integrity.[2657] A law is therefore necessary to limit this freedom.[2658] Unfortunately, the two statutory provisions of the LPTh are not the best examples of legal draftsmanship.[2659] It would have been helpful to have clarifying stipulations in the OClin.

But for personal informed consent, research on incapable subjects must satisfy all other requirements applicable to clinical trials.[2660] Compliance should even be particularly strict when research involves people who cannot give their consent. The LPTh also introduces supplementary protections for these subjects.

2652 *See* GUILLOD, *supra* note 77, at 164 and note 446.

2653 *See id.* at 163-64. However, according to a survey by CenterWatch (a pro-industry group), 76% of subjects answered that they understood the study protocol very well. *See* CenterWatch (Word from), *supra* note 681, at 3.

2654 For practical reasons, I use the term *incapable* subjects to refer to both incompetent (Article 55 LPTh) and incapacitated (Article 56 LPTh) subjects. Generally, the terminology in this area is not very uniform. Incapacity and incompetence are often used as synonyms.

2655 Articles 55 and 56 LPTh.

2656 *See, e.g.,* the Federal Council's Message accompanying the LPTh, at FF 1999 3151, at 3228.

2657 See, under Swiss law, ATF 114 Ia 350, at 357-58, at point 5; ATF 111 Ia 231 at 232-33, at point 3.a); ATF 108 II 59, at 62, at point 3; ATF 104 Ia 480, at 486. *See also* SPRUMONT, *supra* note 16, at 214; GUILLOD, *supra* note 77, at 38-39. Of course, in situations where a medical intervention is urgently needed and the patient is not in a position to give his consent, the urgency justifies an intervention performed without consent.

2658 ATF 111 Ia 213 (striking down a cantonal ordinance which, without a statutory basis in a Parliament's law, granted public medical institutions the right to conduct autopsies despite the prior objections of the deceased or his family. One of the ordinance's purposes was to facilitate medical research).

2659 The fault does not rest entirely with the Swiss legislator as Article 55 LPTh, especially its paragraph 2, was modeled on Article 17 of the Convention on Human Rights and Biomedicine. *See also* Article 15 COE Research Protocol; Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 279.

2660 See the added comment to point D.6 of the SAMS 1997 Guidelines, *supra* note 110, at 12.
In the European Union, see Article 5 of Directive 2001/20/EC (which, however, only states this principle in connection with research on incapacitated adults).

Although the LPTh distinguishes between two categories of subjects deserving special protections (Article 55 LPTh on one hand, and Article 56 on the other hand), I have chosen to cover their respective protection in a single subsection. Two reasons justify this structure. First, even under Swiss law, the similarities exceed the differences.[2661] Second, the distinction at work in Articles 55 and 56 LPTh is debatable: by comparing the requirements of these two provisions, I underscore the illogical choices made by the legislator.

I have summarized the requirements of Articles 55 and 56 in the following table.

Article 55	Article 55	Article 56	Article 56
55.1 (what)	*Nothing specific said as to the type of trial.*	Situation of emergency. Exceptional	56 (what/who)
		A procedure allows, during the available deadline, to …	56.1 (condition)
		The procedure was approved by the REC	56.1 (condition)
55.1 (who)	Minors, legally incompetent, factually incompetent	*Nothing specific as to what type of subjects*	(who)
55.1.a (when)	No equivalent results otherwise	*No explicit subsidiarity condition*	(when)
55.1.b (condition)	Proxy consent of LR after information for all mentioned subjects	Proxy consent of LR for minors and legally incapable subjects	56.a.1 (condition)
		Determine subject's will by consulting relatives.	56.a.2 (condition)
55.1.c (condition)	Assent for subjects capable of judgment	*See cell above*	
55.1.d	No hint of refusal for subjects incapable of judgment	No hint of refusal.	56.b (condition)
55.2	Nontherapeutic trials are exceptional	*Nothing specific stated, but see cell below*	
55.2.a. (condition)	Important indirect benefits	Important indirect benefits	56.c (condition)
55.2.b. (condition)	Minor risks and inconveniences	*Nothing said on level of risk*	
	No equivalent condition	A non-implicated physician defends the interest of the subject	56.d (condition)

8.4.1. Two main categories

While prior consent is the rule, the law admits exceptions out of medical necessity.[2662] The LPTh creates two broad categories in which prior consent by the subject himself is either impossible or raises serious difficulties.[2663]

[2661] These similarities are especially obvious under E.U. law: compare Article 4 and Article 5 of the 2001/20/EC Directive.

[2662] In the past, other exceptions had been invoked such as when informing the patient would alarm him and impede his recovery (see also sujection 8.3.1. above). The 1983 version of the Helsinki Declaration stated that "If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee." Paragraph II.5, text at http://www.cirp.org/library/ethics/helsinki/.

8.4.1.1. Article 55 LPTh: research on incompetent subjects

The first category (Article 55 LPTh) comprises persons who have reduced capacity for, or right to, self-determination (hereinafter "incompetent subjects"). This category is in turn subdivided in three subgroups.

The *first* subgroup comprises *underage children,* that is individuals under the age of 18.[2664] Article 55 LPTh applies even if they are psychologically mature.[2665] Under Swiss law, children with parents, orphans and wards are all treated in the same manner.[2666]

The *second* subgroup consists of adults placed under legal guardianship by a judical decision.[2667] These adults have been deprived by courts of their legal capacity ("legally incompetent"); they are usually mentally feeble.[2668] However, they have not necessarily lost all capacity for judgment or for self-determination.[2669] At least in theory, they may even be mentally capable of reaching sophisticated medical decisions for themselves.

The *third* subgroup consists of persons who are, in fact and at the relevant time, incapable of judgment,[2670] even though their incompetence has *not* been recognized by a judge (hereinafter "factually incompetent"). Due to demographic trends[2671] combined

---

2663 Articles 55 and 56 LPTh. *See also* paragraphs 24 and 26 Helsinki Declaration.

2664 The ICH proposes a further classification by distinguishing five groups of children: "preterm newborn infants, term newborn infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years), adolescents (12 to 16-18 years (dependent on the region))." ICH E11 Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population, Step 4 of the ICH Process, July 20, 2000, at chapter 2.5 (p.8), at http://www.ich.org/cache/compo/475-272-1.html#E11 [hereinafter ICH E11].
In the United States, certain regulations hold that an individual is a child until the age of 21! *See* NIH, NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, at section V.A. (Mar. 6, 1998), at http://grants.nih.gov/grants/guide/notice-files/not98-024.html [hereinafter NIH (Inclusion of Children)]. For the FDA, children become adult at 16. *See* 21 C.F.R. § 201.57(f)(9).
See also chapter 2 of EMEA Guideline on Clinical Investigation of Medicinal Products in Children, (Mar. 1989), at http://pharmacos.eudra.org/F2/eudralex/vol-3/pdfs-en/3cc8aen.pdf [hereinafter EMEA (Investigation in Children)].

2665 The difference in mental ability is however taken into account at Article 55.1.c. LPTh, whereby only minors who are capable of judgment are asked for their assent (see also subsection 8.4.4.4. below).
In the European Union, clinical trials involving minors are governed by Article 4 of the Directive 2001/20/EC. The requirements are similar to those of Switzerland, though somewhat more precise. I prefer them to the Swiss system at Article 55 LPTh.

2666 By contrast, U.S. law contains additional protection for wards. *See* 45 C.F.R. § 46.409; IRB Guidebook, *supra* note 411, at chapter VI.C. Similarly, the CIOMS calls for additional protection for orphaned children or those in institutions. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 14 (commentary).

2667 *See* Articles 368 to 372 CC. Under the proposed modification of the Civil Code, these provisions would be replaced by Articles 377 to 384 (governing "*curatelle*"). *See* draft revised articles of the CC (June 2003), at http://www.ofj.admin.ch/themen/vormund/entw-zgb-f.pdf; Expert Group for the total revision of guardianship law, "*Protection de l'Adulte, Rapport relatif à la révision du code civil*" [Protection of adults, report regarding the revision of the civil code], (June 2003), at
http://www.ofj.admin.ch/themen/vormund/vn-ber-f.pdf [hereinafter CC Revision Report].

2668 Guardianship mainly aims to protect these adults from undertaking undue financial commitments. Once legally incapacitated, they cannot validly enter into a contract without the agreement of their guardian. As a result, the present institution of legal guardianship is not well adapted to address medical issues.

2669 In this thesis, I mostly use the expression "capacity for judgment," a translation from the French "*capacité de discernement*." In the United States, the term generally used is "decision-making capacity."

2670 In the literature, these people are also said to lack complete ability for self-determination or for decision-making.

2671 In the United States, "[f]rom 1950 to 2000, the proportion of the population age 65 years and over rose from 8 to 12 percent. By 2050, it is projected that one in five Americans will be 65 years of age or over."

with Alzheimer disease, an increasing percentage of elderly people enter this subcategory. Yet, the next of kin rarely goes through the trouble of asking for a judge's decision of official incompetency.[2672] Hence, most of these mentally diminished seniors are not *legally* incompetent.

While it is relatively easy to verify whether a potential subject is underage or officially incompetent, determining whether he is cognitively impaired (i.e., factually incompetent) is significantly more difficult. Given its legal consequences (i.e., the applicability of special norms of protection pursuant to Article 55 LPTh), this is an important decision.

The law does not require a "perfect" capacity of judgment, which is an idealized notion anyway.[2673] Hence, a subject is capable of judgment (and thus competent) if, first, he is able to understand the research explained to him and, second, if he is able to make a choice as to whether he should participate.[2674] According to the CC and as routinely observed in practice, capacity is context-specific. An individual may be able to consent to a "simple" trial, while not being deemed competent for a more "complex" trial. Even the investigator's explaining skills may have an effect on the decision as to the subject's capacity.[2675]

Although the law establishes a rebuttable presumption of capacity for adults, investigators should be careful not to rely too much on it. On the contrary, depending on the class of subjects involved, they may have to test the mental capabilities.[2676] Thus, for example, investigators should not assume full capacity when enrolling very elderly or extremely sick patients[2677] – although this may appear discriminatory to some. Tests should be described in the protocol, and hence are to be (at least implicitly, but prefera-

---

Health USA Population (Feb. 28, 2004), at http://www.medicalnewstody.com/medicalnews.php?newsid=6216. Compare with Switzerland, Swiss Federal Statistical Office, at http://www.bfs.admin.ch/bfs/portal/fr/index/themen/bevoelkerung/uebersicht/blank/wichtigste_kennzahlen.html.

2672 The U.S. IRB Guidebook resists initiating legal proceedings in order "to establish guardianship for the purpose of obtaining consent for research participation. Despite a temptation to recommend this course of action 'to be on the safe side,' depriving individuals of their freedom should not be taken lightly." *Supra* note 411, at chapter VI.D.

2673 *See* Mauron (psychogériatrie), *supra* note 2420, at 1175-1178. *See also* subsection 8.3.3. above.

2674 According to the NBAC, "the standards for assessing decisionmaking capacity include the ability to evidence a choice, the ability to understand relevant information, the ability to appreciate the situation and its consequences, and the ability to manipulate information rationally." NBAC (Mental), *supra* note 1250, at chapter II. Others have distinguished four key elements to assess decision-making competence: understanding, appreciation, reasoning and the ability to express a choice. *See How to Get Informed Consent From Decisionally-Impaired Patients – and Why We Must*, 6(5) BROWN UNIVERSITY GERIATRIC PSYCHOPHARMACOLOGY UPDATE 3-4 (2002).

2675 Similarly, conveying the information to the subject may require using bigger font size in written material, repeating the information several times, having family members present to reassure the subject and re-explain the material. *See* NBAC (Mental), *supra* note 1250, at chapter II.

2676 *See* Jason H. T. Karlawish, *Research Involving Cognitively Impaired Adults*, 348 NEW. ENG. J. MED. 1389-1392 (2003), *at* http://content.nejm.org/cgi/content/full/348/14/1389; Nicole Vogt et al., *Gériatrie et recherche clinique: problèmes pratiques, questions éthiques*, 39(2) CMS 191, at 195 (1995) (describing a study in which doctors' ability to detect reduced capacity for consent among their elderly patients was found to be particularly poor); BEAUCHAMP & CHILDRESS, *supra* note 16, at 73-74. *See also* Article 14.3 COE Research Protocol.

2677 Stress is acknowledged as a cause of capacity impairment. Hence, patients who are very sick, under great pain or in a state of shock may not be able to stand the intellectual burden of the informed consent process. *See, e.g.,* NIH (Questionable Capacity), *supra* note 2547.

bly explicitly) endorsed by the ethics committee.[2678] The tests should be conducted by a person specially qualified for this task – which may not necessarily be the investigator.[2679]

Instruments have been developed to test subject's capacity to reach informed decisions. The MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) is perhaps the most well known.[2680] It can be adapted to fit any clinical trial. The claimed advantage of such an instrument is that it provides standardized results that can later be compared across subjects, research sites or studies.

However, tests have limitations. For example, elderly patients may have fluctuating judgment abilities.[2681] They may be able to give consent on a "good day," yet forget who their doctor is on the next "bad day." This raises the thorny legal question of what happens when a subject who has given consent when he was competent then loses his judgment during the trial. Should Article 55 apply? Should the subject be automatically withdrawn from the study pending permission by a representative? Or more pragmatically, should the answer depend on the study stage and on the risks involved (e.g., only one radiography left before the end of the study)? In my view, a reasonable solution would be for the investigator to consult with the REC to determine whether permission by a representative is necessary, particularly in view of the risks over the remaining course of the trial.[2682]

The law does not envisage that courts be called upon to judicially ascertain the mental (in)capacity of prospective subjects.[2683] Ethics committees are usually not involved in this assessment, since they do not attend the consent process. However, leaving this assessment entirely to investigators is undeniably risky, both for them and for the concerned subjects.[2684] The U.S. NBAC correctly calls attention to the weighty consequences attached to the investigator's determination of the subject's competency:[2685]

> An assessment that a capable person is incapable of exercising autonomy is disrespectful, demeaning, and stigmatizing, and it may result in the unwarranted deprivation of an individual's civil liberties. Conversely, a judgment that an incapable person is capable leaves that individual unprotected and vulnerable to exploitation by others.[2686]

2678 *See* NBAC (Mental), *supra* note 1250, at chapter II.

2679 *See id.* at chapter II (evoking the debate on this issue).

2680 See the webpage of http://www.prpress.com/mactcrfr.html.

2681 *See* NBAC (Mental), *supra* note 1250, at chapter II.

2682 *See id.* at chapter III.

2683 Courts do come into play in procedures leading to a judgment of legal incapacity. On the disadvantages of such judicial involvement, see NBAC (Mental), *supra* note 1250, at chapter III.

2684 See in the United States, the decision in T.D. et al. v. New York State Office of Mental Health, 228 A.D.2d 95, at 119 (S.Ct.N.Y. 1996).

2685 In "normal" medical care, the consequences are not as grave because the requirements for informed consent are – both legally and practically – significantly lower.

2686 NBAC (Mental), *supra* note 1250, at chapter II.

Other texts recommend that adult subjects found to be incompetent should be informed of this assessment and told that surrogate consent will be sought.[2687] This offers the subjects an opportunity to object to the proposed procedure.

8.4.1.2. Article 56: emergency research

The *second category* of clinical trials without personal consent (Article 56 LPTh) pertains to emergency research. Although the LPTh deplorably fails to articulate this clearly, the underlying assumption is that the subject is *momentarily* incapacitated and therefore presently incapable to give his informed consent.[2688] Yet, nowhere at Article 56 LPTh is it mentioned that the subject is *incapable* of giving consent. The existence of an emergency does not rule out *per se* the capacity of judgment of the subject. For example, a person may be brought to the hospital requiring immediate care because he cut his finger off, yet be sufficiently conscious to understand what he is told. Obviously, Article 56 LPTh does not make good sense if the subject is fully capable of judgment. Surprisingly, the Federal Council's message maintains, or even heightens, this ambiguity;[2689] it mentions the subject's consent twice. However, I fail to see why additional safeguards (set forth at Article 56 LPTh) are necessary in situations where the subject is fully capable. The emergency itself and the ensuing necessity to give consent within a very short deadline do not – in my view – justify these strict safeguards. It is therefore more rational to posit that the subject at issue at Article 56 is (temporarily) incapable of judgment.[2690]

Because this is an emergency medical situation, waiting for the patient to recover his capacity (if ever) could put him at risk. The medical procedures called for by the protocol must imperatively be implemented rapidly or else they will not be (as) effective. Typically, Article 56 LPTh applies when unconscious persons are brought to a hospital in need of immediate care (e.g., persons having suffered a stroke or a car accident).

8.4.1.3. Classification difficulties

The main difference between Article 55 and Article 56 LPTh lies in the protocol. In the second category, the protocol calls for the rapid execution of the procedures in an emergency setting, where it can be anticipated that i) subjects with the studied medical condition will generally not have the full capacity to decide whether or not to give con-

---

2687 *See* University of California, Davis, Office of Human Research Protection ("OHRP/UCD"), Surrogate Consent for Research, at 3, at http://research.ucdavis.edu/documentDisplay.cfm?documentKey=131&documentType=pdf [hereinafter OHRP-UCD (Surrogate Consent)].

2688 Compare with Article 19.1.i. COE Research Protocol.

2689 FF 1999 3151, at 3231-32.

2690 If his incapacity existed before the emergency, there would be no reason to differentiate between Article 55 and Article 56 LPTh

sent,[2691] and ii) the procedures will not be effective (or as effective) if not carried out immediately after hospitalization or entry into the research facilities.[2692]

The two categories (Articles 55 and 56) occasionally merge, for instance when emergency research must be conducted on children.[2693] Ideally, the two provisions – Article 55 and Article 56 LPTh – should then apply concurrently. However, the language at Article 56.a.1. LPTh rather suggests that Article 56 LPTh is solely applicable.[2694]

Interestingly, the European Union draws differently its two categories: Article 4 of the Directive 2001/20/EC deals exclusively with clinical trials on *minors*, while Article 5 focuses on all *incapable adults* (both incompetent and incapacitated adults).[2695] Emergency clinical research belongs, implicitly, to the second category.[2696]

The 2002 Federal Regulation makes no mention of a third possible category, that is situations where the administration of an investigational drug is necessary in an emergency but no research protocol has been prepared nor a fortiori submitted to the authorities. In this case, the investigational drug offers the best medical prospects for the incapacitated patient facing a life-threatening situation, for example because all other available drugs have been tried in vain. Because this is an emergency, there is no time to prepare a protocol and submit it for review to a REC and to Swissmedic. Either the investigational drug is administered immediately or it cannot be used at all. U.S. law allows such emergency use and grants an exemption from prospective IRB approval. The investigator must provide first basic and then more complete information as soon as possible. It is assumed that a complete application will only be lodged after emergency use.[2697]

Can such an emergency use of an investigational drug be permitted under Swiss law? The first question that has to be answered is whether this use is to be qualified as research, and more specifically, as a clinical trial under the OClin. The answer depends on the circumstances: If the only purpose is to save the life of the patient, then this use should no be considered as research, but as emergency medical care; the rules of the OClin are then inapplicable. However, if the doctor also plans to exploit the information acquired during this event to investigate more closely the safety and efficacy of the experimental drug or if she plans to publish a case report describing the effects of the drug in this particular case, one should admit that this is no longer "ordinary" medical care. The second question is whether this emergency research which does not follow the procedure of Article 56 LPTh is permissible. The likely answer is negative. The purpose of Article 56 LPTh is to ensure that subjects "drafted" into emergency research

---

2691 *See* note 2690 above.

2692 *See* Nicole Davis et al., *Improving the Process of Informed Consent in the Critically Ill*, 289 JAMA 1963-1968 (Apr. 16, 2003), at http://jama.ama-assn.org/cgi/reprint/289/15/1963.pdf (describing how informed consent is generally sought in an Intensive Care Unit – outside the clinical trial setting).

2693 *See, e.g.*, AAP (Guidelines), *supra* note 385.

2694 *See* subsection 8.4.4.2. below.

2695 The two provisions are very similar except for Article 4(e), 4(f), 5(e), and 5(i).

2696 However, Article 5 of the Directive 2001/20/EC appears better suited to clinical trials on incapable persons outside emergency situations. *See* Ernst A. Singer & Marcus Müllner, *Implications of the EU directive on clinical trials for emergency medicine*, 324 BMJ 1169 (May 18, 2002), at http://bmj.bmjjournals.com/cgi/reprint/324/7347/1169.pdf.

2697 On the requirements, see the detailed explanations given in the UCSD's guidelines. UCSD-SOPP, *supra* note 485, at 45-46.

benefit from the best safeguards. This objective would be eroded if emergency research without prospective REC approval was tolerated. Therefore, doctors who want to use investigational drugs in emergency situations must choose between following the rules of Article 56 LPTh or renouncing to use the information acquired for research purposes.

8.4.2. Special medical and ethical considerations

8.4.2.1. Special considerations in pediatric trials

Allowing that research be conducted on incompetent subjects is a controversial issue. In Switzerland, the Biomedicine Convention gave rise to disagreements during the consultation proceedings and then during parliamentary sessions because it allowed such research.[2698] A few cantons had prohibited nontherapeutic research on incompetent subjects.[2699] In the European Union also, this type of research, especially when conducted on children, has been contentious.[2700] It was thought that the potential for abuse would be too great if the law allowed incompetent and incapacitated persons to be enrolled in research.[2701] In numerous past occurrences, children have been exploited for research purposes.[2702] Cases of pediatric trials that went awry include the administration of high doses of oxygen to treat premature babies; the parents were not informed that their babies had been enlisted in a clinical trial to test the relative efficacy of low and high doses of oxygen. High doses were later found to cause blindness (in fact, retrolental fibroplasis or RLF).[2703] In the infamous Willowbrook experiment of the mid-1960s, mentally ill children institutionalized at the U.S. Willowbrook mental hospital were intentionally injected with the hepatitis virus to see whether early infection led to some degree of protection.[2704] The investigator justified the study by asserting that, at

---

2698 *See* Federal Council's Message regarding the Convention, *supra* note 107, at 274 and 277.

2699 *See id.* at 316 (mentioning the cantons of Jura, Neuchâtel and Thurgau).

2700 *See* EFGCP, The EFGCP News, at 1 and at 16 (Spring 2002), *supra* note 44. *See also* C. Lenk et al., *Non-therapeutic research with minors: how do chairpersons of German research ethics committees decide?*, 30 J. MED. ETHICS 85 (2004), at http://jme.bmjjournals.com/cgi/content/full/30/1/85.

2701 Particularly criticized were trials not intended to confer any direct therapeutic benefits to enrolled children. *See* Sprumont & Béguin, *supra* note 134, at 898. *See also* Glantz, *supra* note 83, at 192.

2702 *See* LEDERER, *supra* note 54, at 51 (smallpox experiment), 61-62 (syphilis and lumbar puncture experiments), 69 (staphylocci experiment), 79-83 (tuberculosis test and syphilis test experiments), 89 (tuberculosis and ringworm experiments), 106 (scurvy experiment), 107-8 (dysentery and polio experiments). See also the many examples provided by Beecher (Ethics), *supra* note 232, at 1354-60. *See also* Burns, *supra* note 81, at 131 ("A preponderance of the children involved in early research were poor, institutionalized, mentally ill, or physically disabled."); *Grimes*, 782 A.2d 807 (which describes an experiment that took place in 1939 to turn children of an Iowa orphanage into stutterers to prove that stuttering is provoked by psychological and environmental factors).
See also William J. Curran & Henry K. Beecher, *Experimentation in children. A reexamination of legal ethical principles*, 210 JAMA 77-83 (Oct. 6, 1969) (proposing regulations for pediatric clinical trials, especially non-therapeutic ones) [hereinafter Curran & Beecher (Children)].

2703 *See* Burton v. Brooklyn Doctors Hospital, 452 N.Y.S.2d 875 (N.Y.App. 1982).

2704 The parents of the children had given their consent. However, their decision was constrained by the fact that the Willowbrook management did not admit newcomers unless they took part in the experiment. *See* Burns, *supra* note 81, at 132; BEAUCHAMP & CHILDRESS, *supra* note 16, at 428-30.

the Willowbrook institution, all children sooner or later became infected with hepatitis; hence, he was only hastening an inevitable event.[2705]

Past exploitation of children in research can be attributed to several factors in addition to the fact that young children cannot give consent.[2706] Immunization treatments were easier to test on children since most adults were already naturally immunized.[2707] Compared to adults, children were more prone to diseases and, as a result, in regular contact with physicians. In the past, orphans were particularly ill-treated, sometimes under the pretence that participation in research was a valid way for them to "repay their debt to society" for orphanage care provided.[2708] More generally, institutionalized children were convenient "research material" because they lived in controlled conditions (e.g., same housing, same diet).[2709]

Even today, experimentations with children sometimes go wrong. The case of 18-year old Jesse Gelsinger is a glaring reminder (see subsection 5.3.2.4.1. above).[2710] However, other commentators point out that children are doubly victimized if they are automatically excluded from clinical trials and if no medicine is developed for their own (presently unmet) needs.[2711] Indeed, children are referred to as "therapeutic orphans" because they are prescribed drugs that by and large have only been tested on, and approved for, adults.[2712] But safety and efficacy information derived from clinical trials performed on adult subjects does not provide similar guarantee when the drug is administered to children, even if the dosage is reduced according to weight (e.g., Seroxat for depression[2713]). The classic saying is that children should not be viewed as small adults.[2714]

2705 In 1972, television reports of dismal conditions at Willowbrook shocked the public. *See* GERALDO RIVERA, WILLOWBROOK, A REPORT ON HOW IT IS AND WHY IT DOESN'T HAVE TO BE THAT WAY, (Random House 1972).

2706 *See* OHRP (Children), *supra* note 1636, at 3.

2707 *See* Burns, *supra* note 81, at 131.

2708 *See* LEDERER, *supra* note 54, at 106-7.

2709 *See* Burns, *supra* note 81, at 131.

2710 *See* subsection 5.3.2.4.1. above. Gelsinger's death did not remain an isolated event. *See, e.g.,* FDA, Warning letter to Jacqueline M. Halton at the Children's Hospital of Eastern Ontario, (Apr.14, 2003), at http://www.fda.gov/foi/warning_letters/g3946d.htm. *See also supra* note 987.

2711 "There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents." AAP (Guidelines), *supra* note 385. *See also generally* Mauron (psychogériatrie), *supra* note 2420, at 1175-1178.

2712 *See, e.g.,* John P. Niles, *Pediatric Subjects and Their Parents Respond to a Survey*, APPLIED CLINICAL TRIALS 46, (Sept. 2003), at http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/352003/68141/article.pdf.
Ninety-four percent of drugs administered in intensive hospital care have no pediatric indication, 67% of those administered in hospital settings and 30% in private practice. *See* Elisabeth Autret-Leca et al., *Particularité de l'évaluation des médicaments en pédiatrie et son application à la prescription en pédiatrie*, 13 PAEDIATRICA 48-51, at 48 (2002), at http://www.swiss-paediatrics.org/paediatrica/vol13/n3/pdf/48_52.pdf. See *also* O'Reilly & Dalal, *supra* note 429, at 298; AAP (Guidelines), *supra* note 385 (in 1991, "81% of listed drugs contained language disclaiming use in children or restricting use to certain age groups.").
Exceptions would be drugs that are only intended for children, such as drugs intended for preterm babies. *See* chapters 2.3.1. (p.3) and 2.5.1. (p.8) ICH E11; chapter 3.3 of EMEA (Investigation in Children), *supra* note 2664.
See also ARNO AND FEIDEN, *supra* note 125, at 202-4; Schreiner, *supra* note 630, at 949-51; GAO (Pediatric), *supra* note 608, at 1-2.

2713 "Dear Colleague" letter from Gordon Duff, Chairman, Committee on Safety of Medicines, (June 10, 2003), at http://www.essentialdrugs.org/edrug/archive/200306/msg00029.php.

2714 *See* chapter 1.1 of EMEA (Investigation in Children), *supra* note 2664; AAP (Guidelines), *supra* note 385; Burns, *supra* note 81, at 131; Claire-Anne Siegrist, *La cause des enfants*, 39(2) CMS 203-208 (1995).

In other cases, it is not the efficacy of the drug which is questioned, but the lack of an appropriate pediatric formulation (e.g., inhalers are difficult to administer to young children, syrups containing alcohol are not suitable).[2715] Thus, it is estimated that information on pediatric use is lacking for three quarters of available prescription drugs.[2716] Of all new drugs approved by the FDA between 1991 and 2001, only 20% included a pediatric label.[2717]

Pharmaceutical companies have few reasons to develop pediatric information about their drugs.[2718] Since physicians can prescribe off-label – and often do so –, companies can make money out of pediatric prescriptions without having to go through the marketing approval process. Moreover, drugs prescribed off-label to children are reimbursed by insurance companies.

Eager to solve this problem, the FDA pressed the pharmaceutical industry to systematically test new drugs on children. Its first attempts – measures of encouragement – were not successful.[2719] Then, Congress gave the FDA power to grant a six-month marketing exclusivity period to sponsors of pediatric clinical trials.[2720] This incentive produced very positive results. Pediatric testing increased significantly, with some 100 duly completed pediatric trials in 2004.[2721]

Subsequently, the FDA incorporated a more uncompromising approach: a regulation compelling all sponsors of new drugs to test their products on children, whenever it could be anticipated that the drug would ultimately be prescribed (off-label) to children.[2722] However, this regulation – called the 1998 Pediatric Rule – was struck down by

---

2715 The ICH notes that "[t]here is a need for pediatric formulations that permit accurate dosing and enhance patient compliance." Chapter 2.2 of ICH E11 Guideline.

2716 *See* Robert Steinbrook, *Testing Medications in Children*, 347 NEW. ENG. J. MED. 1462-1470 (2003), at http://content.nejm.org/cgi/content/full/347/18/1462 [hereinafter Steinbrook (Children)] (observing however that "[a]ggregate statistics … can be misleading, because many medications are not used in children.").

2717 *Id.* This percentage (69 out of 341) is for new molecular entities (NCEs), i.e., drugs with entirely new active ingredients.

2718 "Between 1991 and 1996, drug sponsors promised [to the U.S. FDA] to complete 71 post-marketing pediatric studies but completed only 11." Steinbrook (Children), *supra* note 2716. *See also* Siegrist, *supra* note 2714, at 206-207.

2719 *See* Ass. American, Physicians and Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, at 207 (D.D.C. 2002); GAO (Pediatric), *supra* note 608, at 3.

2720 The exclusivity (a protection against competitors akin to a patent) is granted provided that the FDA approves the clinical trial for the drug's pediatric indication. The drug must be one that is or could be prescribed to children. Moreover, there must be insufficient information about the efficacy and/or safety of this drug for children. Thus, a sponsor cannot obtain an exclusivity for testing a drug which will never be administered to children (e.g., a drug against Alzheimer). *See* Food and Drug Administration Modernization Act ("FDAMA"), Pub. L. No.105-115, 111 Stat. 2296 (1997), text at http://www.fda.gov/cder/guidance/105-115.htm; and 21 U.S.C. § 355a(a).

2721 *See* FDA, Approved Active Moieties to Which FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act, (Mar. 2004), at http://www.fda.gov/cder/pediatric/exgrant.htm. *See also* GAO (Pediatric), *supra* note 608, at 2 and 4.

2722 FDA, Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 21 C.F.R. §§ 201, 312, 314, 601, at 63 Fed. Reg. 66,632 (Dec. 2, 1998), at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-31902-filed.pdf. *See also* Steinbrook (Children), *supra* note 2716, at 1462-70.

an American Court in 2002.[2723] In 2003, the Congress gave a legal basis to the FDA's defeated testing requirement.[2724]

The European Union has followed the example of the FDA and is planning its own measures to promote pediatric testing.[2725] In particular, sponsors would get a six-month exclusivity when they perform pediatric clinical trials.[2726] The E.U. also encourages sponsors to prepare emergency protocols to study the problems related with drug accidental overdoses in children.[2727]

The ICH also supports pediatric clinical trials. It has issued a guideline spelling out the special considerations to be observed for such studies.[2728] It advises sponsors to determine early in the development of a new drug whether the drug is likely to be used in children. Even if pediatric trials are usually conducted only after adult studies have demonstrated the safety and efficacy of the compound,[2729] the ICH recommends initiating an early dialogue with the drug agency.[2730] The ICH enunciates a list of factors that influence the need for, and timing of, pediatric clinical trials (e.g., prevalence and seriousness of the disease, existing alternative pediatric treatments, probable differences in the mechanism of action of the drug and in the disease course).[2731] Obviously, when no satisfactory therapy is available to treat a life-threatening disease affecting a large pediatric population, the need to initiate early pediatric clinical trials for a promising new compound is higher.[2732] In such a case, the trial should be conducted on children of all ages (but usually not under two) affected by the disease, although the trial may start with comparatively older subjects.[2733] The ICH also asks that pediatric study results be submitted with the main marketing application.[2734] Conversely, when the need is less

---

2723 The District Court found that the FDA lacked a proper statutory basis to enact its regulation mandating pediatric testing. *Ass. American, Physicians and Surgeons*, 226 F. Supp. 2d 204. This judgment was – quite rightly – criticized. Since this decision, "more than 110 new medications and biologics have gone on the market without testing in children." Tanya Albert, *Congress gives FDA authority to require drug testing in children*, AMED NEWS (Dec. 8, 2003), at http://www.ama-assn.org/amednews/2003/12/08/gvsb1208.htm.

2724 *See* Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936, at http://www.fda.gov/opacom/laws/prea.html.

2725 *See* European Commission, Better Medicines for Children Proposed regulatory actions on Paediatric medicinal products, (Feb. 28, 2002) (consultation document), at http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2002/feb/cd_pediatrics_en.pdf; EMEA, Medicines for Children – The European Paediatric Initiative, at http://www.emea.eu.int/htms/human/peg/pegfaq.htm. *See also* O'Donnell (IT), *supra* note 1793, at 22-23.

2726 See European Commission, Proposal for a Regulation on Medicinal Products for Paediatric Use, (2004/0217 (COD)), (Sept. 2004), at http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=COM:2004:0599:FIN:EN:PDF; European Generic Medicines Association ("EGA"), Position Paper, EGA Comments on Proposed Regulation on Incentives for the Development of Medicines for Paediatric Use, (Apr. 2004), at http://www.egagenerics.com/doc/ega_paed_2004-04-08.pdf.

2727 Chapter 1.2.d) of EMEA (Investigation in Children), *supra* note 2664.

2728 ICH E11.

2729 See chapter 2.1. (p.2) of ICH E 11 Guideline.

2730 *See id.* and also at chapter 2.3 (p.3).

2731 *See id.*

2732 *See id.* at chapter 2.3.2. (p.4).

2733 *See id.* at chapter 2.5. (p.8) and chapter 2.6.3 (p.11).

2734 The ICH adds that "lack of data should be justified in detail." *See id.* However, the ICH's Guidelines are not compulsory unless they are adopted by States as mandatory regulations. The U.S. FDA typically adopts ICH's

pressing (for example because the pediatric population is smaller and other treatments are available), pediatric clinical trials will often be conducted only once adult testing is completed or after some level of experience has been accumulated with the approved drug.[2735] Moreover, in some cases, safety and efficacy of a drug on pediatric population can be extrapolated from the adult clinical data and from simpler pharmacokinetics trials on children.[2736] Aware that clinical trials on children pose multiple medical, practical and ethical problems, the ICH stresses the importance of postmarketing pediatric studies.[2737]

Among the practical difficulties are those related to the recruitment of patients. Recruiting a sufficient number of pediatric subjects is harder than recruiting adult subjects.[2738] The pool of patients tends to be smaller to begin with. It becomes even smaller if children must be divided in several age groups (e.g., infant, children, teenagers). Other difficulties relate to the added complexity of medical procedures to be performed on children (e.g., blood taking).[2739]

Preliminary evidence shows that subjects enrolled in clinical trials, whether adult or children, fare better than patients who choose not to enroll.[2740] A survey of children enrolled in U.S. clinical trials and their parents found that both were very satisfied with the level of care received in clinical trials.[2741] Both responded positively when asked whether they would agree to enroll their children in another clinical trial.[2742] However, the survey also found that payments offered influenced the decision to enroll. "Half of the subjects (51%) and a quarter of the parents (27%) cited financial compensation as a factor in their decision to participate."[2743] While the European Union opposes payments in pediatric clinical trials,[2744] the United States has no uniform policy on that matter.

8.4.2.2. Special considerations in emergency trials

For a long time, it was disputed whether clinical trials without either subject's consent or third party ("proxy") consent were at all permissible. In emergency research, a subject may be enrolled and undergo risky investigational procedures only with the "go-

---

Guidelines as internal Guidances. FDA's Guidances are recommendations, not obligations, and industry compliance with guidances can vary depending on the subject matter of the guidance.

2735 *See id.* at chapter 2.3.3. (p.4).

2736 *See id.* at chapter 2.4 (p.4-5).

2737 *See id.* at chapter 2.4.4 (p.7).

2738 *See* Steinbrook (Children), *supra* note 2716.

2739 *See* Siegrist, *supra* note 2714, at 206.

2740 *See* Barbara Schmidt, *Do Sick Newborn Infants Benefit From Participation in a Randomized Clinical Trial*, 281 BMJ 1776 (May 19, 1999). *See also* ECRI (Guide), *supra* note 869, at 19 and 33; Deborah Borfitz, *Are Industry Trials Safer?*, 10(11) CENTERWATCH 1-9 (Nov. 2003) (suggesting that commercial clinical trials are safer and better conducted than publicly sponsored trials).

2741 "A majority of parents (72%) and subjects [children] (69%) [commented that the level of care] was better than expected." John P. Niles, *supra* note 2712, at 44.

2742 *Id.* at 44.

2743 *Id.* at 43. The author notes however that many children enrolled were in fact teenagers "who as a group are more responsive to monetary incentives." *Id.* at 44. On this issue, *see also* Steinbrook (Children), *supra* note 2716.

2744 Chapter 1.3.f) of EMEA (Investigation in Children), *supra* note 2664.

ahead" of the ethics committee. On the face of it, this is a serious breach of the informed consent principle.[2745] Some commentators find that such a breach cannot be tolerated, even when the investigational treatment promises exceptional benefits. They argue that the doctor must give his patient the best treatment available, whether or not investigational, but should not enroll him in the clinical trial. The obvious downside is that the information about the safety and effectiveness of the available treatments (whether or not investigational) will remain piecemeal. Each doctor will make decisions based on partial evidence and intuition, which may prove to be entirely incorrect.[2746] Only if rigorous science is introduced can the medical community and their patients truly get the best treatment. There is therefore a very genuine need for emergency clinical research.

This need has only been acknowledged of late. The United States revised its position in 1996,[2747] whereas previously such research had been illegal or severely obstructed.[2748] That the research was illegal did not mean that it was not conducted at all. Rather, it was conducted under the guise of "off-label" treatment combined with emergency compassionate use.[2749] As mentioned above (subsection 3.4.4.), under their own responsibility, doctors are allowed to select any treatment they see fit; in particular, they can decide to prescribe non-standard treatments or use a drug "off-label." As doctors, they must secure their patient's informed consent, except when an emergency makes this unfeasible. In other words, in emergency situations, doctors have the right to administer a non-standard treatment to patients who cannot give their consent.[2750] Before 1996, they did not have the right to do so in the context of research. In practice, however, the lines between research and medical practice can be blurred, with, for instance the doctor (still acting in his capacity) also collecting systematic information.

In the United States, emergency research is understood as including only trials where the patient is *suddenly* incapacitated and a medical intervention is *immediately* required. When there is no urgency to treat the patient or when the incapacity does not occur unexpectedly, the rules governing emergency trials do not apply.[2751] This U.S. interpretation should be equally valid in Switzerland. Thus, Article 55 LPTh (and not 56) applies when these two conditions are not satisfied.

2745 *See, e.g.,* S. Lötjönen, *Medical research in clinical emergency settings in Europe*, 28 J. MED. ETHICS 183-87 (2002), at http://jme.bmjjournals.com/cgi/content/full/28/3/183.

2746 *See* Council on Ethical and Judicial Affairs of the American Medical Association, Report on Waiver of Informed Consent for Emergency Research, (June 1997), at http://www.ama-assn.org/ama1/pub/upload/mm/369/report80.pdf [hereinafter AMA (Emergency)].

2747 *See id.* at 1. *See also* Norman Fost, *Waived Consent for Emergency Research*, 24 AM. J. L. AND MED. 163, at 171 (1998); Gina Kolata, *Ban on Medical Experiments Without Consent Is Relaxed*, N.Y. TIMES, Nov. 5, 1996, at A1; M. H. Biros et al., *Informed consent in emergency research. Consensus statement from the Coalition Conference of Acute Resuscitation and Critical Care Researchers*, 273 JAMA 1283-1287 (Apr. 26, 1995); Roger J. Lewis, *Monitoring a Clinical Trial Conducted Under the Food and Drug Administration Regulations Allowing a Waiver of Prospective Informed Consent*, 286 LANCET 2647 (Dec. 5, 2001).

2748 For a description of the previous regime, see AMA (Emergency), *supra* note 2746, at 2-3. *See also* Fost, *supra* note 2747, at 165-71 (1998) (discussing, in particular, the "minimal risk" condition).

2749 *See also* BRODY, *supra* note 447, at 105-106.

2750 *See* AMA (Emergency), *supra* note 2746, at 1. "Traditionally, life-saving treatment in the event of an illness or injury which incapacitates the patient is assumed to be in compliance with patient preferences." *Id.* at 2.

2751 The FDA gives the example of a long-term coma. *See* CDER, FDA, INDs: Exception from Informed Consent Requirements for Emergency Research, at 4 (MAPP 6030.8) (2003), at http://www.fda.gov/cder/mapp/6030-8.pdf [hereinafter FDA (MAPP 6030.8)]; FDA (Emergency Guidance), *supra* note 261, at 19.

In Switzerland, the LPTh does not set any explicit restriction as to the medical condition of subjects enrolled in emergency research. Provided that the benefits are found to outweigh the risks, it seems that any disease could be studied under an emergency protocol. The word "exceptionally" at the beginning of Article 56 LPTh however suggests that emergency protocols should not be approved too easily. In contrast, in the United States, emergency clinical trials (where the subject does not give his prior informed consent) are only possible if the subject is facing a life-threatening condition.[2752]

8.4.3. Subsidiarity

According to Article 55.1.a LPTh, research on incompetent subjects can only be conducted if research on fully competent adults cannot yield "equivalent results" (the "subsidiarity" requirement).[2753] Surprisingly, Article 56 LPTh on emergency research does not reiterate this requirement (that is, that research outside emergency setting would not yield "equivalent results").[2754] However, the fact that emergency trials are envisaged only in "exceptional" circumstances should be taken as an indication that the legislator nevertheless intended such a requirement.

This subsidiarity requirement is the expression of an even more general notion that requires that research on human beings be only pursued as a last alternative.[2755] As a consequence, clinical trials (on human beings) should only be launched when necessary to answer an important medical question. Similarly, vulnerable populations should only be enrolled if research on less vulnerable groups is not feasible.

The requirement of Article 55.1.a LPTh is regrettably vague. How strictly should these notions of subsidiarity and equivalence be appreciated? Article 55.1.a does not go as far as requiring that research on competent adults be *absolutely* impossible. Can practical considerations (e.g., duration of the study) be taken into account to appreciate equivalence? Probably not. Since Article 55.1.a LPTh is applied by RECs before the clinical trial has started, how can they appreciate with any certainty the future "results"? When the REC receives the protocol, the latter only contains a hypothesis that will be validated or refuted by the trial; at this stage, there are no results, only projections.

Even more importantly, Article 55.1.a LPTh apparently could preclude adolescents, children and incompetent persons from participating in a clinical trial, even if the tested drug has a life-saving potential. For example, an adolescent infected with AIDS could be barred from participating in a phase III trial of a promising AIDS cure when the in-

---

2752 A life-threatening condition is present "where the likelihood of death is high unless the course of the disease or condition is interrupted." FDA (MAPP 6030.8), *supra* note 2751, at 4.

2753 *See also* Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 315 (invoking the principle of subsidiarity); paragraph 26 Helsinki Declaration; MANAÏ (CONTEMPORAINE), *supra* note 16, at 257.
See also Article 4(e) Directive 2001/20/EC. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 13 (commentary), Guideline 14 and Guideline 15.

2754 *See also* Article 5(e) Directive 2001/20/EC.

2755 *See* SAMS 1997 Guideline, *supra* note 110, at point D.2. at 9; *see also* Article 16.i. Biomedicine Convention (setting forth the criteria of "no alternative of comparable effectiveness"); Article 5 of the COE Research Protocol and the COE Explanatory Report, *supra* note 417, at paragraph 24, page 6.

vestigator could gather the same information by enrolling adults. Such a rule disregards the important benefits that participation in certain studies can confer.[2756] True, the same benefits may sometimes be available in expanded access programs (i.e., outside the trial), but such an opportunity is in no way guaranteed. When the anticipated benefits clearly outweigh the risks, notably because the patient is not responding to available treatments and is risking death, Article 55.1.a LPTh should not stand in the way of enrollment. Additional safety measures could be implemented (such as the review of individual situations by the ethics committee or the appointment of a special advocate). At any rate, the outright ban clearly has undesirable consequences.

The United States has a very different – and more sensible – stance on the inclusion of pediatric research subjects: Children should be included *systematically* in all clinical trials unless there is a valid ground to exclude them.[2757] The reasoning is that a lot more data are required to tailor existing and future drug treatments for children. If the emphasis is not placed on systematic inclusion, the consequence will be that physicians will be forced to administer drugs to children without knowing whether these drugs are truly safe and effective – in other words, the unfortunate situation that exists today. The same logic applies to clinical trials on other vulnerable populations, such as patients with impaired decision-making capacity or minority ethic groups.[2758]

In my opinion, the U.S. position is wiser at this juncture. The lack of pediatric clinical information about existing drugs constitutes a more serious threat to the health of children than the opportunity for them to participate in clinical trials. Moreover, clinical trials often represent the best treatment alternative to severely ill patients. An a priori exclusion of any group of patients is therefore unfair. Children and their parents, possibly counseled by patient associations, should be able to exercise their right to make their own decisions.

8.4.4. Substitute to consent

8.4.4.1. Proxy consent for incompetent subjects

Besides the subject's assent* or indicative behavior (see below subsections 8.4.4.4. and 8.4.4.5.),[2759] the LPTh requires the consent of his legal representatives;[2760] clinical trials conducted with minors and (factually or legally) incompetent persons are only possible if the subject's representative gives his consent. In the United States, the preferred term

---

2756 *See generally* subsection 2.1.5. above.

2757 *See, e.g.,* NIH (Inclusion of Children), *supra* note 2664.

2758 *See* NIH (Women Inclusion), *supra* note 55, at section II.A.

2759 Article 55.1.c. and d. LPTh.

2760 Article 55.1.b. LPTh.
In the European Union, see Article 4.(a) (for pediatric research) and Article 5(a) (for research on incapacitated adults).
In the United States, see the 1941 case of Bonner v. Moran, 126 F.2d 121 (D.C. Cir. 1941) (which held that the sole "consent" of a 15-year old subject was not sufficient for nontherapeutic research). For a discussion of this case, see Curran & Beecher (Children), *supra* note 2767, at 78-79.

for the representative's consent is permission.[2761] The terms "proxy," "surrogate" or "substituted" consent are also used.[2762]

The process leading to the grant of permission is the same as the one typically followed for adult subjects capable of judgment.[2763] The representative (e.g., the parents of minors, the guardian of a person placed under legal guardianship) must receive information about the objective of the trial, its risks, its inconveniences, its benefits (see generally subsection 8.3.2. above). He will receive both oral and written information. If he decides, on behalf of the incompetent subject, to consent to the latter's inclusion in the trial, he will sign the consent form. The (U.S.) Belmont report additionally recommends that the representative be given the "opportunity to observe the research as it proceeds" in order to know when to withdraw his consent.[2764]

The first problem with proxy consent is to *identify* the proper representative. For *children*, the question may be whether the permission of one parent (instead of both) suffices. When the parents are divorced or not living in the same home, getting permission from both of them may hamper the child's enrollment. Under Swiss law, the permission of one parent (provided he has parental authority) suffices. However, Swiss law does not say what should happen if one parent gives his approval while the other explicitly refuses. It is likely that in such a situation the refusal will prevail over the approval, if only out of fear of possible liability in case of subsequent injuries.[2765] In the United States, IRBs may recommend having the permission of both parents, notably if, given the risk/benefit ratio, the necessity of enrollment is not self-evident.[2766]

While the majority of children (in Switzerland) have either a parent or a guardian, the situation is quite different for incompetent *adults*.[2767] In practice, legal custodians are appointed only when it is necessary to help or protect these adults in their everyday life. This necessity arises chiefly for adults possessing an important fortune which could be mismanaged either by themselves or by crooks.[2768] Less prosperous people and people living in institutions are rarely appointed guardians, because no imperious need is perceived. If there is no *legally authorized* representative at hand to give consent, the incompetent patient simply cannot be enrolled.[2769] The consent of the patient's relatives

---

2761 *See* 45 C.F.R. § 46.402.c. *See* Burns, *supra* note 81, at 135 ("Only a competent adult (generally a person of legal age and with the adequate decisional capacity) may give consent."). *See also* OHRP (Children), *supra* note 1636, at 8.

2762 *See, e.g.,* AMA (Emergency), *supra* note 2746, at 4. The third expression – substituted judgment – however has a slightly different meaning as it relates to what would be the likely wishes of the research subject. *See, e.g.,* BEAUCHAMP & CHILDRESS, *supra* note 16, at 99.

2763 *See, e.g.*, Article 6.4. of the Biomedicine Convention.

2764 Point C.1 of the report. See also, for pediatric research, the CIOMS 2002 Guidelines, *supra* note 105, at Guideline 14 (commentary).

2765 With respect to emergency research, objection by one family member can bar enrollment of the incapacitated subject. *See* FDA (Emergency Guidance), *supra* note 261, at 14 ("If family members were to disagree, the researcher and family members would need to work out the disagreement."). See also OHRP-UCD (Surrogate Consent), *supra* note 2687, at 3.

2766 *See* OHRP (Children), *supra* note 1636, at 5 and 8; NIH (Inclusion of Children), *supra* note 2664, at section VII (both parents' consent is necessary when a pediatric trial entails greater than minimal risk and no prospect of direct benefit).

2767 *See* Karlawish, *supra* note 2676.

2768 *See* APPELBAUM, *supra* note 2553, at 90-91. *See also* BEAUCHAMP & CHILDRESS, *supra* note 16, at 71.

2769 For the incompetent patient to be included in a clinical trial, a guardian (e.g., the son or daughter of an elderly patient suffering from Alzheimer) must first be appointed by Swiss courts and then give his or her

is not admitted as a substitute.[2770] It would trigger other problems anyway; for instance, who should decide for an incompetent father? His son or his daughter?[2771] The consequence of this (i.e., the impossibility to participate in the trial) may appear overly harsh, especially when the trial represents the subject's best therapeutic chance.[2772] As a result, even though the law does not admit substitution of relatives for legal representatives, investigators and doctors are likely to accept it.[2773] Another solution is to encourage patients to appoint, while they still can, and preferably in writing, a representative (e.g., a spouse, a close friend) (see also below subsection 8.4.4.7. below).[2774] Even when such an appointment does not follow the legal channels – the representative is not a guardian under the Swiss Civil Code –, such a choice ought to be respected. The law should also be modified to encourage this sensible behavior.[2775] Approved representatives would have authority to enroll the patient in a clinical research should the need arise at a point in time when the patient is no longer capable of judgment.

A third problem arises with legally incompetent adults. Court-appointed guardians are usually given wide powers to manage the assets of their ward. However, does their expertise qualify them to give opinions in a very personal and sensitive area such as health care? This is quite doubtful.[2776] Such situations call for prior consultation with family members and/or the appellate authority.

The LPTh does not *guide* the decision of the representative. While other legal provisions may oblige parents or guardians to act in the best interests of their children or wards,[2777] the LPTh leaves representatives theoretically free to base their decision on

---

consent. This procedure being neither fast nor straightforward, it may deter sponsors from conducting clinical trials on these sub-groups of incapable subjects. Sprumont suggested the application of the Swiss Civil Code Article 419 (administration without mandate). However, this solution is no longer available once the legislator has set such a clear rule. *See* SPRUMONT, *supra* note 16, at 214. See also generally the study by G. Bravo et al., *Knowledge of the legislation governing proxy consent to treatment and research*, 29 J. MED. ETHICS 44-50 (2003), at http://jme.bmjjournals.com/cgi/content/full/29/1/44 (finding that concerned patients and families generally are not aware that relatives *cannot* consent on behalf of incompetent adults under Canadian law governing proxy consent; the Canadian law on research on incompetent adults is similar to Swiss law).

2770 Compare with the proposed Article 434 of the draft revision of the CC (allowing certain relatives to give consent for medical procedures if the family member is incapable of judgment). *See also* CC Revision Report, *supra* note 2667, at 3 and 11.

2771 In the context of organ transplants, the Swiss Supreme Court has had to decide in which order relatives should be consulted. It ruled that the intensity of the relationship with the relative and the person involved (as an organ donor, or here as a subject) should matter more than the proximity in the family tree. The order of the family tree should only serve as a general first indication. *See* ATF 101 II 177 = JdT 1976 I 362, at 377-78, point 5.b). *See also* Karlawish, *supra* note 2676. Compare in the United States, the list of possible surrogate decision-makers, OHRP-UCD (Surrogate Consent), *supra* note 2687, at 3.

2772 Compare with the U.K. Department of Health, Draft Guidance on Consent by a Legal Representative on Behalf of a Person Not Able to Consent, at paragraphs 11-15 (Mar. 2003), at http://www.mca.gov.uk/inforesources/publications/mlx287consent.pdf [hereinafter U.K. Draft Guidance on Consent].

2773 *See also* CCNE N°79, *supra* note 1251, at 12. Compare with the U.K. Draft Guidance on Consent, *supra* note 2772, at paragraphs 26, 31-35 (allowing surrogate consent by professional legal representatives such as doctors when no relative of the prospective subject is available).

2774 *See* NBAC (Mental), *supra* note 1250, at chapter III.

2775 *See* CCNE N°79, *supra* note 1251, at 11.

2776 *See, e.g.,* CCNE N°58, *supra* note 117, at 21.

2777 *See also* Article 8.3 *in fine* of the (future) LTransplant.

any motives.[2778] In particular, the representative is not explicitly required to "put himself in the subject's shoes" (i.e., "substituted judgment").[2779] If the representative is, for example, risk-averse but knows that his ward is risk-loving, the representative is still entitled to refuse his consent.[2780] The representative could theoretically refuse his consent even if his child or ward clearly expresses his desire to participate in the trial. Several foreign guidelines rightfully specify that the representative's decision must be reached based on the *presumed will* of the incompetent subject.[2781] The European Union's Directive 2001/20/EC indicates that the informed consent of the minor's parents or of the incapacitated person's legal representative "must represent the [subject's] presumed will."[2782] However, preliminary evidence casts doubts on the reliability of substituted judgments.[2783]

This problem is even more obvious when the subject is clearly *capable* of judgment (e.g., a seventeen year old minor).[2784] The difficulties are also compounded when the field of research relates to sensitive issues such as teenagers' sexuality or drug abuse.[2785] Because the LPTh insists on the parents' consent, the capable minor cannot override his parents' objections.[2786] The LPTh does not permit RECs to grant waivers either.[2787] This

---

2778 See however the 1988 Swiss Supreme Court decision at ATF 114 Ia 350, at 363, at point 7.b)bb) (whereby legal representatives asked for proxy consent must reach their decision taking into account only the subject's interests and the latter's expressed or presumed wishes).

2779 Compare with Article 56.a.2. LPTh.
See also APPELBAUM, *supra* note 2553, at 96-97; Vogt et al., *supra* note 2676, at 197 (describing an experiment on substituted judgment).
In the United States, "substituted judgment" is sometimes contrasted with the "best interest" standard. In substituted judgment, the surrogate or proxy must decide what the subject would have decided for himself had he been capable. The "best interest" standard requires that the proxy weigh as objectively as possible all risks and benefits. In the United States, this second standard is particularly apposite when there is no available information about the wishes of the subject. *See* NIH (Questionable Capacity), *supra* note 2547.

2780 The problem may be particularly acute when the representative is a court-appointed guardian. The guardian may feel that he faces fewer risks if he systematically excludes his ward's participation in clinical trials. If the ward incurs an injury, the guardian may feel that his liability is less likely to be engaged if he refused his consent (for example, on the ground that the medical risks of the investigational substance were still largely unknown) than if he gave it.

2781 Compare with the proposed Article 435.2 and 436 of the draft revision of the CC.

2782 Article 4.a and Article 5.a. *See also* U.K. Draft Guidance on Consent, *supra* note 2772, at paragraphs 14, 24-25, 29-30, 36.

2783 "Just as in clinical care, proxies cannot consistently make accurate substituted judgments for enrollment in research. The claim that the person would want to enroll is as likely to be wrong as it is to be right." Karlawish, *supra* note 2676.

2784 Sprumont also cites the case of officially incompetent adults who are nonetheless fully capable of judgment. The author considers that these persons should be allowed to take medical decisions for themselves, without the intervention of their guardians. *See* SPRUMONT, *supra* note 16, at 212. *See also* ATF 114 Ia 350, at 360-61, at point 7.a) (upholding the cantonal requirement to have the legal representative give his consent in addition to that given by the pediatric patient capable of judgment).
Compare also with the future Federal Law on human genetic analysis ("LAGH"), which lets competent minors decide independently whether to undergo a genetic analysis. Article 5 LAGH and accompanying message of the Federal Council, FF 2003 I 6841, at 6877.

2785 *See* OHRP (Children), *supra* note 1636, at 6 and 17. *See also* SPRUMONT, *supra* note 16, at 211-12 (recommending that, for these special kinds of medical research, capable minors should be allowed to decide without their parents' consent).

2786 In the United States, it is accepted that "[t]he requirement for parental permission may be inappropriate in some cases. … In these cases, IRBs should devise alternative procedures for protecting the rights and interests of the children asked to participate, including, perhaps, the court appointment of special guardians." IRB Guidebook, *supra* note 411, at chapter VI.C. *See also* SPRUMONT, *supra* note 16, at 211.

rule contrasts markedly with the principle applied to ordinary (or even extraordinary, for example genetic) medical treatment, where it is generally accepted that competent minors can make their own decisions.[2788]

The LPTh does not address this possible *conflict of will*; other statutes may offer tentative solutions (e.g., emancipation for minors, appeal to a supervision authority for persons under legal guardianship). However, these administrative solutions are burdensome and hence impractical.

8.4.4.2. Proxy consent in emergency research

According to Article 56.a.1. LPTh, the protocol must set forth a procedure (duly approved by the REC), whereby representatives of children or legally incompetent persons are asked for their (proxy) consent. The underlying idea seems to be that research can take place when the representatives could not be contacted in the available time. It is when the representatives were located in time, but refused to give their explicit consent (e.g., outright refusal or silence) that enrollment of the subject is barred. While the legislator should have articulated this more clearly, this interpretation appears to correspond to the intent of the legislator.[2789] The Biomedicine Convention also sets forth this principle.[2790]

Surprisingly, Article 56.a.1. LPTh on proxy consent only applies to minors and people officially incompetent. Adults who have lost their capacity of judgment, but have not been deemed officially incompetent, are not mentioned in Article 56.a.1. LPTh. It is doubtful that Article 56.a.2 LPTh (requiring that their will be ascertained by consultation) should apply to them. The omission of factually incompetent persons in Article 56.a.1. LPTh is probably a mistake. Another viable explanation is that the legislator could not identify the right language to differentiate between exceptional incapacity due to the emergency (e.g., person in a coma) and general incompetency due to lack of judgment (e.g., Alzheimer patient).

As mentioned above, minors as well as a factually or officially incompetent persons can find themselves in a situation of medical emergency. If an investigator intends to enroll them in a clinical trial, the situations contemplated by Article 55 and by Article 56 LPTh are combined. It appears however that Article 56 should have priority over Article 55, given that Article 56 constitutes the most specific provision and contains an ad hoc provision governing proxy consent (Article 56.a.1. LPTh).

2787 *See however* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 14 (commentary) (allowing RECs waivers of parental permission when parental knowledge "may place the adolescents at some risk of questioning or even intimidation by their parents").

2788 *See, e.g.,* SAMS (genetic investigations), *supra* note 363, at 4 and 5.

2789 Article 56.a. LPTh appears to only require that the implemented procedure allows to contact representatives (or establish the will of the research subjects by consulting the next of kin). It contains no provision as to what should happen when the representative or the next of kin cannot be contacted, when they have no opinion to give, or when they disagree between each others. In fact, the law does not even *explicitly* prohibit enrollment when the available next of kin indicates that the subject would have refused, although such a prohibition is obviously what the legislator had in mind.

2790 In an emergency situation, "[a]ny medically necessary intervention may be carried out" even though the consent of the subject or that of his representative could not be obtained. Article 8 of the Biomedicine Convention.

Given that minor or incompetent subjects can be enrolled when their representatives could not be reached within the allocated time, the next question is whether the investigator is nonetheless obliged to continue her efforts to contact the representatives to seek their *deferred* consent,[2791] this time, to maintain the subject in the clinical trial. The words "within the available timeframe" at Article 56.a LPTh suggest that the legally mandated procedure to seek consent must take place before, *not after*, enrollment. However, it makes more sense to give equal weight to the representatives' decision obtained after enrollment.[2792] Hence, if the representative then refuses his permission, the subject must be immediately withdrawn from the trial.[2793]

Another question is whether the consent referred to in Article 56.a.1 LPTh must follow the general rules stated in Article 54.1.a LPTh. The emergency of the medical situation may hinder written consent. Once the representatives (e.g., parents of the minor or guardian of the ward) have been located, for example by telephone, there may not be enough time left for the complete informed consent process to take place. Oral consent is probably more realistic.[2794] However, neither the LPTh nor the OClin indicates whether this is legally admissible.

A third problem is whether emergency research can take place when it is expected that the therapeutic window[2795]* will always be too short to get proxy consent (or, for that matter, consult relatives). In other words, if it is known beforehand that no procedure as per Article 56.a LPTh will ever be feasible, does the law prohibit emergency research? Apparently, the answer is yes.[2796] This legal stance is not only regrettable, but also hypocritical. To the extent that the investigational procedure can benefit directly the incapacitated subject, it is unfair that its availability be dependent on the length of the therapeutic window. It is hypocritical because in many cases the ethics committee will have to base its decision on very theoretical considerations as to the length of this window and the ease to locate representatives (or relatives). If the REC interprets Article 56.a LPTh flexibly, it enables most emergency protocols. If it adopts a strict view of the feasibility of getting proxy consent, it stops most emergency research.

8.4.4.3. Consultation in emergency research

When the subject was formerly a competent adult, the requirements for emergency clinical trials are slightly more accommodating.[2797] The representative's proxy consent (required for minor and legally incompetent subjects by Article 56.a.1. LPTh) is replaced

---

2791 Both the terms "deferred consent" and "ratification" are used in the United States. On this notion, see Robert J. Levine, *Research in Emergency Situations, The Role of Deferred Consent*, 273 JAMA 1300-1302 (Apr. 26, 1995).

2792 See, in the United Kingdom, the Draft Guidance on Consent, *supra* note 2772, at paragraphs 64-67.

2793 The withdrawal must be performed in a way that preserves the safety of the subject. This may render immediate withdrawal impossible in some cases. *See generally* subsection 8.3.3.10. above.

2794 Insisting on the representative signing immediately a form may also put the latter under significant pressure. For similar considerations in the case of organ transplant, see ATF 98 Ia 508 = JdT 1973 I 490, at 503, point 8.c). *See also* U.K. Draft Guidance on Consent, *supra* note 2772, at paragraph 57.

2795 The therapeutic window is the interval of time during which a medical intervention can be performed with reasonable chances of success.

2796 *See* Article 56.a LPTh.

2797 Article 56.a LPTh.

at Article 56.a.2 LPTh, by the consultation of available relatives or next of kin (hereinafter: relatives).[2798] Although this second provision does *not explicitly exclude* minors and legally incompetent subjects, it would make little sense if *both* provisions applied to minors and legally incompetent subjects. It is more logical to consider that Article 56.a.2 is the alternative to Article 56.a.1. for subjects who do not have a legal representative.

These individuals are not asked to *consent on behalf* of the subject; they are only questioned about the hypothetical will of the subject.[2799] In other words, they are asked if they know whether the subject already had a position in favor or against participation in clinical trials. If no one is available or if the persons at hand have no idea if the subject had a stance on the issue, should the trial be allowed to go ahead with the subject?[2800] A literal interpretation of Article 56.a LPTh would lead to a negative answer. However, the purpose of this provision is to make emergency research possible. Requiring that the will of the incapacitated subject be always established would bar most, if not all, emergency trials. Therefore, the consultation of relatives should operate in the opposite sense. It is only if a relative is available to inform the investigator or her team that the subject would have refused participation that enrollment should be prohibited.

In practice, finding relatives who are able to enlighten the investigator as to the subject's will is far from simple. Only exceptionally does an individual tell his relatives that he is opposed to *any* participation in *any* clinical trial. This may happen for example with Jehovah witnesses. More commonly, an individual will tell his family or close friends that he is against therapeutic intransigence and that he refuses to be artificially maintained alive. More often, family or representatives can only infer the will of the prospective subject based on general statements (e.g., the subject is in favor of research, the subject was intent on seeing the birth of his grand-child, the subject has always been risk-loving). In these circumstances, relatives asked in emergency settings about the will of their loved one may end up being more distraught than pleased. Neither the LPTh nor the OClin explains to them the meaning of the terms "subject's will." They do not know if they should disclose their opinion or educated guess about the subject's hypothetical will or if they should only tell what they are absolutely sure of.

For investigators, the situation is not comfortable either. By definition, the procedures dictated by the protocol must be implemented immediately after the occurrence of the incapacitating event and hence rapidly after the patient is hospitalized or enters the treatment center. In the medical jargon, there is only a brief window of opportunity (the "therapeutic window") during which the investigator can decide, in compliance with the LPTh, whether or not to enroll the patient.[2801] For many diseases, the longer the waiting, the greater the risks.[2802] Therefore, the investigator may have mixed feelings. On the one hand, she wants to comply with the LPTh by taking the time to locate relatives, to explain them fully the situation and to obtain their opinion as to the subject's

---

2798 Article 56.a.2. LPTh.

2799 Article 56.a.2. LPTh.

2800 The CIOMS sets the *opposite* rule: The subject's participation in the trial should be discontinued if permission from a third party with appropriate authority was not – or could not be – obtained. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6 (commentary).

2801 *See, e.g.,* FDA (Emergency Guidance), *supra* note 261, at 5.

2802 *See id* at 5. *See also* Letter of UCLA Stroke Study Network to the U.S. Office for Protection of Research Subjects (Aug. 26, 2002), p.25, at http://www.fda.gov/ohrms/dockets/dailys/03/May03/050803/95s-0158-rpt0009-01-vol5.pdf.

wishes. On the other hand, she wants to improve the subject's health prospects by giving him the treatment as soon as possible. Once again, the law cannot reasonably set a uniform time limit (e.g., two hours after hospitalization); so the investigator and the sponsor are left with this heavy burden. It is the sponsor's role to set the therapeutic window in the protocol, taking into account all the available evidence.[2803] It is the investigator's role to make the best possible use of this window, by deciding how much time to spend seeking consent from the subject's representatives or family members.[2804] The ethics committee's role is to comment on the length of the therapeutic window and the procedures to be followed to seek this consent.[2805]

Under Swiss law, emergency research in situations where it is known that there will not be enough time to ask for any proxy consent or opinion appears to be impossible.[2806] Article 56.a LPTh insists that there be a procedure allowing to seek and obtain such consent or opinion. Thus, for instance, a clinical trial investigating possible cardiac treatments performed in ambulances on persons having just suffered a heart attack could probably not take place in Switzerland.

8.4.4.4. Assent

Even though his consent is not legally sufficient, the minor and the legally incompetent adult may be capable of judgment.[2807] In this case, both of them are given the opportunity to give or refuse their "approval."[2808] This approval is referred to as an *assent*.[2809] The principle underlying clinical trials is that self-determination by the subject leads to fairer results than a decision made exclusively by a third party, even one intent on acting in the subject's best interest. Thus, a minor and a legally incapable adult who are capable of self-determination cannot be enrolled if they refused their assent. Published clinical studies now tend to mention whether assent of pediatric subjects was sought and obtained;[2810] this is viewed as important to uphold ethical principles.

Valid assent logically implies that the person has received as much information as his state and intellectual capacity permit. Assent is more than non-refusal; it should be an affirmative decision to take part in the clinical trial.[2811] Although the LPTh does not explicitly state so, assent like consent can be withdrawn at any time.[2812] In order to

---

2803 *See* FDA (Emergency Guidance), *supra* note 261, at 5.

2804 *See id.* at 5 and 13.

2805 *See id.* at 5-6 and 13.

2806 Article 56.a LPTh *a contrario*.

2807 *By definition*, adults who are factually incompetent lack this capacity of judgment.

2808 Article 55.1.c LPTh.

2809 Article 55.1.c LPTh uses the same expression for both consent and assent. *See also* paragraph 25 Helsinki Declaration; CIOMS 2002 Guidelines, *supra* note 105, at Guideline 14 (commentary); Article 6.2. Biomedicine Convention.
In the United States, the FDA does not require children to give their assent although it acknowledges that IRBs usually and rightly impose such a requirement. *See* FDA (FAQ-IRB), *supra* note 1814, at questions 47 and 48.
In the European Union, see E.U. Guidance (Ethics Committee), *supra* note 270, at 7.

2810 *See* K. D. Wagner, *supra* note 973, at 1034.

2811 *See* OHRP (Children), *supra* note 1636, at 4. *See also* 45 C.F.R. § 46.402.b.

2812 *See* Articles 4.(c) and 5.(c) of the E.U. Directive; AAP (Guidelines), *supra* note 385.

avoid undue pressure on the subject, the assent of a minor should be solicited *only after* the legal representative has given his own consent.[2813] However, for subjects with normal decision-making capacity (e.g., a legally incompetent adult), assent should probably be asked before proxy consent, since this is more respectful of their autonomy.[2814]

The Swiss LPTh requires assent only for subjects who are *capable of judgment*.[2815] There are two problems with the reference in the LPTh to the Swiss notion of capacity. First, under Swiss law, a person is either competent or incompetent for a given type of decision, with the consequence that assent must or must not be asked. There is no intermediate category whereby assent would be asked whenever appropriate in the opinion of the doctor and of the parents or relatives. The other difficulty with the Swiss notion of capacity is that it is normally to be assessed separately for each decision. A person can be capable of judgment for a given set of decisions, but not for others. In the context of the LPTh, the investigator may have to decide whether to treat the clinical trial as a unique decision. If there is only one decision (i.e., whether or not to participate), the threshold to admit the capacity of judgment will necessarily be high, because the minor subject must be able to understand all aspects of the trial. If the clinical trial is treated as a series of decisions (for example the different procedures involved), then the capacity of judgment can be admitted more easily for at least some aspects of the trial; in such a case, assent may be requested for some decisions, but not others.

The E.U. Directive and the ICH hold a slightly different position. In the European Union, minors must receive "information according to [their] capacity of understanding from staff with experience with minors."[2816] The ICH recommends that past a certain age and intellectual development, minors sign a written form.[2817] In contrast, Swiss law does not state in which manner the child is to express his "consent."

Neither the ICH nor Swiss law stipulate at *what age* a minor acquires the capacity of judgment.[2818] Confronting young children with an exposé of the health risks may be too much for them to bear, especially if a prolonged illness or pain is putting them under severe stress.[2819] For instance, a five-year old will probably not be asked for assent since his capacity of judgment is likely not to be recognized under Swiss law. Under Swiss law, each case must be appreciated on its own merits (to determine whether or not the

---

2813 *See, e.g.*, AAP (Guidelines), *supra* note 385.

2814 The guideline of the University of California (San Diego) describes in detail how consent should be sought from subjects with impaired decision-making capacity. *See* UCSD-SOPP, *supra* note 485, at 67-68.

2815 Article 55.1.c LPTh.
In the European Union, the 2001/20/EC Directive is less explicit as it mentions neither consent nor assent. Rather, it asks that the explicit wish of the subject be "considered by the investigator." *See* Articles 4(c) and 5(c) of Directive 2001/20/EC. *See also* EMEA, CPMP, Note for Guidance on Clinical Investigation of Medicinal Products in Children, (CPMP/EWP/462/95) (Mar. 17, 1997), at 1 (chapter 1.1), at http://www.emea.eu.int/pdfs/human/ewp/046295en.pdf [hereinafter CPMP (Children)].

2816 Article 4(b) of Directive 2001/20/EC. The same rule applies for incapacitated persons; Article 5.b of the same Directive.

2817 *See* section 4.8.12 (p.17) of ICH E6, suggesting that, "if capable," subjects should sign and personally date the form. *See also* chapter 2.6.3. (p.11) of ICH E11. For model assent forms, see the three provided by the San Francisco University on its website: at http://www.research.ucsf.edu/chr/Guide/MNR-assent1-1204F.doc, http://www.research.ucsf.edu/chr/Guide/MNR-assent2-1204F.doc, and http://www.research.ucsf.edu/chr/Guide/MNR-assent3-1204F.doc.

2818 *See however* Article 8.7 of the (future) Federal Law on transplants (allowing minors *aged 16 or older* to donate organs for transplant purposes).

2819 That of course can be true also of adults.

minor is capable of giving his assent).[2820] The American Academic of Pediatrics has set a more general rule; it recommends that children of age seven or older be asked for their assent.[2821] Swiss authors seem to place the bar higher (ten years or older).[2822]

Under Swiss law, provided that the subject is capable of judgment, assent is a mandatory requirement. If, for example, the teenager subject has refused his assent, enrollment is prohibited. The teenager does not need to justify his choice. In contrast, under U.S. law, a legal representative can override the subject's refusal when the research augurs important benefits for the subject.[2823] The language of the E.U. Directive is vaguer: The investigator must "consider" the subject's refusal.[2824]

8.4.4.5. Signs of refusal

Article 55.1.d LPTh introduces a different safeguard for subjects incapable of judgment: The clinical trial cannot proceed if there are any indications that the subject would have refused to participate in the trial.[2825] This hypothesis concerns subjects – children or adults[2826] – who are deemed incapable of judgment;[2827] they are, for example, young children unable to understand the objectives of the trial as well as its risks and benefits; these children cannot assent precisely since they are not capable of judgment.[2828] The LPTh requires that the investigator do not enroll anyone whose behavior denotes objection or refusal to participate.[2829]

This clause corresponds to a similar, yet slightly less severe, rule adopted by the SAMS. According to the SAMS 1997 Guidelines, only unequivocal (in French, "*manifeste*") refusal to take part in the study constitutes a bar.[2830] The LPTh is stricter, since

---

2820 *See* chapter 2.6.3. (p.11) of the ICH E11.

2821 *See* AAP (Guidelines), *supra* note 385; *see also* Burns, *supra* note 81, at 135; OHRP (Children), *supra* note 1636, at 7.

2822 *See* Olivier Guillod, *Le consentement à l'acte medical: une longue convalescence*, *in* ASPECTS DU DROIT MÉDICAL, 83, at 85 (Editions Universitaires Fribourg 1987). *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 14 (commentary) (stating that a child aged 12 or 13 is capable of giving assent). See also the interesting survey of parents, children and health professionals about the appropriate age to ask for assent, The EFGCP News (Spring 2002), *supra* note 44, at 10 (the majority of answers fell in the age range of 11 to 15).

2823 "Assent may be waived in therapeutic research studies in which in the opinions of the parents, investigators, and the IRB, the child's participation in an investigational treatment may be of such benefit that the child's welfare would be significantly jeopardized by failing to provide assent." AAP (Guidelines), *supra* note 385. *See also* IRB Guidebook, *supra* note 411, at chapter VI.C.

2824 Article 4(c) and 5(c) of the 2001/20/EC Directive ("the explicit wish …to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator ….").

2825 Article 55.1.d LPTh ("*si aucun indice ne laisse supposer que les sujets de recherche incapables de discernement auraient refusé de participer aux essais*," "*keine Anzeichen vorhanden sind, die erkennen lassen, dass sich urteilsunfähige Personen einer Teilnahme an einem Versuch widersetzen würden*," "*non vi sono indizi in base ai quali le persone incapaci di discernimento sarebbero state contrarie a sottoporsi a una sperimentazione*.").

2826 *See* Mauron (psychogériatrie), *supra* note 2420, at 1175-1178.

2827 If the subject is capable of judgment, Article 55.1.c LPTh applies instead.

2828 *See* Article 55.1.c LPTh.

2829 Article 55.1.d LPTh.

2830 *See* SAMS 1997 Guideline, *supra* note 110, at point A.1, p.2.

any sign ("*aucun indice,*" "*keine Anzeichen*," "*sono indizi*") of refusal must be taken into account.

This provision was not unanimously embraced. Detractors give the example of a young child who, for his own good, must undergo a painful medical treatment (e.g., repeated injections); it is quite probable that the child will show signs of refusal: he will cry, protest or even fight the doctor. If Article 55.1.d LPTh was to be interpreted and applied literally, few children could ever participate in clinical trials, even if these trials represented their best therapeutic chance. Parents (or guardians) who have given their consent as legal representatives would be at pain to understand why their children are not enrolled if participation in a trial is clearly in the children's best interests. The same dilemma exists with other groups of incompetent persons, such as mentally-ill patients. Yet, the wording of Article 55.1.d LPTh is quite plain: A subject can be enrolled only if there is *no hint that suggests* that the incompetent individual would have refused to participate in the trial. Apparently, a single clue is enough to exclude participation.[2831] That the subject's behavior or tacit refusal to participate may not be rational is indifferent; once again, if a subject shows signs of refusal, even out of an instinctive fear of white coats, Article 55.1.d LPTh appears to prohibit his inclusion in the trial.[2832] A potential solution – if it is one – is to comfort incompetent subjects, to explain again and again why they have to undergo painful procedures, to use pain relievers whenever possible and to improve the atmosphere and the setting by having bright and colorful rooms or by having leisure programs adapted to their ages (e.g., clowns). These are certainly good ideas and they partially address the problem of Article 55.1.d LPTh. However, for life-threatening diseases, I remain of the opinion that this provision goes too far.

The ICH contains a much more balanced rule. It considers that the decision of the parent supported by the investigator should prevail over the child's wishes, when the child's medical condition is particularly serious and his welfare "would be jeopardized" by not participating in the study.[2833] Similarly, the (U.S.) Belmont report is more reasonable as it allows for an exception when "the research entails providing them [persons such as children whose comprehension is severely limited] a therapy unavailable elsewhere."[2834]

The limit between situations calling for subject's assent and those where only signs of refusal are to be taken into account is imprecise. However because the procedural requirements are essentially similar, distinguishing these two situations should not

---

2831 In the European Union, the rule is different: The only element taken into account is the "explicit wish of a minor who is capable of forming an opinion and assessing this information [i.e., about the trial, its risks and benefits] to refuse participation." Article 4(c) of Directive 2001/20/EC. The same rule applies for incapacitated persons; Article 5.c of the Directive.
The CIOMS also has a more balanced rule and distinguishes "deliberate objection" from the instinctive reactions of a very young child. Moreover, parents are allowed to bypass even deliberate objections if the investigational treatment appears indispensable. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 14 (commentary).

2832 According to the SAMS 1997 Guidelines, children do not have to state any reason for their refusal to participate and their choice cannot be overridden by the consent of their parents (legal representatives). See the added comment to point D.6 of the SMAS 1997 Guidelines, *supra* note 110, at 12.

2833 Chapter 2.6.3 (p.11) of ICH E11 Guideline.

2834 Point C.1. Belmont Report, *supra* note 61. *See also* NBAC (Mental), *supra* note 1250, at chapter III.

matter much in practice .[2835] In any case, the investigator should impart as much information as the subject can usefully absorb and solicit the latter's opinion.

The rule of Article 55.1.d is duplicated at Article 56.b LPTh applicable to clinical trials in emergency settings.[2836] Here the problems are less daunting. First, the subject is more likely to be an adult suffering from only temporary incapacity due to external causes (e.g., an accident or a sudden ailment). Second, since the window of opportunity is typically short for the investigator to decide whether or not she may enroll the patient, there are less opportunities for clues against participation to appear. Finally, the patient being usually unconscious, he can hardly express hints that he would rather not participate in the trial. The only situation where such hints would be readily available concerns known Jehovah witnesses who are opposed to most medical interventions, especially blood transfusions.[2837]

8.4.4.6. Recovered or newly acquired capacity

What happens when a subject becomes capable of judgment or recovers his capacity?[2838] Or when a minor subject reaches the age of 18? In both cases, the individual should be asked to give his consent, even if, previously, his legal representatives had given their permission and he had given his assent. Ideally, the whole consent process, including the prior informative phase, should be initiated from scratch.[2839]

In emergency research, the protocol itself may foresee that enrolled subjects will recover their full capacity at a certain stage before all medical procedures have been completed. For example, the unconscious subject has undergone heart surgery and has received the first doses of the investigational compound when he wakes up from narcosis; from then on, he will receive the other doses of his investigational treatment only if he gives his consent according to the full-scale procedure. Under U.S. law, the subject must still be asked for his consent if he recovers his capacity *after* all procedures under the clinical trial have been completed.[2840] This rule ought to be followed also in Switzerland as it promotes respect for subjects.

8.4.4.7. Advance consent

Emergency clinical trials do not rule out all forms of consent. There may be situations where the patient and the physician can anticipate the possibility that the former will find himself in a position where the question of his participation in a clinical trial will arise without him being able to give informed consent. For example, a patient with se-

---

2835 The subject's assent is not sufficient to permit his enrollment in the trial: The representative must also give his consent.

2836 One could wonder why Article 56.b LPTh is at all necessary since Article 56.a.2 LPTh already requires that the subject's will be established.

2837 *See also* FDA (Emergency Guidance), *supra* note 261, at 4.

2838 The American Belmont report stresses that "[t]he judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations." Part.B.1 Belmont Report, *supra* note 61.

2839 *See also* U.K. Draft Guidance on Consent, *supra* note 2772, at paragraphs 74-75.

2840 *See* FDA (Emergency Guidance), *supra* note 261, at 14.

vere heart problems is aware that he may suffer from a stroke at any time and that, should this happen, he may be in a situation where he cannot give his consent. Similarly, a patient undergoing classic surgery may be told that if the surgery should fail, there is the opportunity to participate in a clinical trial as a second-line intervention. The same is true for research on incompetent adults under Article 55 LPTh. A patient may know that his Alzheimer disease is going to progress until he loses his capacity to consent.

There is therefore ample room for prospective directives or advance consent.[2841] The CIOMS Guidelines stresses that advance consent in emergency research should be sought whenever possible.[2842] The Biomedicine Convention confirms that previously expressed wishes should "be taken into account."[2843]

The literature distinguishes between advance consent and advance directive. An advance *directive* indicates the patient's *general* preference to receive – or not to receive – a given medical treatment; it may encompass participation in a clinical trial.[2844] They are akin to "do not resuscitate" or "living will" directives.[2845] In contrast, advance *consent* is given for a specific trial, the details of which the subject has been apprised of. It is however very difficult to draft instructions that properly take into account all possible future health situations. The decision to participate in a trial calls for the evaluation of pros and cons based on full information. Stating *in advance* how these (yet unknown) advantages and disadvantages are to be weighted is nearly impossible. Therefore, patients resort to designating an agent endowed with the authority to make decisions on their behalf.[2846] The agent will, for instance, assess the risk-benefit ratio before enrolling the incapable subject in a trial.

In Switzerland, several cantons have acknowledged the validity of advanced dispositions.[2847] However, they are not dealt with under the current legislation on clinical trials.[2848] The ongoing revision of the Civil Code plans to fully admit their validity.[2849] Presently, under a literal interpretation of Articles 55 and 56 LPTh, advance consent cannot replace proxy consent. Such a consequence appears, however, plainly unreasonable. It disrespects patients' explicit will, without advancing any valid interest, let alone

---

2841 *See* AMA (Emergency), *supra* note 2746, at 4 (finding however such mechanism to be generally "unwieldy" and "impractical").

2842 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6 (commentary).

2843 Article 9 of the Biomedicine Convention.

2844 *See* Karlawish, *supra* note 2676. Regarding advanced directives for *ordinary medical practice*, see Olivier Babaïantz, *Les directives anticipées et la représentation thérapeutique*, 3-44, Institut du droit de la santé ("IDS"), Cahier N°6 (1998); BEAUCHAMP & CHILDRESS, *supra* note 16, at 152; U.K. Draft Guidance on Consent, *supra* 2772, at paragraphs 5-6 and 38.

2845 *See, e.g.*, NBAC (Mental), *supra* note 1250, at chapter III. *See also* GUILLOD, *supra* note 77, at 181.

2846 *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 153.

2847 In Geneva, see Article 5.3 of Geneva Regulation K 1 30, *supra* note 136. *See also* Dominique Sprumont, *Les droits des patients dans la législation cantonale romande: l'exemple de la règle du consentement*, 58 MED. et HYG. 2016, at 2017 (Oct. 11, 2000); Guillod & Dumoulin, *supra* note 382, at 7 and n.46; Marinette Ummel, *Testament et directives anticipées, in* MÉDECIN ET DROIT MÉDICAL 72, at 78 (Médecine & Hygiène, 1999) http://www.revmed.ch/article.php3?sid=20810.

2848 However, a patient is allowed to designate a trusted person to allow or refuse the donation of organs or cells for transplant purposes. *See* Article 8.6 of the (future) LTransplant.

2849 *See* Articles 360 to 373 of the CC's proposed revision, in particular Article 370 and 373. See also the accompanying report, *supra* note 2732, at 10.

a public interest. It is therefore better to interpret the LPTh "creatively" and to recognize advance consent as valid.[2850] Advance consent should also prevail over opposition from relatives or legal representatives.[2851] In addition, safeguards should be implemented under the supervision of the investigator and the ethics committee; these safeguards would address the problems that may arise after enrollment (e.g., what happens if the subject fares badly in the trial?).[2852]

In the United States, when the subject is able to give advance – also called anticipated or prospective[2853] – consent, the rules governing emergency research do not apply.[2854] The American Medical Association also recommends that whenever advance consent could reasonably have been obtained beforehand, a waiver of informed consent for emergency research should not be granted.[2855] This recommendation may have the unwanted consequence of depriving patients of promising investigational treatments, just because their doctor forgot to tell them about the clinical trial.

8.4.5. Level of benefits and risks

8.4.5.1. Defining direct and indirect benefits

Both types of research – research on incompetent subjects (Article 55 LPTh) and emergency research (Article 56 LPTh) – must aim to bring some kind of benefit. A benefit is *direct* if it the treatment is expected to improve the health of subjects;[2856] the trial is then said to have a therapeutic purpose (see subsection 6.1.1.3. above). Nontherapeutic trials are those which do not confer direct benefits.[2857]

Articles 55 and 56 LPTh lay out a *subcategory* of nontherapeutic trials, those that generate *important indirect benefits*.[2858] Such benefits consist in the acquisition of important new knowledge about the subject's medical condition, including pain endured.

2850 Of course, if the design of the trial is changed after the subject has given his advance consent, this change in circumstances invalidates the consent.

2851 However, it appears that health care professionals are still reluctant to accept advance directives at face-value, particularly when they feel that the directive is not in the best medical interest of the patient. See the study by Trevor Thompson et al., *Adherence to advance directives in critical care decision making: vignette study*, 327 BMJ 1011-18 (Nov. 1, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7422/1011.pdf (describing the reactions of physicians, nurses and parents to a fictitious case of an advance directive established by an aged patient now suffering from dementia).

2852 *See, e.g.,* subsections 8.3.3.10. and 8.3.3.11. below.

2853 *See* NBAC (Mental), *supra* note 1250. *See* AMA (Emergency), *supra* note 2746, at 4.

2854 *See* FDA (MAPP 6030.8), *supra* note 2751, at 4; FDA (Emergency Guidance), *supra* note 261, at 19.

2855 *See* AMA (Emergency), *supra* note 2746, at 7 (recommendation n°4).

2856 Normally, both the investigational treatment and the control treatment (if there is one) are supposed to produce a benefit. If only the investigational drug is expected to confer benefits, then the requirement of equipoise may be breached. On the notion of equipoise, see subsection 6.3.5.1. above.

2857 *See* FDA (MAPP 6030.8), *supra* note 2751, at 5.

2858 According to Articles 55.2.a and 56.c LPTh, such benefits exist if the trial is "expected to produce important knowledge concerning the status, illness or suffering of the trial subjects, and if this knowledge will bring long-term benefits for the trial subjects concerned or for persons of the same age group [only in Article 55.2.a] or for persons suffering from the same illness or presenting the same characteristics."

Additionally, this knowledge should ultimately help either the subject or other patients in a similar situation (e.g., patients suffering from the same disease).

These criteria are difficult to apply. Can a phase I/safety trial for a promising drug ever confer important indirect benefits? How can the significance of the knowledge be assessed at this stage, when all that is known is the safety and efficacy profile in *animal* models? What is the admissible time interval between the occurrence of the trial and that of the future benefits? Knowing that there can be several years between a phase I trial and the marketing of an approved drug, the foreseeability of these benefits is highly debatable.[2859] Thus, these two provisions regarding important indirect benefit are of limited practical assistance; they probably serve mainly to bar nontherapeutic research on non-serious medical conditions (e.g., eczema).

It is interesting to note that Article 54.5 LPTh envisages the possibility of a mandatory authorization for nontherapeutic trials on incompetent subjects (Article 55 LPTh). The Federal Council has chosen *not* to exercise this option (which would have such trials go through a procedure similar to that applicable to somatic gene therapy or GMMO clinical trials). Thus, it is left to the REC to ensure that incompetent (and incapacitated) subjects are duly protected; in particular, the REC must assess the extent of the proclaimed indirect important benefits.

8.4.5.2. The rule and the exception

Although Article 55.2 LPTh (research with incompetent subjects) and Article 56.c LPTh (emergency research) contain about the same definition of important indirect benefits, there are key differences between these two categories of trials. At Article 55 LPTh, (clinical trials on incompetent subjects), nontherapeutic studies with important indirect benefits must remain the exception, while therapeutic studies (i.e., conferring direct benefits) are the rule. In contrast, Article 56 LPTh on emergency research contains only a clause on important indirect benefits.[2860] It is as if emergency trials never confer direct benefits to the subject. This implausible result is probably due to faulty legislative drafting.[2861] Indeed, the Federal Council's message takes the opposite stance as it assumes that subjects will derive direct benefits.[2862] Similarly, in the United States, emergency research should hold the prospect of direct benefits to subjects.[2863]

The situation in the European Union is particularly unsatisfying. The provisions are couched in a language so convoluted as to make it unintelligible. According to Article 4.(e), "some direct benefit for the group of patients [must be] obtained from the [pediatric] clinical trial." In addition, the clinical trial "must relate directly to a clinical condition from which the minor concerned suffers or be of such nature that it can only be carried out on minors."[2864] According to Article 5 on clinical trials on incapacitated

---

2859 See subsection 4.2.2. above.

2860 Article 56.c LPTh only mentions indirect benefits. Compare with Article 55.2 LPTh.

2861 To make the point clear, the legislator should have used a language similar to that of Article 55.2 LPTh ("Exceptionally, clinical trials that do not confer direct benefits to subjects …").

2862 See however the Federal Council's Message accompanying the LPTh, at FF 1999 3151, at 3231-32. *See also* section 4.8.13 (p.17) of ICH E6.

2863 *See* FDA (Emergency Guidance), *supra* note 261, at 4.

2864 *See* Article 4(e) of Directive 2001/20/EC.

adults, there must be "grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all."[2865] Moreover, the trial must related "directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers."[2866] Does the "group of patients" mentioned at Article 4 necessarily include the subject himself? If at Article 5, there is "no risk at all," can the clinical trial provide no benefit? According to the introductory statements of the Directive, pediatric clinical trials should "normally" be therapeutic, but narrow exceptions appear possible.[2867] For research on incapacitated adults, the conditions are said to be "even more restrictive," and some "direct benefit to the patient" is required.[2868]

It is unclear whether Swiss law allows nontherapeutic trials on *healthy* children. The language of Article 55.2.a LPTh rather evokes nontherapeutic trial on sick children, but it does not ban outright nontherapeutic research on healthy children. A U.S. court answered this question in the negative when the study entails risks for the children:

> Otherwise healthy children should not be the subjects of nontherapeutic experimentation or research that has the potential to be harmful to the child. It is, first and foremost, the responsibility of the researcher and the research entity to see to the harmlessness of such nontherapeutic research. Consent of parents can never relieve the researcher of this duty. We do not feel that it serves proper public policy concerns to permit children to be placed in situations of potential harm, during nontherapeutic procedures, even if parents, or other surrogates, consent.[2869]

The Court went on to recommend that nontherapeutic research involving children should require the specific authorization of a State authority subject to judicial review.[2870]

8.4.5.3. How must benefits be assessed?

Another difficulty with Articles 55.2.a and 56.c LPTh relates to the assessment of the important indirect benefits. These two provisions are framed in *hypothetical* terms: The sponsor is not required to prove beyond a doubt: i) that the trial will spawn important new knowledge, and ii) that this knowledge will eventually produce a direct benefit to subjects or patients (i.e., typically a new drug). On the contrary, it seems that it is up to the REC to determine whether these two conditions are met.

How should the REC appreciate the first condition (i.e., new knowledge)? By definition, a clinical trial *aims* at generating new knowledge; practically it is impossible to forecast whether this knowledge will be important (unless, of course, the disease studied is not a serious one). Moreover, this knowledge does not necessarily pertain to a

---

2865 *See* Article 5(i) of Directive 2001/20/EC.

2866 *See* Articles 5(e) of Directive 2001/20/EC.

2867 Whereas (3) to Directive 2001/20/EC.

2868 Whereas (4) to Directive 2001/20/EC.

2869 *Grimes,* 782 A.2d at 850 and also at 858.

2870 *See id.* at 855.

future cure; knowledge acquired about subjects' suffering also has to be taken into consideration.

The second condition (i.e., the trial must aim to bring a direct benefit to subjects or future patients) is not easier to handle. Since drug development lasts years, this objective is necessarily a long-term one. Moreover, drug development being highly risky, the objective is also largely hypothetical. Ethics committees are obviously not in a position to guess whether the trial will be successful and result in the marketing of a new drug, simply based on the protocol, the brochure and the other documents they receive.[2871]

All in all, I wonder whether it would not have been more adequate to replace Articles 55.2.a and 56.c LPTh with a clause saying that ethics committees must be particularly strict in their (scientific, legal and ethical) assessment of clinical trials involving non-consenting subjects. The investigator should demonstrate to these committees why this inclusion is justified.[2872] An analogous idea (i.e., that trials on incompetent subjects must be appreciated stringently) is expressed at Article 55.1.a LPTh (for research on incompetent patients), which requires that there be no way to obtain equivalent results with fully competent adults (see subsection 8.4.3. above).

8.4.5.4. Level of risks

Another difference between Articles 55 and 56 LPTh relates to the level of risk.[2873]

Neither Article 55 nor Article 56 sets specific risk thresholds for *therapeutic* trials. However, Article 55.2.b LPTh does stipulate that *nontherapeutic* trials on incompetent subjects must entail *no more than slight risks or inconveniences*.[2874] Nontherapeutic trials that exceed this threshold simply cannot take place;[2875] the importance of the expected scientific contribution is of no relevance in this respect.[2876] In contrast, Article 56 LPTh on emergency research does *not* mandate any specific risk ceiling, even for *nontherapeutic* trials.

"Minimal risk" is not defined in the LPTh or in the OClin.[2877] The Federal Council in its message proposed the following explanation: Minimal risks must not exceed those

---

2871 When the trial's sponsor is not a pharmaceutical company, but for example a university research laboratory, ethics committees should not infer that no drug development will ever ensue. On the contrary, the licensing of the trial's findings to a third party is not only possible, but common.

2872 Ideally, the investigator or the protocol itself should state the reasons behind every inclusion or exclusion criteria. Only, when "ordinary" capable adults are selected as potential subjects, is this explication self-evident.

2873 Generally, Swiss law does not set an explicit limit on the acceptable level of risks in trials enrolling competent adults.

2874 Article 55.2.b LPTh. According to the German text, "*die Risiken und Unannehmlichkeiten, welche die Versuchspersonen auf sich nehmen müssen*, [müssen] *geringfügig* [sein]"; according to the Italian text: "*i rischi e i fastidi che le persone sottoposte alle sperimentazioni devono subire sono minimi*."

2875 *See T.D. et al.*, 228 A.D.2d at 124.

2876 Under certain conditions, the American Academy of Pediatrics tolerates nontherapeutic trials with more than minimal risks. *See* AAP (Guidelines), *supra* note 385.

2877 For the U.S. definition of "minimal risk," see 2062 above.

that a reasonable person would accept to incur, in the course of day-to-day life or ordinary medical exams.[2878]

Under U.S. law, *nontherapeutic pediatric* research is admissible only if it involves either i) minimal risk or ii) a minor increase over minimal risk.[2879] Nontherapeutic trials that entail more than a minor increase over minimal risks are normally not permissible (see however subsection 8.4.6.3. below). "Minimal risk" for nontherapeutic pediatric trials requires that:

> the probability and magnitude of harm or discomfort anticipated in the research are no greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.[2880]

Commentators have questioned whether the appropriate standard should be that of *sick or healthy* children (i.e., a *relative* versus an *absolute* definition of minimal risk).[2881] The absolute approach (i.e., a benchmark referring to healthy subjects) results in expanding the protections offered to all children, while limiting the kind of clinical trials that can be carried out on pediatric populations.[2882] The American Academy of Pediatrics ("AAP") recommends construing the notion of risks broadly so as to include notably "fright, separation from parents or familiar surroundings."[2883]

Deciding whether risks are minor is far from easy. U.S. authorities qualify as such non-invasive physical exams, analysis of urine and feces and a single taking of modest (10 ml) amount of blood (venipuncture). Trying to categorize other interventions is difficult.[2884] A survey of IRB chairpersons done in the United States came across wide-ranging divergence and a disturbing ignorance of existing guidelines.[2885]

In the European Union, *all* clinical trials involving minors and incapacitated persons must be designed so as "to minimize pain, discomfort, fear and any other foreseeable risk in relation to the disease and the development stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored."[2886]

2878 *See* Federal Council's Message accompanying the LPTh, at FF 1999 3151, at 3231 (the risk should not "*dépasser ceux qu'une 'personne raisonnable accepterait, dans la vie quotidienne ou dans le déroulement habituel d'examens ou de tests physiques ou physiologiques, de s'exposer ou d'exposer les personnes dont elle a la charge.*'"). *See also* section 4.8.14(b)&(c) (p.18) of ICH E6.

2879 On the U.S. definition of minimal risk, *see supra* note 2062. *See also* IRB Guidebook, *supra* note 411, at chapter VI.C.

2880 45 C.F.R. 46.102(i) and 21 C.F.R. § 50.3(k).

2881 *See* Burns, *supra* note 81, at 134 ("Failure of the federal regulations to clarify whose daily life one should consider has lead to considerable ambiguity in attempts to interpret the risk exposure."). *See also* NBAC (Mental), *supra* note 1250, at chapter IV; IRB Guidebook, *supra* note 411, at chapter VI.C.

2882 "Based upon the diverse comments received regarding the interpretation of minimal risk, and the critical importance of this interpretation to the overall effectiveness of applying the regulation, it would be premature to adopt an absolute standard without further discussion that fully engages all of the relevant parties, including both Federal and private organizations, and the public, before definitive guidance on this point is issued." OHRP (Children), *supra* note 1636, at iv and 7.
See also NBAC (Issues in Research), *supra* note 244, at 13 (in favor of the absolute approach).

2883 *See* AAP (Guidelines), *supra* note 385.

2884 *See* Shah et al., *supra* note 2011, at 476-82. See also the similar survey conducted in Germany by Lenk et al., *supra* note 2700, at 86-87.

2885 *See* Shah et al., *supra* note 2011, at 479.

2886 Articles 4(g) and 5(f) of the Directive 2001/20/EC.

This rule, though not particularly well written (e.g., "in relation to the disease and the developmental stage") seems so self-evident that it should be applied as a matter of course to all clinical trials, regardless of whether they involve minors.

As for the ICH's Guideline, it contains only general language stipulating to minimize pain and distress in all pediatric trials.[2887] For that purpose, the ICH asks that investigators involved in pediatric studies have special relevant training and experience, in particular so as to properly evaluate and manage adverse events.[2888]

8.4.6. Additional requirements

8.4.6.1. Additional requirements under Article 55 LPTh?

Swiss federal Law has no specific restrictions on payments offered to pediatric subjects or their parents, while both the ICH and the European Union view them grudgingly. According to the aforementioned E.U. Directive, "no incentives or financial inducements" can be given.[2889] The language in the ICH Guideline is less precise.[2890] The United States allows small token payments as well as reimbursement of parental expenditures.[2891] A survey by the U.S. OHRP indicated that recruiting practices targeted at children still fall short of ethical standards.[2892]

E.U. Guidance also requires that the investigator and her team have experience working with children.[2893] This prerequisite is necessary to lessen children's anxiety. Similarly, U.S. advisory groups have recommended that IRBs reviewing research on incompetent subjects have members who are familiar with the concerns of the studied population.[2894] The ICH Guidelines recommends that ethics committees reviewing pediatric trials have members or external experts "who are knowledgeable in pediatric ethical, clinical, and psychosocial issues."[2895] The E.U. 2001/20/EC Directive has implemented this requirement.[2896] According to the ICH, ethics committees should be given a protocol that has been designed specifically for the pediatric population, and

---

2887 See chapter 2.6.5 (p.12) of ICH E11 Guideline.

2888 See chapters 2.6.4 and 2.6.5 (p.12) of ICH E11 Guideline.

2889 Article 4(d) of Directive 2001/20/EC. *See also* CPMP (Children), *supra* note 2815, at 1 (chapter 1.1).

2890 "Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)/legal guardian or the study participant." Chapter 2.6.2. (p.10) of ICH E11 Guideline.

2891 "If remuneration is to be provided to the child, it is best if it is not discussed before the study's completion." AAP (Guidelines), *supra* note 385. *See also* OHRP (Children), *supra* note 1636, at 11.

2892 OHRP (Children), *supra* note 1636, at 14.

2893 *See* CPMP (Children), *supra* note 2815, at 3 (chapter 1.4).

2894 *See* NBAC (Mental), *supra* note 1250. In addition, "at least one of these [two] IRB members should be a member of the population being studied, a family member of such a person, or a representative of an advocacy organization for this population." When the IRB does not regularly review protocols enrolling such vulnerable groups, it can retain the services of ad hoc consultants. *Id.*

2895 *See* chapter 2.6.1 (p.10) of the ICH E11.

2896 According to Article 4(h) of the Directive, the ethics committee endorsing a pediatric trial must have "pediatric expertise" or must have taken "advice in clinical, ethical and psychosocial problems in the field of paediatrics." In the United States, see 21 C.F.R. § 56.107(a). *See also* AAP (Guidelines), *supra* note 385.

not simply adapted from an adult protocol.[2897] Swiss law imposes no such obligations.[2898]

8.4.6.2. Additional requirements for emergency trials

Article 56.d LPTh contains an interesting constraint: The interests of the subject enrolled in an emergency research must be defended by a physician not otherwise involved in the clinical trial.[2899] Surprisingly, this requirement is not applicable in the context of Article 55 LPTh, in particular its paragraph 2 (nontherapeutic trials on incapable subjects).

This provision says that this physician will also assure the medical care of the subject, without it being clear whether this person is the main physician in charge of the subject's medical care. The provision is also silent as to who appoints this physician.[2900] The role of this third party advocate is scantily described. Does she report to the ethics committee? To the investigator? Directly to the sponsor? What prerogatives does she have? Can she decide alone to withdraw the subject from the research? Can she modify the protocol to improve the treatment received by the subject? All these questions are answered neither by the LPTh nor by the OClin.

Nevertheless, the provision is interesting as it contends with the notion of *independence*. We saw in subsection 7.1.1.3. that each REC must comprise at least one unaffiliated member, but that all other members may have connections with the investigator's institution (while still being deemed independent under Article 31.b OClin[2901]). Here in Article 56.d OClin, the legislator felt the need to bring in a third party as an advocate for the subjects. Normally, RECs are responsible for defending subjects' rights. Yet, as we saw in subsection 7.1.3., RECs are unable to supervise the progression of clinical trials. Once they have given their initial favorable opinion, they rely on occasional reports.[2902] They are seldom present at the research site to observe the care given to subjects. They rarely send a member or an agent to attend subjects' information session and consent process. Consequently, the physician mentioned in Article 56.d LPTh is in a perfect position to fill in the void left by the REC. She is present at the research site; she has medical qualifications to understand the protocols' procedures and the trial's findings. I would therefore suggest broadening the scope of application of Article 56.d LPTh so as to have an independent physician representing subjects' interests in *all* large or risky clinical trials, whether or not vulnerable subjects are enrolled. Moreover, this physician should – ideally – not be employed by, or affiliated to, the investigator's institution.

U.S. regulations also require the presence of an independent physician, but the latter must be a member of the IRB. The IRB cannot approve an emergency trial, if it does

---

2897 *See* chapter 2.6.5 (p.11) ICH E11 Guideline.

2898 *See* Article 55 LPTh.

2899 According to Article 56.d LPTh, the physician is one who is "*non impliqué,*" "*nicht am Versuch beteiligt ist*," "*che non partecipa.*"

2900 Under the previous intercantonal system, the independent physician had to be appointed by the ethics committee. *See* Article 1.15 of the GCPs accompanying the (former) IOCM 1995 Regulation.

2901 *See also* Article 57.2 LPTh.

2902 See also subsection 9.2.1. below.

not have at least one licensed and independent physician IRB member.[2903] If the IRB does not have a member who satisfies this condition (e.g., for reasons related to a conflict of interest), then it must mandate such a person as external consultant.[2904] This person must then approve the protocol and her endorsement must be duly documented in the minutes of the IRB meeting.[2905] In addition, the sponsor of an emergency clinical trial must set up a Data and Safety Monitoring Board (see subsection 5.8. above).[2906] The DSMB's task is to review periodically the interim results of the emergency trials. By analyzing the *unblinded* data,[2907] it makes sure that the benefit/risk ratio stays positive.[2908]

8.4.6.3. Public feedback in the United States

In the United States, pediatric research must normally entail only minimal risk or a minor increase over minimal risk (see subsection 8.4.5.4. above). Exceptionally, a pediatric clinical trial that exceeds this threshold can be authorized but has to clear additional hurdles. The study must go through a public review process.[2909] The FDA must appoint and consult external experts.[2910]

Such a situation arose in 2002 with respect to a pediatric clinical trial of a smallpox vaccine.[2911] The trial was sponsored by a public entity. It would have tested the vaccine Dryvax on children age 2 to 5. The study was felt to be of importance in the context of possible bioterrorist attacks. Ultimately, it was not approved because the perceived terrorism threat had abated by January 2003.[2912]

8.4.6.4. Community information in U.S. emergency research

In the United States, emergency clinical trials performed without the subject's consent require prior consultation: The community in which the trial will take place must receive prior information.[2913] This way, people who know they do not want to be enrolled

---

2903 *See* FDA (Emergency Guidance), *supra* note 261, at 6.

2904 *Id.*

2905 *Id.*

2906 *See id.* at 15.

2907 *Id.* at 15-16.

2908 *Id.* at 15.

2909 *See* 21 C.F.R. § 50.54.

2910 *See* 21 C.F.R. § 50.54(b). For examples of expert reviews, see review of the Dryvax pediatric clinical trial by expert Mary Faith Marshall (Oct. 27, 2002), at http://www.hhs.gov/ohrp/dpanel/marshall.pdf; review by expert Neal A. Halsey, at http://www.hhs.gov/ohr/dpanel/halsey.pdf; letter of David S. Stephens to the FDA (Oct. 28, 2002) at http://www.hhs.gov/ohrp/dpanel/stephens.pdf.

2911 *See* FDA, Solicitation of Public Review and Comment on Research Protocol, Notice, 67 Fed. Reg. 66,403-4 (Oct. 31, 2002), at http://www.fda.gov/OHRMS/DOCKETS/98fr/103102a.pdf.

2912 Letter of OHRP and FDA to Harbor-UCLA Medical Center (Jan. 24, 2003), at http://www.hhs.gov/ohrp/dpanel/determ.pdf.

2913 *See also* Michael C. Kennedy, *Clinical trials without consent: some experiments simply cannot be done*, 177 MJA 40-42 (July 1, 2002) at http://www.mja.com.au/public/issues/177_01_010702/ken100251_fm.pdf (discussing a proposed emergency clinical trial comparing "two regimens of management of patients with acute myocardial infarction").

(should they face an emergency of the kind under study) can voluntarily opt out.[2914] The consultation is also an opportunity for the IRB to learn the opinions of the community; it can then take them into account in order to decide whether or not to grant its approval.[2915]

The initial consultation must take place *before* the study is started. The community to be consulted includes both people living close to the research site and the group of patients from which subjects may be drawn.[2916] The sponsor, the investigator and the IRB should work together to establish and carry out the plan to reach this community.[2917] The plan generally entails meeting with community representatives.[2918] Television and radio announcements may also be used.[2919] Specialists should be contacted because they can act as channels of information for patients and potential subjects.[2920] In some cases, the sponsor may establish a sub-IRB, whose members are representatives of the community.[2921]

A second consultation must take place *after* the trial has been completed.[2922] At this point, the community is informed of the trial results.[2923] This information must also benefit other researchers, as one of its purposes is to avoid duplication of emergency clinical trials.[2924] The sponsor is responsible for preparing the information to be disseminated.[2925] The IRB should make sure that the information provided is adequate.[2926] The investigator normally reviews the information before it is circulated.[2927]

Neither Switzerland nor the European Union have adopted such consultation procedures,[2928] but certain international Guidelines, such as the CIOMS, already recommend them.[2929]

2914 On how to organize such an opting-out, see Fost, *supra* note 2747, at 182.

2915 *See* FDA (Emergency Guidance), *supra* note 261, at 6 and 9. The IRB must document how it took into account the opinions expressed by the community during the consultation. *Id.* at 9.

2916 *Id.* at 7.

2917 *Id.* at 7-8.

2918 See for example the scheme devised in the stroke study and described in the accompanying documents to the letter from UCLA Stroke Study Network to the FDA, (May 5, 2003), at http://www.fda.gov/ohrms/dockets/dailys/03/May03/050803/95s-0158-rpt0009-01-vol5.pdf.

2919 See FDA (Emergency Guidance), *supra* note 261, at 8.

2920 *Id.* at 11.

2921 *Id.* at 8.

2922 *See id.* at 6-7.

2923 *Id.* at 7. *See, e.g.,* ICOS' letter to the FDA (Jan. 6, 2000) on the disclosure of study results, at http://www.fda.gov/ohrms/dockets/dailys/00/feb00/020700/sup0021.pdf.

2924 FDA (Emergency Guidance), *supra* note 261, at 7.

2925 *Id.* at 12.

2926 *Id.* at 12-13.

2927 *Id.* at 12.

2928 *See* the critical appreciation by the U.S. Department of Health, *in* U.K. Draft Guidance on Consent, *supra* note 2772, at paragraphs 53.

2929 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6 (commentary).

8.4.7. Other exceptions to informed consent under U.S. law

Under Swiss law, aside from the situations discussed above, there are no exceptions to the general principle of informed consent. In contrast, U.S. IRBs can, under certain conditions, waive the requirement of informed consent.[2930] Research done without prior consent must entail no more than minimal risks for the subjects and the lack of consent must not cause any harm to the subjects. The waiver must be indispensable to conduct the study. Finally, as soon as feasible, the subjects must receive information about the study.

The U.S. government may also dispense with the informed consent of *soldiers* in combat-related situations. During the first Gulf War, the Department of Defense ("DoD") applied for a waiver from the FDA to administer two investigational drugs without the soldiers' consent.[2931] The Agency had to establish an *ad hoc* regulation and rapidly granted the waiver on this basis.[2932] The drugs were intended to be used (preventively as well as post-exposure) if Iraq were to use chemical/biological weapons against U.S. troops. The DoD's intended use was more akin to treatment than research,[2933] although the DoD did plan to collect some scientific data. However, because the drugs lacked approval for this military-related indication, their use fell within the jurisdiction of the FDA.[2934] Ethical constraints had made it impossible to test these drugs in advance.[2935] Ultimately, more than a quarter of a million soldiers received some doses of the investigational drugs, experiencing no life-threatening side effects.[2936] However, both recordkeeping[2937] and information to soldiers and their physicians[2938] were found to be very poor. Yet, American Courts have refused to hold invalid the FDA

2930 *See* Glantz, *supra* note 83, at 191. This exception does *not* apply to drug trials submitted to the FDA.

2931 The investigational drugs were pyridostigmine bromide (PB) and botulinium toxoid vaccine (BT). The FDA had already approved PB, but for another therapeutic indication.

2932 In October 1990, the DoD asked the FDA to establish a waiver program. In December 1990, the FDA issued its Interim Rule. This Rule adds a section 23(d), at 21 C.F.R. § 50.23(d)(1) (Informed Consent for Human Drugs and Biologics, Determination that Informed Consent is Not Feasible, 55 Fed. Reg. 52,814 (Dec. 21, 1990)). This section authorizes the Commissioner of the FDA to waive the legal requirement of informed consent in the context of military operations. On December 28, 1990, the DoD applied for waivers for PB and BT. The FDA granted the requested waiver on January 8, 1991.

2933 Based on the intent of the DoD, the administration of the two drugs qualified as medical practice. Based on the investigational status of these possibly risky drugs, their administration could be deemed research. *See* Rand Report, *supra* note 254, at chapters 1 and 3.

2934 *See id.* at chapter 3.

2935 Testing the drug would have required to expose subjects to weapon-grade nerve gas and botulism. Clearly, this would have fallen foul of ethical principles. *See* Rand Report, *supra* note 254, at chapter 1.

2936 However, "PB was implicated as a possible risk factor in Gulf War veterans' illnesses…[and] BT and AX were also cited as possible causes for some veterans' illnesses." *See* Rand Report, *supra* note 254, at chapter 1.

2937 Appropriate collection of data regarding use on and by military troops proved much more difficult than initially expected. *See id.* at chapter 1.

2938 "Information provided to service members and to health care providers was inadequate. …[T]he actual distribution of information to the troops was highly variable, and postwar testimony by many veterans revealed that the information they received was unsatisfactory, at least in retrospect. This deficiency is perhaps the most telling of all, since authority to waive informed consent throws a heavy burden on the obligation to inform." *See id.* at chapter 2.

regulation under which the waiver was granted.[2939] In 1998, the authority to grant waivers was transferred from the FDA to the President of the United States.[2940]

8.5. Enrollment of "vulnerable" subjects

The typical human research subject is said to be a young white male with a college education and a decent income;[2941] he is fluent in the language of the trial; he has insurance; he lives close to a treatment center.[2942] Subject with these characteristics are more likely to be aware of research opportunities. Once enrolled, they are also more likely to complete the trial.[2943]

Sponsors feel safer by enrolling educated and reasonably well-off subjects, even though it may take more time to assemble a large enough group of such subjects. Sponsors may believe that this category of subjects follow more attentively the instructions received from the investigator and thus adhere better to the treatment (e.g., they take all the pills at the right time, they comply with a set diet, they quit smoking and drinking).

However, restricting the pool of volunteers to this class of subjects would jeopardize the generalizability of the study findings. It would also cause unacceptable discrimination against those who were not offered to participate (see subsections 2.1.5. and 8.1.6. above).

The following subsections discuss the difficulties arising out of the participation of certain vulnerable classes of subjects.[2944] It does not encompass all vulnerable groups. For example, the FDA also classifies illiterate persons and employees of the sponsor as vulnerable subject population.[2945] Moreover, a vulnerable subject can also belong to a category of subjects who cannot give consent, as we have seen in the previous subsection.

The LPTh and the OClin make no mention of clinical trials on vulnerable subjects (aside from Article 55 and 56 LPTh on incapable subjects and emergency research). In

---

2939 In the latest case of a series, the plaintiff argued that the FDA had stepped beyond its statutory authority in enacting the waiver regulation. *See* Doe v. Sullivan, 938 F.2d 1370 (D.C. Cir. 1991). *See also* Doe v. Sullivan, 756 F. Supp. 12 (D.D.C. 1991).

2940 The American Congress passed the "Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (Public Law 105-261), (Oct. 17, 1998)." Rand Report, *see* note 254, at preface and chapter 1.

2941 *See* Marwick (Talk), *supra* note 2303, at 1833.

2942 *See* T. E. King, *supra* note 2311, at 1400-402; Allen L. Gifford et al., *supra* note 2299, at 1373-1382 ("Patients who were cared for in private health maintenance organizations were less likely to participate in [HIV] trials than those with fee-for-service insurance." *Id.* at 1373).

2943 *See* Gifford et al., *supra* note 2299, at 1375.

2944 The ICH E6 Guideline contains a broad definition of "vulnerable subjects" as it encompasses all "individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate." Section 1.61 (p.8) of ICH E6; and also its section 3.1.1 (p.9). *See also* paragraph 8 Helsinki Declaration.

2945 *See* FDA (FAQ-IRB), *supra* note 1814, at questions 40 and 64.

contrast, the former IOCM 1995 Regulation invited ethics committees to exercise special care when called to review such trials.[2946]

8.5.1. Prisoners

In the wake of the Nuremberg trials, many countries banned or severely restricted clinical trials on prisoners.[2947] In Switzerland, research on prisoners would be possible only if indispensable because it focuses on medical conditions found typically in prisons.[2948] Presently, the OClin and the LPTh do not tackle this issue. Probably the issue has never come up in practice (i.e., no such protocol has ever been submitted for approval).

The situation in the United States differs from that of most other countries. Until the mid-1970s,[2949] this country viewed prisoners as an ideal subject population.[2950] Research on prisoners was an ingrained tradition.[2951] Estimates suggest that up to 90% of all research subjects were prisoners.[2952] It was even proposed that death row inmates should be handed over to scientists – instead of dying pointlessly on an electric chair...[2953] Sometimes, the prisoners did give informed consent, but in most cases they were coerced or misled into participating.[2954] Many reasons explain prisoners' "popularity."

First, this population exhibits a higher prevalence of several diseases, including rare diseases. Second, it is a particularly homogeneous (e.g., roughly the same age group) and lives in a controlled environment (e.g., same diet, same pollutants).[2955]

2946 Article 6.1 of the (former) IOCM 1995 Regulation.

2947 Brian Paul Wyman, *Biomedical and Behavioral Research on Juvenile Inmates: Uninformed Consent and Coerced Participation,* 15 J.L. & HEALTH 77, at 88 (2001).
In France, see ROUZIOUX, *supra* note 1270, at 86 (for France); CCNE N°2, *supra* note 57, at 4 (for non-therapeutic trials). *See also* Article 20 COE Research Protocol.

2948 *See* SAMS 1997 Guideline, *supra* note 110, at point D.5. at 10. Although this Guideline is not mandatory, it is likely that it nonetheless effectively bars other research projects conducted on inmates populations.

2949 "Prior to 1973 there was infrequent mention and little, if any, public debate over conditions of confinement as an element to be considered in evaluating consents." Bailey v. Lally, 481 F. Supp. 203, at 223 (D. Md. 1979). The Court goes on to describe the broad acceptability of studies involving prison inmates before 1973. Thus, for example, "[m]edical journals accepted articles describing the results of the experiments and their methods." *Id.*
See also Cain v. United States, 643 F. Supp. 175 (S.D.N.Y. 1986) (describing an experiment in the 1950s during which the U.S. government had Sing Sing prison inmates infected with syphilis apparently without their consent; the government then attempted to conceal its actions).

2950 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 12 (commentary).

2951 See the description of clinical trials on prisoners in U.S. court case of *Bailey*, 481 F. Supp. 203. *See also* LEDERER, *supra* note 54, at 76 (describing the cholera vaccine experiment), 110-12 (describing the pellagra experiment).

2952 "Prison inmates had become such an integral part of the preliminary testing that they constituted nearly 100 percent of the Phase I experimental populations across the country, according to Dr. Alan B. Lisook, former chief of clinical investigations for the FDA." ALLEN M. HORNBLUM, ACRES OF SKIN, 43 (Routledge 1998).

2953 *See also* LEDERER, *supra* note 54, at 45.

2954 *See also* Schroeter, *supra* note 191, at 158 (reporting, for instance, that "[f]or eight years, inmates at Oregon and Washington state prisons received X-rays to their testes to examine the effects of ionizing radiation on human fertility and testicular function. The University of Washington Medical School conducted the experiments.").

2955 *See, e.g.,* HORNBLUM, *supra* note 2952, at 38.

Third, it is conveniently accessible: All inmates are housed together and have little occupation that could preclude their participation (i.e., no regular jobs, no family obligations). Four, at least in the past, consent was relatively easy to obtain because participation in a clinical trial offered many benefits to prisoners. They would receive better health care.[2956] Health facilities were more comfortable than their cells (e.g., less crowded, better food). Payments were significantly more generous than any salary the prisoners could earn by working at the prison. Clinical trials gave them a chance to interact with people outside their usual circle of fellow inmates and guards.[2957] Prisoners could be given assurance that they would not be transferred to a less desirable prison.[2958] Authorities might take their participation into consideration when granting parole.[2959] Five, participation of prisoners in research was viewed, at least by non-prisoners, as a way for the former to pay their debt to society. In the wartime atmosphere of the first half of the 20th century, public opinion was that everyone ought to contribute in some manner to the war effort; since prisoners were not sent to fight, they should instead take part in research ![2960] Finally, prisoners were probably less likely to complain or to sue if injured through participation in a trial.[2961]

In the early 1970s, the U.S. Department of Health started to question the enrollment of prisoners in clinical trials, underlining that "[m]any aspects of institutional life may influence a decision to participate, [an influence that could] amount to coercion, whether it is intended or not."[2962] Opponents of such research charged that prisoners can *never* give a truly free consent.

The subsequent publication of various guidelines reduced drastically the participation of prisoners in U.S. clinical research.[2963] Clinical trials with prison inmates is now ridden with obstacles[2964] to the point that commentators worry that inmates are discriminated against because denied access to potentially beneficial clinical trials.[2965] In-

---

2956 Compare with the similar argument made to justify the Willowbrook studies on institutionalized mentally handicapped children. *See* SPRUMONT, *supra* note 16, at 19 and 21.

2957 The U.S. Department of Health noted in 1974 that participation in clinical trials could offer inmates "relief from boredom." 38 Fed. Reg. 31,743.

2958 *See Cain*, 643 F. Supp. at 177.

2959 The Maryland District Court stated in its 1979 decision that "[t]he prisoners testified (and the doctors did not contest) that prisoners volunteered principally because of the money inducement and because they also hoped that their participation in the MRU [Medical Research Unit] would influence their chance for parole. While prisoner volunteers were told, either as a matter of course or upon question being raised, that participation in the MRU program would have no impact on parole, 'hope springs eternal in the human breast' and almost surely so did in the breast of each volunteer at the MRU." *Bailey*, 481 F. Supp. 203, at 219. *See however id.* at 221.

2960 *See* ARNO AND FEIDEN, *supra* note 125, at 25; HORNBLUM, *supra* note 2952, at 46.

2961 For instances of particularly offensive treatments administered to control the behavior of prisoners and institutionalized mentally incompetent patients, see Knecht v. Gillman, 488 F.2d 1136 (8th Cir. 1973).

2962 *See* 38 Fed. Reg. 31,738, at 31,743.

2963 *See, e.g.*, 45 C.F.R. § 46.301 to § 46.306, introduced in 1978 by 43 Fed. Reg. 53,655.
These guidelines did not prevent the occurrence of a minor scandal when news of a clinical trial enrolling *juvenile inmates* surfaced: in 1997, Stanford University had enrolled minors jailed for violent crimes in a study of a drug intended to reduce aggressiveness. *See* Wyman, *supra* note 2947, at 77.

2964 According to Principle 7 of the Council of Europe's R(90)3 Recommendation, prisoners can participate as subjects in research only if the research "is expected to produce a direct and significant benefit to their health." *See supra* note 115.

2965 The (American) Belmont report highlighted this conflict: "Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing

deed, prisoners suffer a higher prevalence of AIDS and hepatitis, but could not (at a time) get valuable treatments offered available only through clinical trials. Reluctance also comes from the sponsor and the investigator who may well be loath to risk deteriorating their public image. The risk to their reputation may exist even if the clinical trial is conducted according to GCP; it is linked to the reminiscence of past scandals that the medias could easily revive if anything during the trial went wrong.

U.S. law requires that IRBs evaluating a research project involving prisoners must satisfy at least two additional conditions.[2966] First, a majority of IRB members must not be affiliated with the prison in which the trial is to take place.[2967] Second, at least one prisoner or prisoner representative must sit on the IRB.[2968] Other conditions under U.S. law pertain to the selection of subjects,[2969] payments and benefits offered to them,[2970] and the risks incurred.[2971] Finally, the type of research that can be conducted in U.S. prisons is limited in several ways, whenever the study is not intended to confer direct therapeutic benefits to prisoners-subjects.[2972]

I would recommend that Switzerland endorse the position adopted by the United States, as the latter balances adequately the benefits and the risks of enrollment. An outright ban on prisoners' enrollment would be discriminatory, especially when the clinical trial holds the prospect of direct and individual health benefits for the research subjects.

8.5.2. Women

Past scandals created the impression that women participating in research were exposed to excessive risks. For instance, in the 1970s, women who had asked for contraceptives were enrolled without their consent in a placebo-controlled trial studying the effects of hormonal treatment. Several women who took the placebo (instead of the contraceptives they were expecting) had unwanted pregnancies.[2973]

Women of child-bearing age face the additional risk of giving birth to babies with physical defects.[2974] In the thalidomide disaster, pregnant women in Europe were pre-

---

competing claims urged by the principle of respect itself." Part B.1 Belmont Report, *supra* note 61. *See also* BEAUCHAMP & CHILDRESS, *supra* note 16, at 178-79.

2966 *See* OHRP, HHS, OHRP Guidance on the Involvement of Prisoners in Research, (May 23, 2003), at http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.pdf [hereinafter OHRP (Prisoners)]. *See* Glantz, *supra* note 83, at 191-92.

2967 *See* 45 C.F.R. § 46.304.a.

2968 *See* 45 C.F.R. § 46.304.b. On who can be a "prisoner representative," see OHRP (Prisoners), *supra* note 2966, at section D.

2969 *See* 45 C.F.R. § 46.305.a.4.

2970 *See* 45 C.F.R. § 46.305.a.2 and 6. In particular, participation in clinical trials must not be taken into consideration when deciding on parole.

2971 *See* 45 C.F.R. § 46.305.a.3. *See also generally* SPRUMONT, *supra* note 16, at 148-49.

2972 *See* 45 C.F.R. § 46.306.a.2. *See also* OHRP (Prisoners), *supra* note 2966, at section F (listing four categories of permissible research).

2973 *See* THE SHAPIROS, *supra* note 4, at 181-82.

2974 *See* FDA, Thalidomide, Important Patient Information, at http://www.fda.gov/cder/news/thalidomide.htm. In addition, the drugs being tested could impair their fertility.

scribed by their physicians a drug whose efficacy had not been properly tested and which was later found to systematically cause birth defects (see also subsection 4.1.1.2.1. above).[2975] The U.S. FDA had refused to grant marketing approval to the drug for lack of sufficient efficacy and safety information.[2976] In the diethylstilbestrol (DES) case, not only did the drug (manufactured by Eli Lilly) cause birth defects and increased risks of cancer in the subject's progeny, but women were enrolled without their consent in the clinical trial aiming at assessing the drug's efficacy.[2977]

On the other hand, although real incidents are not known, the mother is not the only one at risk of transmitting a toxic drug to her offspring. At least in theory, the father can also be at the cause of a teratogenic* effect affecting his baby.[2978] Despite this risk, men enrolled in clinical trials are typically not required to use contraceptive devices.[2979] Restrictions are rarely placed on their participation in research.

In the United States, the perceived threat facing women justified – until 1993 –legal restrictions as well as an implicit ban on the enrollment of women of child-bearing age (interpreted as practically all women having not reached menopause).[2980] The consequence was that many approved drugs were more harmful for women than for men, as prior clinical trials had focused chiefly on side effects in male subjects.[2981] This only made women the "guinea pigs" later in the process, that is after the drug was approved

---

2975 *See, e.g.*, Grow, *supra* note 249, at 40-41.

2976 Frances Kelsey at the FDA is credited for having stopped the drug from being broadly sold in the United States. *See* FDA, CDER News Along the Pike (Nov. 2000), at http://www.fda.gov/cder/pike/nov2000.htm#Kelsey. *See also* Grow, *supra* note 249, at 42-49. However, thalidomide was still distributed to American doctors and, through them, to patients, under the guise of investigational use "tinged with commercial intent." *Id.* at 40. "Records from drug manufacturers showed that 2,528,412 tablets were distributed to doctors in the United States for investigational use. Interviews with doctors suggested that the drug had been given to 19,822 patients." *Id.* at 50-51. *See also* ARNO AND FEIDEN, *supra* note 125, at 30. For a complete story of thalidomide, see for example ROCK BRYNNER & TRENT STEPHENS, DARK REMEDY, THE IMPACT OF THALIDOMIDE AND ITS REVIVAL AS A VITAL MEDICINE (Perseus Publishing 2001).

2977 *See* Mink v. University of Chicago, 460 F. Supp.713 (N.D. Ill. 1978) (describing the experiment conducted at the University of Chicago on some 1000 pregnant women without their consent); Noah, *supra* note 4, at 373.

2978 "The potential role of male-mediated risk factors has not been extensively investigated, probably largely because of the prevailing view that male-mediated effects are unlikely. … However, recent work is beginning to suggest possible pathways that might explain associations between paternal exposures and congenital anomalies in offspring." Merton, *supra* note 130, at 401-402.

2979 *See id.* at 398; Jonathan D. Moreno, *Ethical Issues Related to the Inclusion of Women of Childbearing Age in Clinical Trials*, *in* WOMEN AND HEALTH RESEARCH, ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES, VOLUME 2, at 30 (Institute of Medicine 1999). *See however* ICH E8, *supra* note 533, at 3.2.2.1.

2980 Enrollment of women in Phase I and II studies was prohibited by a 1977 Guideline. Later guidelines were not as explicit, but still failed to compel sponsors and investigators to include women of child-bearing age. For a history of the movement towards a greater inclusion of women in clinical trials, *see* David J. Harris & Pamela S. Douglas, *Enrollment of Women in Cardiovascular Clinical Trials Funded by the National Heart, Lung, and Blood Institute*, 343 NEW. ENG. J. MED. 475-480, at 478 (2003), at http://content.nejm.org/cgi/reprint/343/7/475.pdf. *See* 45 C.F.R. § 46.201 to § 46.211. *See also* Frank A. Chervenak & Laurence B. McCullough, *Ethical consideration of maternal participation in clinical research*, 11(6) CURR. OPIN. OBSTET. GYNECOL. 549-51 (Dec. 1999); Merton, *supra* note 130, at 370-71 and at 390-95 (analyzing the 1977 Guidelines).

2981 Many drugs have distinct effects on women and men. According to a review of 185 NMEs approved by the FDA between 1995 and 1999, reviewing officers found gender-related differences in – at least – 17% of the drugs. Differences are most frequent with cardio-renal and metabolic/endocrine, neuropharmacological, antiviral, oncologic products. *See* Evelyn B. Toigo et al., *supra* note 687. *See also* Anne-Françoise Allaz & Valérie Piguet, *La cause des femmes*, 39(2) CMS 209, at 210 (1995).

and placed on the market rather than before.[2982] Moreover, women suffering from serious diseases for which no available treatment was effective could not benefit from innovative therapies offered in clinical trials. This became particularly apparent with the AIDS crisis: Women with AIDS could not enter the early clinical trials because only male subjects were admitted.[2983]

Starting in the mid-1980s, the American NIH, followed in 1993 by the FDA, decided to reverse its policy and encourage the inclusion of women of child-bearing age in all clinical trials.[2984] The policy reversal was quite effective in that women now constitute half of all enrolled subjects.[2985] Other countries followed a similar trend: First, excluding women of child-bearing age, and then encouraging their inclusion.[2986] However, Switzerland has not adopted any explicit legal policy nor does it make figures available.

8.5.2.1. Pregnant women

In 1989, the SAMS issued guidelines that severely limited research on pregnant or breast-feeding women.[2987] A subsequent note by the SAMS now encourages investigators and sponsors to include female research subjects in clinical trials.[2988] The note acknowledges that women tend to face greater therapeutic risk when using pharmaceuticals, since these are chiefly tested on men.

However, the problem related to pregnant women in research has subsisted.[2989] Women who are pregnant before the beginning of a trial are still habitually disqualified pursuant to the protocol, while women who become pregnant during the trial are withdrawn.[2990] Enrolled women of child-bearing age often are required to use contra-

---

2982 *See* Merton, *supra* note 130, at 380.

2983 *See* ARNO AND FEIDEN, *supra* note 125, at 47, and also 200-02.

2984 The first NIH policy to encourage inclusion of women in clinical trials dates back to 1986. It was regularly revised, in particular in 1994 and in 2001. The initial NIH policy only encouraged inclusion of women. In 1994, such inclusion was made mandatory for researchers wishing to get NIH funding. *See, e.g.,* NIH, Outreach Notebook for the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research, (Dec. 2002) at 3-4, at http://orwh.od.nih.gov/inclusion/outreach.pdf.

2985 For NIH-sponsored clinical trials, see the NIH annual reports, such as the 2000-2001 Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research, at 13-14, (June 2003), at http://orwh.od.nih.gov/inclusion/GoldReport_2000-01.pdf [hereinafter NIH (Monitoring Women)].
See also Evelyn B. Toigo et al., *supra* note 687 ("When the gender-specific products such as those for ovarian or prostate cancer … are excluded from the analysis [of 2,581 clinical trials for 185 NMEs approved between 1995 and 1999], participation by women (48%) is slightly less than of men (52%). … women participated to a greater extent in later phases of study than earlier phases.").
Another study found that women were generally well represented in most cardiovascular-related clinical trials, except for those investigating heart failure. *See* Harris & Douglas, *supra* note 2980, at 477.

2986 *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 16.

2987 According to Point 7.3 of the (former) SAMS 1989 Guidelines (*supra* note 142), pregnant or breast-feeding mothers could be enrolled in research only if the research entailed no risk of significance for the child and if it generated results that could benefit other women or children during this period of their lives. The SAMS 1997 Guidelines contain a similar language. *See* SAMS 1997 Guideline, *supra* note 110, at point D.5. at 9-10.

2988 Comment to point D.5 of the SAMS 1997 Guideline, *supra* note 110, at 11-12.

2989 Neither the LPTh nor OClin contains any provisions on pregnant women participating in research.

2990 *See* ICH E8, at section 3.1.4.3.a). The Council of Europe's R(90)3 recommendation in its Principle 3 only allows such research under restrictive condition: "[p]regnant or nursing women may not undergo medical research where their health and/or that of the child would not benefit directly unless this research is aimed

ceptive methods, including for a washout period after the end of the trial.[2991] Women with babies are asked not to breastfeed.[2992] The consequence is perfectly predictable: little or nothing is known about the effect of approved drugs on pregnant or nursing women and on their fetuses. Pregnant women do not enjoy the security of the marketing authorization procedure. However, except for pregnancy registries,[2993] no solution has been proposed.

Three categories of research can involve pregnant women.[2994]

First, *nontherapeutic* research on a pregnant woman should be permissible only if it entails minimal risk to both the subject and the fetus (e.g., blood taking).[2995] Women are not allowed to confront their fetus to important risks if no direct benefit is expected.[2996] The principal underlying idea is that, if the woman chooses to keep her baby (instead of aborting), the fetus may be borne with physiological or mental defects caused by the research.[2997] Harm caused to a living newborn baby can never be justified by the scientific information gained through the research. Furthermore, ethical principles object to a woman committing irrevocably to abort her fetus.[2998] Hence, even a woman who resolutely intends to abort cannot engage in nontherapeutic research that would be dangerous to her fetus.[2999] To address this problem, some commentators have proposed to design trials whereby the tested drug is administered very shortly before a previously planned abortion.[3000]

Second, a woman may take part in a therapeutic trial for her own benefit, whether or not the studied disease is one caused by pregnancy (e.g., nausea or breast cancer). To the extent that the woman derives a personal benefit, she can accept risks that are more

---

at benefiting other women and children who are in the same position and the same scientific results cannot be obtained by research on women who are not pregnant or nursing." *See supra* note 115.

2991 *See* ICH E8, at 3.2.2.1; Article 22.2 COE Research Protocol. See also for example Protocol Number 02-C-0130, Clinical Research Studies, at http://clinicalstudies.info.nih.gov/detail/A_2002-C-0130.html ("Pregnant or nursing women are not eligible; neither are women or men of childbearing potential unless using effective contraception as determined by the patient's physician."). *See also* Stanford University, Research Policy Handbook, Women as Subjects in Research, at 4, (Document 7.2.) (Feb. 10, 1995), at http://www.stanford.edu/dept/DoR/rph/rph_pdf/7-2.pdf [hereinafter Stanford (Women in Research)].

2992 *See* Stanford (Women in Research), *supra* note 2991, at 4.

2993 See subsection 8.5.2.3. below.

2994 *See* Article 18 COE Research Protocol.

2995 *See* 45 C.F.R. §46.204(b) (Common Rule).

2996 *See* John Robertson, *Ethical Issues Related to the Inclusion of Pregnant Women in Clinical Trials* (I), *in* WOMEN AND HEALTH RESEARCH, ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES, VOLUME 2, at 19 (Institute of Medicine 1999).

2997 "Except for persons who view the fetus as a person or moral subject in its own right, the moral concern with research or other impacts on fetuses arises because fetuses generally go to them and become offspring. More than minimal risk to a fetus is of ethical concern because of the impact which that risk will have on the resulting child." *Id.* at 20. *See also* Bonnie Steinbock, *Ethical Issues Related to the Inclusion of Pregnant Women in Clinical Trials (II)*, *in* WOMEN AND HEALTH RESEARCH, ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES, VOLUME 2, at 24 (Institute of Medicine 1999).

2998 *See* IRB Guidebook, *supra* note 411, at chapter VI.A.

2999 "[O]nly those research procedures that would be acceptable for a fetus going to term may be performed in anticipation of abortion." *Id. See also* J. Robertson, *supra* note 2996, at 22 (criticizing this strict stance introduced by the U.S. National Commission for the Protection of Human Subjects).

3000 *See, e.g.,* J. Robertson, *supra* note 2996, at 22; B. Steinbock, *supra* note 2997, at 24-25.

than minimal to both herself and her fetus.[3001] These risks must be commensurate to the expected benefits. Very minor benefits cannot justify significant risks to the fetus; once again, the principal purpose of this rule is to protect fetuses that may be borne with deformities. On the other hand, if the risky intervention necessarily kills the fetus (so that there is no risk that the fetus be borne injured), the risk should be accepted provided the woman derives a personal benefit. Since Swiss law now liberally allows abortion during the first trimester of pregnancy, the benefit for the woman could even be minor.[3002] However, after the first trimester, abortion is illegal unless the woman faces an important health risk that cannot be avoided otherwise.[3003]

Third, a woman may enroll in a therapeutic clinical trial aimed to benefit directly her fetus (or, more accurately, her future living child).[3004] For instance, the fetus requires an *in utero* medical treatment only available in the context of a clinical trial. In this hypothesis too, the risks may be important, but must be commensurate with the benefits expected. A question that may arise is whether a woman should be allowed to risk her life to save her fetus. In my view, the answer is yes if it is her choice.[3005] The autonomy of the competent patient must be respected.

In Switzerland, research entailing procedures involving *a pregnant woman* falls within the scope of the OClin. These three categories of trials should therefore be governed by the OClin, provided the other conditions of Articles 2 and 5 OClin are satisfied. The OClin does not set forth any specific requirement for such research. General rules must be obeyed.[3006]

U.S. law imposes various additional requirements intended to protect both the fetus and the freedom of the woman to decide whether to abort.[3007] For example, in trials that result in the fetus' abortion, the research team must not participate in the decision to abort[3008] and the method of abortion must be chosen independently of research considerations.[3009] The father of the fetus must give his own consent, in addition to that of the mother, when the trial aims to benefit the fetus.[3010]

3001 Many clinical trials still exclude pregnant women even though they hold the potential of a therapeutic benefit. It could be said that, at least indirectly, these women are encouraged to undergo an abortion first so as to then gain access to the clinical trial. *See, e.g.,* Lalezari et al., *supra* note 1591, at 2175-85.

3002 Article 119.2 of the Swiss Penal Code requires that a woman requesting an abortion be in a state of distress ("*détresse*," "*Notlage*," "*angustia*").

3003 Article 119.1 CP.

3004 *See* J. Robertson, *supra* note 2996, at 21.

3005 *See* B. Steinbock, *supra* note 2997, at 26.

3006 In particular, the information provided during the informed consent process must include what pregnant women would want to know (e.g., known reproductive toxicity in animals with this drug or with other drug with similar structure or pharmacological effects). If there is no relevant information at this stage, the fact should be explicitly disclosed. *See* Stanford (Women in Research), *supra* note 2991, at 3.

3007 *See* 45 C.F.R. §46.201 to §46.207 (Common Rule). See also the checklist prepared by the Vanderbilt University Institutional Review Board, on research on pregnant women, human fetuses, neonates, or fetal material (Mar. 5, 2004), at http://www.mc.vanderbilt.edu/irb/Forms/Form1116PregnantWomanSupplemental.doc.

3008 *See* 45 C.F.R. §46.204(i), (h) and (j) (Common Rule). *See also* NBAC (Stem cell report), *supra* note 322, at 46.

3009 *See* UCSD-SOPP, *supra* note 485, at 59. *See* 45 C.F.R. § 46.207 and § 46.208 (common rule).

3010 *See* 45 C.F.R. §46.204(e) (Common Rule). However, this consent is not necessary when the father "is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest." *Id.* On the reasons underlying the requirement of the father's consent, see IRB Guidebook, *supra* note 411, at Chapter VI.A.

8.5.2.2. Research on ex utero embryos

Research on embryos is not regulated by the OClin if performed ex utero (in vitro).[3011] Pursuant to Articles 3 and 5.1 OClin, the OClin applies to living persons and the embryo is not a living person. Of course, once a viable baby is delivered, the OClin applies and the specific protections of Article 55 LPTh must be followed. Starting in March 2005, the LRCS regulates research on embryos, specifically surplus/spare frozen embryos initially produced for in vitro fecundation.[3012] Apart from the requirement to get informed consent from the parents,[3013] the LRCS bears little resemblance to the OClin. However, the LRCS is to be further incorporated in the framework of the future law on research on human beings (see subsection 3.2.1. above).[3014]

Federal U.S. law does not (yet) regulate research on ex utero embryos that have never been implanted. Federal funding of embryonic research has been barred by presidential decree. Researchers doing purely private embryonic research are only constrained by State law.

U.S. federal law does regulate research on neonates (babies immediately after natural or artificial delivery).[3015] If the neonate is viable, then the rules governing research on children apply.[3016] If the neonate is either nonviable[3017] or of uncertain viability, special rules apply.[3018] When research is conducted on neonates of uncertain viability, it must entail either the prospect of a direct benefit (i.e., "enhancing the probability of survival of the neonate to the point of viability")[3019] or, if there are no direct benefits, minimal risk for the neonate; in that last hypothesis, three additional conditions must be met: The research must aim to develop "important biomedical knowledge," the subsidiarity requirement is met, and the research will not result in "added risk" to the neonate.[3020] Research performed on nonviable neonates is by definition nontherapeutic. It must satisfy the requirements mentioned above for nontherapeutic research on neonates of uncertain viability.[3021] Moreover, the neonate's "vital functions" should not be artificially maintained; conversely, the "research will not terminate" his heartbeat or respira-

---

3011 See the similar rules set by Article 2.2 of the COE Research Protocol. In the United States, see 45 C.F.R. § 46.201.

3012 *See supra* note 287 above. The LRCS does not apply to embryonic stem cells obtained following abortion of the embryo (see its Article 1.1).
See also in the European Union, the Commission's Proposal for a Council Decision amending decision 2002/834/REC on the specific programme for research, technological development and demonstration: "Integrating and strengthening the European research area" (July 9, 2003), at http://europa.eu.int/eur-lex/en/com/pdf/2003/com2003_0390en01.pdf.

3013 Article 5 LRCS.

3014 *See* DHA Embryo Report, *supra* note 330, at 3.

3015 *See* 45 C.F.R. § 46.205 on research on "neonates of uncertain viability" and "nonviable neonates" (Common Rule). *See also* SPRUMONT, *supra* note 16, at 149-52.

3016 *See* 45 C.F.R. § 46.205(d) (Common Rule).

3017 A nonviable fetus is "[a]n expelled or delivered fetus wich, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy." IRB Guidebook, *supra* note 411, at chapter VI.A.

3018 *See* 45 C.F.R. § 46.205(a), (b) and (c) (Common Rule).

3019 *See id.* § 46.205(b)(1)(i) (Common Rule).

3020 *See id.* § 46.205(b)(1)(ii) (Common Rule).

3021 *See id.* 46.205(c)(3) & (4) (Common Rule).

tion.[3022] The informed consent of one parent is necessary for research on a neonate of uncertain viability,[3023] whereas both parents must consent to research on a nonviable neonate.[3024]

8.5.2.3. Pregnancy registries

Given the risks in enrolling pregnant women in clinical trials, there is a dearth of information about the safety and efficacy of drugs used by this group of patients (see already subsection 8.5.2.1. above).[3025] The drug may endanger both the woman and her fetus; she may accidentally abort or her child may be born with deformities (teratogenicity*). The catastrophes of thalidomide and diethylstibestrol ("DES") illustrate these risks.[3026] Reproductive toxicity studies routinely conducted on *animals* are not always sufficient in uncovering all safety risks; moreover, they offer no assurance as to the efficacy of the drug on pregnant women.

For these reasons, almost all drug labels warn against use by pregnant women. They contain an exception when the physician explicitly orders the use of the drug. However, the physician is not in a better position to assess the safety and efficacy of a drug on his pregnant patient. The outcome is that many, if not most, sick pregnant women have to go untreated during their pregnancy. This damaging consequence also extends during the time the woman breastfeeds her child, since the mother's milk may contain traces of the drug which could harm her baby.

To gather information about drug effects on pregnant women, pregnancies registries have been set up.[3027] These registries operate in various manners and are not extensively regulated.[3028] In general, a pharmaceutical firm sets up a program allowing physicians to report – prospectively and/or retrospectively – the health outcome of their female patients who took a given (already-approved) drug during pregnancy. Other registries enable women to supply directly the information.[3029] These reports indicate not only how the pregnant woman fared but the possible consequences on her

---

3022 *See id.* § 46.205(c)(1) & (2) (Common Rule).

3023 *See id.* § 46.205(b)(2) (Common Rule).

3024 *See id.* § 46.205(c)(5) (Common Rule).

3025 The FDA has a ranking system about the risks that the use of a given drug entails during pregnancy. The ranking goes from A (no risk found, based on well-controlled clinical trials) to X (drugs that should never be used during pregnancy).

3026 Regarding DES, see for instance Brown v. the Superior Court of the City and County of San Francisco, 44 Cal. 3d 1049 (Cal. 1988).

3027 Registries have also been set up to collect information about cancer patients.
In the United States, see for example ECRI (chemotherapy), *supra* note 316, at 18.
In Switzerland, the Association of Swiss Cancer Registries ("ASRT") gathers information about cancer patients. See its website at http://www.asrt.ch. See also the law of the Canton of Ticino on the tumor registry (Legge sul registro dei tumori) of June 21, 1994, at
http://www.ti.ch/CAN/argomenti/legislaz/rleggi/rl/dati_rl/f/s/18b.htm.

3028 In the United States, the FDA has enacted a guideline on pregnancy registries; FDA Draft Guidance for Industry, Establishing Pregnancy Registries, (Aug.2002), p.1, at
http://www.fda.gov/cder/guidance/3626fnl.pdf.

3029 *See, e.g.,* CDC, Pregnancy Outcomes Following Systemic Prenatal Acyclovir Exposure – June 1, 1984- June 30, 1993, 42(41) MMWR 806-809 (Oct. 22, 1993), at
http://www.cdc.gov/mmwr/preview/mmwrhtml/00022071.htm; Massachusetts General Hospital, Antiepileptic Drug Pregnancy Registry, About the Study, at http://massgeneral.org/aed/providers.htm.

baby both during pregnancy and afterwards. It compares these data with the outcome of non-pregnant women and babies born to women who did not take the drug.[3030]

U.S. pregnancy registries are generally authorized by an IRB. However, patients do not always provide written informed consent.[3031] Waiver of informed consent is permissible when the risks arising from participation are minor. For example, the choice of treatment remains a decision taken jointly by the patient and her physician and reports to the register do not disclose the name of the patient.

These studies based on pregnancy registries differ from clinical trials in several ways. There is no control, since the use of a placebo* would be unethical and the use of an active comparator* also problematic. As a result, there is no point either in masking (blinding) or in randomizing. The fact that there is no formal control group to determine whether women using the drug are faring better or worse than women not using it makes it hard to draw conclusions; the sponsor must weigh its register findings (e.g., percentage of women with disease X treated with drug Y having a miscarriage) against available statistics that may provide only an imprecise point of comparison (e.g., statistics of women having miscarriage).

In the United States, there were over 15 such registries in place as of June-July 2003.[3032] To my knowledge, no such registry exists in Switzerland.

8.5.3. Terminally-ill patients

Other vulnerable groups include terminally-ill patients as well as those suffering from an untreatable and eventually fatal illness.[3033] Common examples are terminal AIDS and cancer patients. The fact that existing treatments have failed puts these subjects in a particularly difficult situation: They have few alternative but to participate in the proposed clinical trial.[3034] Moreover, severe and protracted illnesses typically place a heavy financial burden on these patients and their families, especially in countries like the United States where health care coverage is not universal; thus, financial concerns may induce patients to enroll in clinical trials offering free health care.[3035]

The Helsinki Declaration invites investigators to pay special attention to subjects who are "in a dependent relationship with the physician."[3036] Such subjects could give

---

3030 *See, e.g.,* FDA, Office of Women's Health, Information About Pregnancy Registries, (Aug. 23, 2002), at http://www.fda.gov/womens/registries/general.html.

3031 Compare The Antiretroviral Pregnancy Registry, at http://www.apregistry.com/who.htm and the Merck's Pregnancy registry, at http://www.merckpregnancyregistries.com/.

3032 *See* FDA, Office of Women's Health, List of Pregnancy Registries, at http://www.fda.gov/womens/registries/registries.html.

3033 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 13 (commentary).

3034 *See* L. K. Altman, *note* 2495, at C3; Melina Gattellari et al., *When the Treatment Goal Is Not Cure: Are Cancer Patients Equipped to Make Informed Decisions?*, 20 JOURNAL OF CLINICAL ONCOLOGY 505-13 (Jan. 15, 2002) (studying, outside the clinical trial setting, the process by which Australian cancer patients were explained treatment alternatives).

3035 *See* Grunberg & Cefalu, *supra* note 1605, at 1386-1388.

3036 *See* paragraph 23 Helsinki Declaration.

their consent just to please their physician. The Declaration does not clarify what exactly is meant by a "dependent relationship."

8.5.4. Seniors

Seniors are considered as a vulnerable group, because their frequently diminished mental and physical capacities have the effect of limiting their choices, including the choice not to participate in research.[3037] Seniors living in medicalized homes may also feel pressured into giving their consent. Cultural traits of elderly patients may place them at risk (e.g., seniors' blind trust in doctors).[3038] Seniors may also suffer from several diseases concomitantly and take a variety of drugs concurrently, circumstances which are likely to make their treatment more difficult and to impede the conduct of clinical trials.[3039]

Seniors (aged 65 or older) represent about 15% of the Swiss population,[3040] about 16% of the E.U. population,[3041] and 12.4% of the U.S. population.[3042] Yet, studies have found that seniors are often underrepresented in clinical trials.[3043] "The reasons include misconceptions about the benefits of enrollment in clinical trials for older patients on the part of the patients themselves, their family members, or their physicians; stringent eligibility criteria; coexisting medical conditions; and logistic barriers."[3044] It is true that seniors are frailer and less tolerant to medical treatments.[3045] Hence, they do face greater risks than younger patients when participating in clinical trials or when receiving traditional treatment. Nonetheless, seniors may benefit from enrollment in clinical trials, especially when they are not responding to available approved drugs. Thus, exclusion amounts to age discrimination when primary doctors and sponsors systematically decline to refer or enroll older patients.[3046]

The ICH has adopted a guideline on clinical studies on geriatric populations.[3047] This Guideline has so far not been integrated into Swiss legislation.[3048] However, it re-

---

3037 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 13 (commentary).

3038 *See* Nicole Vogt et al., *supra* note 2676, *at* 191-92 (1995).

3039 *See id.* at 192-93.

3040 *See* Press Release, (Swiss) Federal Statistical Office, Population census 2000, (Mar. 17, 2003), from http://www.bfs.admin.ch/bfs/portal/fr/index/themen/volkszaehlung/uebersicht/blank/medienmitteilungen.Document.24844.html.

3041 *See* EuroStat, EU enlargement, The new EU of 25 compared to EU15, (Mar. 11, 2004) at http://www.eubusiness.com/topics/East_Europe/enlargement-statistics-eurostat-1-11032004-EN-AP-EN.pdf

3042 *See* U.S. Census Bureau, *supra* note 29. *See also supra* note 2736.

3043 *See* Laura F. Hutchins et al., *Underrepresentation of Patients 65 Years of Age or Older in Cancer-Treatment Trials*, 341 NEW. ENG. J. MED. 2061-2067 (1999), at http://content.nejm.org/cgi/reprint/341/27/2061.pdf; Vogt et al., *supra* note 2676, at 186.

3044 *See* Hutchins et al., *supra* note 3043, at 2065.

3045 *Id.*

3046 "In a survey of American oncologists, 80 percent of the respondents agreed with published data showing that patients have better outcomes when they receive treatment in clinical trials, but 50 percent indicated that they declare patients unsuitable for clinical trials on the basis of age alone." *Id.* See *also* T. C. Chalmers, *supra* note 2311, at 865.

3047 ICH Harmonized tripartite guideline, Studies in Support of Special Populations: Geriatrics, E7, Step 4 of ICH Process, June 24, 1993, from http://www.ich.org/cache/compo/475-272-1.html#E7 [hereinafter ICH E7].

mains a helpful guide as to how such trials should be designed. The Guideline starts by repeating the general principle that trials should be conducted on subjects who match the characteristics of the patient population(s) likely to make broad use of the future drug. This implies that the sponsor must first determine which age groups will be using its drug.

Although geriatric patients are defined as those aged 65 and above, the Guidance stresses the importance of including patients over the age of 75, because their health status is not necessary equivalent to that of "younger" seniors.

The aim of the ICH Guideline is to gather information on the efficacy and safety of the tested compound for this complex patient population. Geriatric patients present difficulties because, for example, they tend to suffer from more than one medical condition (e.g., hypertension and high cholesterol). Consequently, they take several medications that they cannot stop even if enrolled in a clinical trial.

When the drug is intended for use by seniors, the ICH Guideline recommends that geriatric patients be incorporated at least in phase III studies. While seniors rarely participate in phase I trials, they can be included in phase II trials if the sponsor finds it helpful. The sponsor can choose between conducting a specific study on geriatric populations or to enroll seniors along with other research subjects in a broader clinical trial. This choice is dictated by the characteristics of the drug under review. For instance, when a medical risk is expected to occur chiefly in elderly populations (e.g., interaction with another drug often administered to elderly patients, effects on another medical conditions affecting this age group such as osteoporosis), a specific study comprising mostly elderly subjects may be more appropriate. When the purpose is to determine whether the efficacy and safety profile of the drug is the same irrespective of the age group, subjects of different ages can be enrolled in a single large clinical trial.[3049]

The number of geriatric subjects enrolled will depend on the expected prevalence of use of the drug in that population. If the drug is to be used mainly by the elderly, such as a treatment against Alzheimer, most of the enrolled subjects should accordingly be seniors. If the drug is to be used by both elderly patients and non-geriatric patients, the ICH recommends having at least 100 geriatric subjects enrolled in the phase III trial. These subjects should be matched against younger subjects in order to assess whether the studied compound achieves different results depending on the characteristics of the tested populations. For instance, the drug may be less effective when used by seniors or the dosage may need to be reduced. Similarly, there may be more or different adverse events when the drug is taken by elderly patients.

The ICH Guideline recommends that sponsors focus on age-related differences with respect to the way the drug is absorbed, distributed, metabolized and excreted ("ADME"). Since these pharmacokinetic characteristics relate to the liver and renal functions of patients, results in old and young patients can differ significantly. A pharmacokinetic study of age-related differences can be conducted as a phase I trial on healthy patients or be incorporated in a broader study of subjects suffering from the disease. The type of study will depend on how large the age-related difference is. When

---

[3048] Switzerland is not obliged to ratify ICH guidelines, but it usually abides by them to maintain euro-compatibility.

[3049] *See also* chapter 2 of ICH E12A.

large differences are identified or suspected, the ICH recommends testing different doses of the compound (a "multiple-dose PK study") in a larger set of subjects.

The ICH points out to certain classes of drugs which generally necessitate specific pharmacodynamic studies. Psychoactive, sedative, hypnotic drugs are among those which call for pharmacodynamic studies. Moreover, when pharmacokinetic studies cannot explain age-related differences, the ICH recommends performing pharmacodynamic studies (an analysis of *how* the tested drug produces its effect).

8.5.5. Indigent people

Poor patients have long been exploited in clinical research.[3050] In the past, new and risky experiments were rarely tried on wealthy people first, but rather on patients seeking medical care from charity hospitals. As seen in the 1993 John Hopkins University lead experiment (see subsection 2.3.1.4. above), poor people continue to face greater risks at the hand of scientists. In almost all countries, poverty goes hand in hand with poor health, lower education level, minority and/or alien status. In the United States, poverty is also linked to lack of medical insurance coverage.[3051] Indigent patients may accept enrollment in clinical trials because they are more easily manipulated by investigators or recruiting agencies (e.g., CROs). They may be induced to give their consent to cash the financial "reward" offered by the sponsor (on that issue, see subsection 8.6.4.1. below). They may accept in order to receive health care that they would not have had otherwise.[3052] These three motives are unacceptable from an ethical perspective that values free and informed consent.

From the point of view of sponsors, poor patients may be easier to enroll. Wealthy patients are less inclined to accept risks, especially if they can access the investigational drug in another way (e.g., a compassionate use programs, a purchase made abroad). Patients in these programs enjoy the benefits of the experimental drug without the risk of being randomized to the control group and without having to undergo the additional medical procedures characteristic of the clinical trial. Statistics also show that rich and educated persons are less exposed to practically all diseases.[3053]

3050 *See* paragraph 8 Helsinki Declaration.

3051 *See* National Center for Health Statistics ("NCHS") at HHS, Health, United States (2004), at http://www.cdc.gov/nchs/data/hus/hus04acc.pdf. ("In 2001, the percent of persons reporting their health status as fair or poor was more than three times as high for persons living below the poverty level as for those with family income more than twice the poverty level (21 percent and 6 percent, age adjusted)." *Id.* at 9.

3052 In the United States, about 15% of the population has no health insurance. *See* NCHS (Health Statistics), *supra* note 3051, at 13. "In 2001, 11 percent of children under 18 years of age had no health insurance coverage." *Id.*

3053 See for Switzerland OFFICE FEDERAL DE LA SANTÉ PUBLIQUE [FEDERAL OFFICE FOR PUBLIC HEALTH], LA SANTÉ EN SUISSE, 13, 31, 41-42, 64-65, 75, 83-84, 150, 159-160, 178, 235-36, 252, 264-65, 279-80, 353-54, 395-97 (Payot Lausanne 1993) (showing that, with a few exceptions, rich and educated persons are less exposed to disease factors, adopt better health habits and suffer from less diseases or medical conditions). *See also* FELIX GUTZWILLER & OLIVIER JEANNERET, MÉDECINE SOCIALE ET PREVENTIVE, SANTÉ PUBLIQUE, at 276, 307-308, 323, 464-65 (Hans Huber 1996). See also for depression in the United States, Walter F. Steward et al., *Cost of Lost Productive Work Time Among US Workers with Depression*, 289 JAMA 3135, at 3138 (June 17, 2003), at http://jama.ama-assn.org/cgi/reprint/289/23/3135.pdf.

Few solutions exist to address this possible inequality. Ethical guidelines insist that subjects must be selected fairly from all segments of the population (see subsections 8.1.3. and 8.5. above). Ethics committees scrutinize payments made to subjects to make sure that they do not represent an excessive lure. The law requires that oral and written information be provided in a language that will be easily understood even by uneducated prospective subjects.

8.5.6. Foreigners

There is no legal prohibition against enrolling foreigners, whether the latter already live in the research site country or are brought there – as in the VanTx affair (see subsection 2.2.2. above). However, such a practice poses several problems.

First, these subjects are likely to have difficulties in fully understanding the research. The oral and written information that they receive should be accurately translated. The investigator must make sure that the translation not only matches the original version, but also takes into consideration possible cultural differences that would make a purely literal translation misleading.[3054] Foreign subjects who do not speak the language of the investigator must be able to direct their questions to someone knowledgeable who can answer them in their own language.[3055]

Second, these subjects may be particularly vulnerable, especially if they are also poor, uneducated and without residence or work permit. Of course, if a rich American patient decides to come to Switzerland to participate in a phase III clinical trial, the risks are very different than if a poor but healthy Estonian is enrolled in a phase I trial. Payments or reimbursements of expenses in Swiss currency and adapted to Swiss standards of living appear appreciably more generous to foreign subjects living in poorer countries.[3056]

Third, organizing the medical follow-up of subjects once the study is completed is more difficult if these subjects live in one or more foreign countries.[3057] In the VanTx case, the CRO had completely disregarded this obligation. When the Swiss authorities finally caught up with VanTx, they were unable to locate the subjects to offer them medical care.[3058]

Fourth, from both an ethical and a political standpoint, importing foreign research subjects is contemptible. There is little rationale for this "transfer" apart from the distasteful fact that local subjects are not willing to bear the perceived risks of research, although they are most likely to reap the ensuing benefits. Governments of these foreign countries may rightfully resent the fact that richer countries are drawing their citizens, usually the most vulnerable ones among them, to participate in research

3054 *See* VanTx Report, *supra* note 148, at 19.

3055 *See id.* at 19.

3056 *See id.* at 32.

3057 *See id.* at 21 (also recommending that the follow-up be organized in the country of residence of the subjects, and not at the Swiss research site).

3058 The companies that had sponsored the clinical trials carried out by VanTx were finally convinced to extend free medical care to the Estonian research subjects. *See* VanTx Report, *supra* note 148, at 9-10.

abroad.[3059] Although the VanTx Working Group observed that the "importation" of subjects was a practice which is increasingly widespread,[3060] it is likely that the VanTx scandal will slow it down considerably, both in Switzerland and in neighboring countries.

8.5.7. Minorities

In the past, minorities, especially blacks, have often been abused in clinical trials.[3061] In the United States, slaves were sold or lent for experimental use.[3062] The consequence is that minorities today are *less likely* to enroll in clinical trials.[3063] Matching minorities' lower enrollment rate in clinical trials is their lower access to medical care.[3064] This is partially attributed to distrust of medical science, shaped by tragic incidents such as the Tuskegee studies.[3065] Moreover, traveling to research sites may pose problems to poor (minority) patients who have to struggle with work and family obligations.[3066] Similarly, these patients (in the United States) may lack insurance coverage that would pay for part of the clinical trial costs (see also subsection 8.6.4.2.3. below).[3067] Other explanations include the lower number of minority physicians trained and hired as investigators.[3068]

From an ethical standpoint, trials that fail to enroll a representative sample of the patient population, including minorities, can be unfair. These minorities may be denied

---

3059 The problems are less burning when subjects come from border countries, in part because there are already frequent and multiple exchanges between the two countries. These subjects also speak the same language and share a very similar culture, if not background.

3060 *See* VanTx Report, *supra* note 148, at 32.

3061 See subsection 2.3.1.1. above on the Tuskegee syphilis study.
See also In Re Cincinnati, 874 F. Supp. 796 (where the cancer patients who were subjected to dangerous radiation experiments were "primarily indigent, poorly educated, and of lower than average intelligence. A majority of the patients selected were African-Americans." *Id.* at 803).

3062 *See* Vanessa Northington Gamble, *Under the Shadow of Tuskegee, African Americans and Health Care*, *reprinted in* TUSKEGEE'S TRUTHS, RETHINKING THE TUSKEGEE SYPHILIS STUDY 431, at 432 (Ed. Reverby, 2000). *See also* LEDERER, *supra* note 54, at 45 and 115-16; GUILLOD, *supra* note 77, at 31.

3063 *See* GAO (Factors Affect), *supra* note 877, at 14; T. E. King, *supra* note 2311, at 1400-402 ("Breaches of trust on the part of the patient or the physician appear to be a major factor contributing to disparities in the care provided to members of racial and ethnic minority groups." *Id.* at 1401.); Allen L. Gifford et al., *supra* note 2299, at 1373-1382 (finding lower enrollment rates of black and hispanic people).
This might, however, be changing: a NIH survey (of NIH-funded phase III trials) found that black patients are the minority group *more likely* to enroll in clinical trials. *See* NIH (Monitoring Women), *supra* note 2985, at 13.

3064 In the United States, poor minority patients often receive health care from the emergency departments of hospitals. *See* Wafaa El-Sadr & Linnea Capps, *The challenge of minority recruitment in clinical trials for AIDS*, 267 JAMA 954 (Feb. 19, 1992).

3065 *See* Allen L. Gifford et al., *supra* note 2299, at 1379; Tuskegee Syphilis Study Legacy Committee, *supra* note 193; SPRUMONT, *supra* note 16, at 16.

3066 *See* El-Sadr & Linnea Capps, *supra* note 3064, at 954.

3067 *See* NCHS (Health Statistics), *supra* note 3051, at 13.

3068 *See, e.g.*, NIH 1997 Report, *supra* note 55, at section IV.(3); Mitka (Help), *supra* note 2269, at 1568.
See generally Lisa A. Cooper et al., *Patient-Centered Communication, Ratings of Care, and Concordance of patient and Physician Race*, 139 ANN. INTERN. MED. 907-16 (Dec. 2, 2003), at http://www.annals.org/cgi/reprint/139/11/907, (finding that patients are more satisfied when they consult a physician of their own race, although the "quality" of the visit is essentially the same). See also the editorial by Tom Delbanco, *Moving beyond Black and White*, 139 ANN. INTERN. MED. 952-53 (Dec. 2, 2003), at http://www.annals.org/cgi/reprint/139/11/952.

the benefits of early access to promising experimental treatments.[3069] Alternatively, majority ethnic groups may be treated unfairly because they contribute "beyond their share" to the progress of medicine.

8.5.8. Subjects in developing countries

In subsection 4.5.3. above, I argued that ethical standards should be higher in developing than in developed countries: Subjects in developing countries should be granted more, not less, rights. Invoking their lower access to health care to deny them benefits commonly available to subjects in developed country is utterly illegitimate; consequently, placebo-controlled trials are possible only under very limited circumstances (see subsection 6.3.5.2. above).

The revised Helsinki Declaration further requires that populations among which clinical studies take place must stand to *benefit* from the research.[3070] This limits the *kind of trials* that can ethically be conducted in developing countries. There should be an objective justification for conducting the trial with this particular subject population.[3071] Customary justifications relate to the disease being studied; for instance, the disease must be specific to, or most prevalent in, the selected country.[3072] If the disease is equally common in developed countries, it should be studied there. Similarly, the trial must be designed so as to address the specific needs of the subject population.[3073] For instance, the treatment under study must be tailored to benefit a specific population; a study of a one-pill drug regimen would be admissible where multiple pill schedules are not feasible. Conversely, it would be unethical to study in a developing country a drug which will only be available in industrialized countries (e.g., because it is too expensive, because its administration requires an infrastructure that developing countries lack).

The CIOMS Guidelines ask that, not only the subject population, but also the *community* in which the study takes place derive some benefits from it.[3074] This can be achieved by *capacity building* measures (e.g., the training of local investigators and nurses)[3075] or by donations (e.g., medical equipment is left in the host country, drugs are

---

3069 Even after the treatment is approved, there may not be enough information as to its efficacy for these minority groups if the trial was underpowered for this specific subpopulation.

3070 *See* paragraph 19 Helsinki Declaration.

3071 *See* EGE, *supra* note 110, at 16. *See* Shapiro & Meslin, *supra* note 245, at 139 (asking that clinical trials be "responsive to the host country's health needs"). *See* paragraph 19 Helsinki Declaration; CIOMS 2002 Guidelines, *supra* note 105, at Guideline 10 (commentary). See COE Explanatory Report, *supra* note 417, at paragraph 30, page 7. In the United States, see for instance AMA, Ethical Considerations in International Research, Policy E-2.077, at point (4), at http://www.ama-assn.org/ama/pub/category/8426.html. But regarding the difficulties related to this "responsiveness condition," see Levine (Helsinki), *supra* note 1248, at 533-34.

3072 *See* NBAC (Developing), *supra* note 254, at 6, and also at 20.

3073 "According to the principle of beneficence and justice, only research that is responsive to these needs [i.e., the health needs of the population being studied] can offer relevant benefits to the population." *Id.* at 7-8.

3074 "[T]he ethical requirement of "responsiveness" can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population." CIOMS 2002 Guidelines, *supra* note 105, at Guideline 10 (commentary).

3075 "External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research. Before undertaking research in a host country with little or no such capacity, external sponsors and investigators should include in the re-

offered at preferential price or their patents are licensed to a local manufacturer, a clinic is built). Thus, clinical trials should aim to improve local health and economic conditions.

These recommendations are controversial.[3076] Commentators have observed that they could have the opposite and unwanted consequence of discouraging research in developing countries to the extent that they force sponsors to assume the significant additional expense of providing long-term treatment and health care facilities to local populations. If this responsibility does not rest with the sponsor, but with the local government, then research may become impossible as the resources to build upon the findings of the clinical trial may be lacking. PhRMA has remarked that a strict interpretation of this rule could prohibit clinical trials on healthy volunteers since these trials generate no benefit for the community.[3077] PhRMA has reacted by recommending broad consultation by investigators and sponsors "with other relevant parties such as local health authorities and host governments to address issues associated with the conduct of the proposed study and its follow-up."[3078]

If strictly interpreted, these prerequisites could indeed bar clinical trials that could nonetheless benefit a small subgroup of the population (e.g., a clinical trial of cardiovascular diseases in urban cities in South Africa). If the subject himself derives a personal therapeutic benefit, is it necessary for the subject also to be representative of the local population? Similarly, one could wonder whether these high ethical standards are indispensable when research subjects are part of a sophisticated elite in developing countries. For example, a study of depression in Jakarta could benefit depressed patients, even though most of the Indonesian population surely battles with more serious diseases.[3079] Therefore, it would be reasonable to give greater weight to the fact that enrolled subjects may belong to a vulnerable category (e.g., poor, uneducated, very sick patients) than simply to the fact that they live in a developing country.

Another ethical safeguard recommended for trials in developing countries is the *dual ethics committee review*.[3080] Both the REC in the host country and in the sponsoring country should give their favorable opinion.[3081] RECs in developing countries are not always as sophisticated as those in developed countries. The expertise of their members

---

search protocol a plan that specifies the contribution they will make. The amount of capacity building reasonably expected should be proportional to the magnitude of the research project." CIOMS 2002 Guidelines, *supra* note 105, at Guideline 20 (commentary). *See also* NBAC (Developing), *supra* note 254, at 89-91.

3076 The World Medical Association ("WMA") has prepared a note of clarification on paragraph 19. *See* WMA, Documentation for the Preparation of Note of Clarification on Paragraph 19 of the Revised Declaration of Helsinki, at http://www.wma.net/e/ethicsunit/pdf/preparation_clarification_paragraph19.pdf.

3077 *Id.* at 3.

3078 PhRMA (Principles on Clinical Trials), *supra* note 902, at 12.

3079 *But see* Bolton et al., *supra* note 2625, at 3122-23.

3080 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 3; NBAC (Developing), *supra* note 254, at 82-85. *See also* Shapiro & Meslin, *supra* note 245, at 141; Kass & Hyder, *supra* note 822, at B-7 to B-8.
In France, see CCNE N°41, *supra* note 853, at 1.
In the United States, see for instance AMA, Policy E-2.077, *supra* note 3071, at point (1).
See also Article 29 COE Research Protocol (instructing "[s]ponsors or researchers within the jurisdiction of a Party to this Protocol" who conduct trials in countries not party to the Protocol to nonetheless abide by its rule).

3081 This rule was breached in the recent scandal related to an FDA-financed Tanzanian plague study. *See* M. Enserink, *African Study Raises Ethical Issues*, 302 SCIENCE 2056 (Dec. 19, 2003).

may be minimal and they may be subject to political or economic pressure.[3082] Moreover, a survey found that a quarter of clinical trials hosted by developing countries are not submitted to local RECs.[3083] Therefore, having a REC in the developed (sponsor) country make its own review contributes to limiting the risks incurred by subjects. Conversely, RECs in developed countries may be unaware of the local circumstances in the host country. Thus, the review process by the host REC should guarantee that these local factors (e.g., different culture, different perceptions of risk, familiarity with the research facilities) are taken into account. Finally, all participants should take responsibility to structure the design as well as the aftermath of the trial so that the host country, its population and above all the enrolled subjects are left better off. Early negotiations should be engaged with the local authorities or representatives, whose inputs should be duly considered.[3084] Specific pledges should be agreed beforehand.

8.6. Other rights of research subjects

8.6.1. Right to receive proper health care

Even though the investigator must abide by the protocol and conform to the protocol's procedures, she assumes responsibility for the health and well-being of subjects.[3085] She must ensure that the subjects' health is duly protected. She must adapt the medical treatment received by a subject if the latter seems to be responding badly to the ongoing treatment. The investigator should inform the subject's primary care doctor if the subject has no objection.[3086] This allows the doctor to take into account the experimental treatment received by the subject when making subsequent medical care decisions for his patient (see subsection 8.3.3.6. above).

In practice, the investigator's duty to supervise subjects' health can be tricky to manage. With so many drug clinical trials being placebo-controlled, randomized and double-blinded, the investigator does not know if the subject's medical problem is due to the investigational compound, to the placebo, to the disease, or to another reason (e.g., nosocomial infection in the hospital). The protocol only allows the investigator to break the blind in case of serious health emergencies. Conversely, not-too-serious adverse reactions are tolerated[3087] and do not necessarily warrant a change in the treatment. The line to be drawn is hence very fine. Of course, no subject should be left to die or to suffer from permanent injury, but side effects are common and bound to happen.

3082 *See* NBAC (Developing), *supra* note 254, at 13.

3083 *See* Nicky Lewis, *Clinical trials still face gaps in ethical review*, SCIDEV.NET, Mar. 1, 2004, at http://www.scidev.net/news/index.cfm?fuseaction=readnews&itemid=1252&language=1. This may have changed since a later study found that 81% of reports of trials from sub-Saharan Africa against HIV, tuberculosis, malaria mentioned ethical committee review. "Of these, all had approval from institutions within the host (African) country; 64% additionally had approval from institutions in non-African sponsoring countries. Trials with both local and nonlocal review were more likely to offer care that did not conform to clinical guidelines on the specified items than trials with local review only," Kent et al., *supra* note 1672, at 240.

3084 *See* NBAC (Developing), *supra* note 254, at 30.

3085 *See* section 4.3.1 (p.13) of ICH E6.

3086 *See id.* See *also* WHO (Operational Guidelines), *supra* note 1379, at point 6.2.3.7 (p.11).

3087 *See* SPRUMONT, *supra* note 16, at 34.

Moreover, the investigator cannot remedy all side effects lest the curative treatment masks the occurrence or the severity of the drug's adverse reactions.

The protocol can assist the investigator by specifying circumstances where the treatment with the investigational drug must be stopped and the subject withdrawn. Thus, a clinical trial might say that a fever of 40° C lasting for 6 hours is a cause for withdrawal.

Yet, a protocol cannot foresee every possible harmful event. The investigator has to exercise caution to balance two partly competing interests: On the one hand, the sponsor's interest to see its trial completed strictly according to protocol and with a maximum number of subjects for statistical significance, and, on the other hand, the subject's interest to receive the best therapeutic treatment. As stated above, the investigator is skating on thin ice.

Moreover, the judgment of what constitutes a serious side effect is permanently evolving. Fifty years ago, subjects' consent was at times interpreted as a green light to do whatever was best for science, including deliberately hurting them. Ten years ago, clinical trials with inert placebo were the norm, even if subjects went untreated for long periods. Today, the use of inert placebos must be properly justified taking into account the risks and inconveniences borne by subjects. While it is (still ?) admissible to test a drug again the common cold against a placebo (because the common cold does not last long, is not too painful and leaves no permanent damage), many clinical trials have had to forego placebos.[3088] For example, the use of placebo in studies of depression is viewed as a borderline case. The mental anguish caused by depression might be enough to call for the use of an active comparator. From a scientific standpoint, the tension is plain. Depression is a good case in point since inert placebos reaches a therapeutic score almost equivalent to that of an antidepressant.[3089] If all clinical trials of depression were done with active comparators instead of placebos, a myriad of drugs could end up being approved, even though none is more effective than a sugar pill.[3090]

8.6.2. Follow-up

8.6.2.1. Debriefing

Subjects can ask questions throughout the trial, however some answers cannot be given immediately (e.g., to which group they have been randomized?) or are yet unknown (e.g., is the investigational treatment efficacious?). Following trial completion, all answers become available.

Subjects should first be told whether they received the investigational compound or the comparator product.[3091] Though this rule seems obvious, a study found that re-

---

3088 *See* subsection 6.3.5.2. above.

3089 *See, e.g.,* Jureidini et al., *supra* note 1575, at 880 (focusing on pediatric subject population).

3090 When, in the 1970s and 1980s, many countries started going through their list of approved drugs to verify their efficacy, they were forced to admit that about up to 80% of drugs that were – at the time – believed to be effective were no better than a placebo. *See* subsection 4.1.1.2.1. above.

3091 *See* point C.1 Belmont report, *supra* note 61.

search subjects are not always told to which treatment arm they were assigned.[3092] Except when the subject has explicitly requested not to be informed,[3093] debriefing should be the rule. Although Swiss law does not mention debriefing, ethical principles demand it.[3094]

Subjects should be told how their condition improved (or worsened) with either the tested drug or the comparator product. They should be informed of the study results at least in general terms (e.g., whether the scientific question stated in the consent form document was answered positively or negatively). Results should be communicated even if they do not call for a change in subjects' current treatment or even if the subject was since then fully cured.[3095] Subjects can also develop a legitimate curiosity as to the efficacy of the treatment. They may want to know if the clinical trial was useful and hence if their participation was "worth it," at least with respect to scientific or medical progress. Ideally, the investigator should give a summary in plain language of the study report; subjects may be even be able and desirous to read the full report. In any case, the investigator should give at least a basic explanation as to the outcome of the clinical study. If a publication is planned, the investigator should signal it to subjects. It should be common courtesy to give subjects basic information on the trial's results before these are published. PhRMA encourages investigators to share with subjects a summary of the study results.[3096]

Debriefing can be a sensitive issue, in particular when the subject is told that his condition improved thanks only to the placebo.[3097] The subject may infer that his symptoms were psychological or psychosomatic.[3098] To minimize the disarray caused by this news, investigators should do their best to explain what the placebo is. If subjects realize that the placebo effect is a significant influence on all medical treatments, their anguish and possible guilt will be assuaged.

Subjects also need to know how they should continue their treatments: Should they take another approved product? Are they considered cured? The investigator should

---

3092 "Of these [107 investigators surveyed], 45% informed either all or most participants in their treatment allocation, and 55% did not inform any of their participants or informed only those who asked. … The most common reasons [not to inform] were that they [the investigators] never considered this option (21 investigators [out of 53]) or that they wanted to avoid biasing results at study follow-up (12 investigators), often referring to studies that were still ongoing. Eight investigators wanted to avoid extra costs and six wanted to avoid both extra costs and administrative work. Six investigators believed that participants did not need to know; two explained that this was because of the crossover nature of the study." Di Blasi et al., *supra* note 1462, at 1330-31.

3093 *See* Ann H. Partridge & Eric P. Winer, *Informing clinical trial participants about study results*, 288 JAMA 363 (July 17, 2002), at http://jama.ama-assn.org/cgi/reprint/288/3/363.pdf. *See also* Article 10.2. Biomedicine Convention.

3094 "At a minimum, trial results should be offered as a reward, acknowledgment, or sign of appreciation for involvement in research, as altruistic motives often influence an individual's decision to participate in a clinical trial." Partridge & Winer, *supra* note 3093. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 5, point 7.

3095 *See* Partridge & Winer, *supra* note 3093. *See also* Article 28.2 COE Research Protocol.

3096 *See* PhRMA (Principles on Clinical Trials), *supra* note 902, at 23.

3097 *See* Di Blasi, *supra* note 1462, at 1329.

3098 "A recent trial evaluating the effects of antidepressants found that when placebo responders were told that they were receiving a placebo their mood deteriorated. Within a month 70% of the patients needed antidepressants." Di Blasi, *supra* note 1462, at 1331 (mentioning however another study where the rate of relapse was similar in both arms of the trial).

explain to each subject what his best alternatives now are (see also subsection 8.6.2.3. below).

Debriefing can also be useful to improve the organization of the next trials. The investigator and perhaps ethics committee's members could ask subjects questions as to what improvements they would have liked in the organization and management of the study. Subjects could be given questionnaire to rate the clinical trial. This would also be one of last occasions to detect deviations from GCP or from ethical principles.

8.6.2.2. Right to follow-up information and care

Negative effects of a drug may surface weeks, months or years after the end of a clinical trial. For example, an autopsy of a former research subject deceased after the end of the trial may reveal unexpected damage attributable to the tested drug. Or the side effects may only affect the subjects' progeny. Hence, regardless of the period elapsed since trial completion, subjects must be able to report such effects and obtain the relevant information. Accordingly, subjects are given the name of contact person whom they can reach at any time. This person or entity is affiliated with either the sponsor or the investigator. If the side effect is indeed due to the drug, Swiss subjects have the right to receive complimentary treatment.[3099] If the investigator or the institution does not pick up the bill, the subject has a reimbursement claim against the sponsor or its insurance company (see subsection 8.6.5. below).[3100]

Some protocols integrate post-completion follow-up supervision, typically achieved by contacting subjects periodically (e.g., twice a year for six years) to check whether they have had any adverse reaction.

Additionally, subjects should be informed of any newly available information regarding the risks of the experimental drug, especially if it is not marketed as an approved product. In the case of DES (diethylstilbestrol), the risks for subjects' offspring were uncovered only some twenty years after the trial. The sponsor was however criticized and sued for having waited another four years before informing the research participants.[3101] A U.S. Court found that both the institution that led the trial and the manufacturer had a duty to inform former subjects.[3102]

The question arises whether the ethics committee and the authorities should also be informed of new information gathered *after the trial's end*. Article 20.1 OClin only refers to new facts occurring *during* the clinical trial, thus apparently excluding such obligation once the trial has ended (see subsection 9.1.2.2. below). The wording of Article 22.1 OClin is more ambiguous: It requires the investigator to report all serious adverse events (including those that may not have been caused by the experimental product) to

---

3099 Article 7.1 OClin. On liability issues, see subsection 8.6.5. below. In contrast, U.S. regulations do not force sponsors to indemnify or treat injured subjects.

3100 Article 7.2 OClin.

3101 *See Mink*, 460 F. Supp.713.

3102 "When the University hospital became aware, or should have become aware, of facts which would induce a reasonable physician under the same circumstances to warn patients of the risks involved in treatment, a duty to notify arose. The fact the knowledge of the risk was obtained after the patient was treated does not alter the obligation. … Defendant Lilly has a continuing obligation as a manufacturer of drugs to warn of risks inherent in its drugs." *Mink*, 460 F. Supp. 720.

the sponsor.[3103] Yet, the sentence ends with the words "during clinical trials of pharmaceuticals" ("*lors d'essais cliniques de médicaments*") possibly suggesting that this obligation ends with the completion of the trial. Article 23 paragraph 1 and 2 contains no temporal limitation. However, paragraph 4 also limits the yearly reporting obligations to the duration of the clinical trial. Taken together, Articles 20 to 23 suggest that reporting obligations to the ethics committees and to Swissmedic come to an end with the trial itself. Such a rule is clearly unsatisfactory.[3104] The OClin should have included a separate provision on post-completion follow-up obligations.[3105]

Another related question is whether interim data generated in the course of the trial should, not only be disclosed to subjects, but also published before the formal completion of the trial (see also subsection 10.4.1.2. below). Both sponsors and investigators may prefer to keep the information confidential at this stage. The sponsor wants to make sure that the trial will maintain a sufficient number of subjects, a task which would become difficult if information regarding the most effective treatment starts circulating. The investigator may want to publish the final study report in a prestigious journal, an objective possibly harder to reach if interim reports are made available. Some authors have taken the position that early disclosure should be the rule.[3106] Indeed, patients contemplating enrollment (in the concerned trial or in another similar study conducted by another group) would certainly want the most current information to make an informed decision.

8.6.2.3. Right to continued supply of the experimental product?

If the investigational product proved particularly efficacious and if there is no better treatment already on the market, subjects will want to continue with it. Depending on the circumstances, the sponsor may agree to set up an extended access program, at least for the patients who participated in the initial clinical trial. If such a program is planned, the investigator should explain to subjects how to enter or apply for it.

A more tricky issue is whether subjects have a *right* to receive, at the end of the trial, continued *supplies* of the investigational treatment.[3107] Since years can separate the end of the trial and the issuance of a marketing authorization, subjects cannot continue the treatment simply by acquiring the drug on the market; they depend entirely on the sponsor for supplies. Leaving subjects whose life-threatening condition has remitted during the clinical trial on their own once the trial is over is unfair. It may amount to

---

3103 See also the more detailed definition of adverse events (AEs) in section 1.2 (p.2) of ICH E6. See, in the United States, 21.C.F.R § 312.32(a) (defining what should be considered serious), and 21 C.F.R. § 312.32(c)(1)(i)(A) (stating the reporting obligations).

3104 Pharmacovigilance does not address this problem as it only starts once the drug is approved.

3105 In its report on the Dr. Olivieri-Apotex case, the Canadian panel stated that investigators should be free to disclose newly discovered risks, including those "identified following the conclusion of a trial in the event there are patients being administered the treatment in a non-trial setting." Olivieri Report, *supra* note 1084, at 40.

3106 *See* Richard J. Lilford et al., *Monitoring clinical trials – interim data should be publicly available*, 323 BMJ 441-442 (Aug. 25, 2001), at http://bmj.com/cgi/reprint/323/7310/441 (discussing the pros and cons of early disclosure).

3107 It is assumed here that the investigational treatment was shown effective either for all subjects or for a subset (e.g., effective only for women).

letting the subjects die, while they could have been saved. The situation is all the more inequitable when subjects agreed to take on significant risks by participating in the clinical trial.

The OClin does *not* compel the sponsor to satisfy subjects' request to receive the investigational drug.[3108] Admittedly, such an obligation could easily spin out of control. First, the information available immediately at the end of the clinical trial might not be sufficient to guarantee the drug's safety and effectiveness, especially for prolonged use. Second, it would be very difficult to supervise the use of the unapproved compound by former subjects, since their usual physicians would know nothing about the compound and the sponsor would find it difficult to keep permanent track of all its former research subjects.[3109] Third, sponsors could be tempted to cease their efforts to secure the marketing authorization if they can already sell the (unapproved) drug to thousands of former subjects. Finally, if the compound were provided free of charge, this would raise the costs of R&D to be ultimately borne by all patients once the drug is finally approved for sale.

Under U.S. law, a Court ruled that sponsors should *not* be forced to continue supply of an experimental drug, except when they explicitly undertook to do so.[3110] This rule was extended to subjects who were withdrawn from a study without their consent.[3111]

Even though existing national laws do not compel sponsors to continue delivering their investigational compounds, *ethical guidelines* consider the addition of such a duty as a moral or ethical obligation.[3112] Under paragraph 30 of the Helsinki Declaration, at the end of the study, patients must receive "the best proven" treatment "identified by the study."[3113] It is unclear whether the use of the word "proven" limits the scope of the rule to treatments about which sufficient scientific evidence have been accumulated. This rule has been mired in controversy.[3114] Proposals made to modify or clarify this provision gave rise to lengthy debates.[3115]

PhRMA has complained that it should not be the role of pharmaceutical sponsors to guarantee or arrange for continued supplies of an experimental drug. The responsi-

---

[3108] However, the clinical trial assessment checklist (prepared by a joint group of REC and Swissmedic representatives) mentions that RECs are responsible for checking whether or not follow-up supplies of the investigational product will be offered to subjects at the end of the study. Point 4.5 of the SAMS checklist, *supra* note 2238.

[3109] *See however* Dahl v. HEM Research, Inc., 7 F.3d 1399 (9th Cir. 1993) (enforcing a contract clause whereby the sponsor promised the research subjects continued supply of the experimental drug under certain conditions).

[3110] Karemer-Katz v. United States Pub. Health Serv., 872 F. Supp. 1235 (S.D.N.Y. 1994); *Dahl*, 7 F.3d 1399.

[3111] *Id.*

[3112] *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 5, point 12. *See also* WHO (Operational Guidelines), *supra* note 1379, at point 6.2.3.8 (p.11); COREC, *supra* note 1379, at point 9.15.i (p.25); AMA (E-2.071), *supra* note 1608.

[3113] Paragraph 30 Helsinki Declaration. *See also* NBAC (Developing), *supra* note 254, at 55-74.

[3114] *See, e.g.,* the survey information reported by Kass & Hyder, *supra* note 822, at B-6 to B-7.

[3115] *See* WMA, Documentation for the Preparation of Note of Clarification on Paragraph 30 of the Revised Declaration of Helsinki, at http://www.wma.net/e/ethicsunit/pdf/preparation_clarification_paragraph30.pdf [hereinafter WMA (Clarification 30)]. *See, e.g.,* Stephen Pincock, *World Medical Association delays decision on Helsinki declaration*, 327 BMJ 642 (Sept. 20, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7416/642-e?etoc.

bility should be that of governments.[3116] They are responsible for approving new drugs; they may have set mechanisms restricting the distribution of unapproved drugs due to health safety concerns. PhRMA considers paragraph 30 to be particularly problematic in developing countries.[3117] A promise to extend supplies to impoverished patients or to the community could amount to an undue inducement to enroll. The U.S. government has also condemned this provision as being unrealistic. In particular, a single trial is rarely sufficient to identify the best treatment.[3118] Others have said that such a rule could deter sponsors from undertaking clinical trials in the first place, if they have to systematically face costly follow-up obligations after completion.[3119] Moreover, the Declaration says nothing about *how long* this obligation should last and if the entire economic burden should fall exclusively on the sponsor.[3120]

The U.S. watchdog organization Public Citizen has come in support of the rule.[3121] It strongly objects to the additional condition put forward by the pharmaceutical industry that the superior treatment must have been *authorized* by the national drug agencies before clinical trial subjects can receive it as a follow-up therapy. The European Group on Ethics in Science ("EGE") also endorses the rule and admits that the sponsor may have to supply the treatment "for a lifetime if necessary."[3122] It also calls upon sponsors to do the same for the wider community.[3123] When the sponsors are public institutions or receive public funding, the EGE asks them to waive IP rights in the developing countries where the trial took place.[3124] The European Union attaches significant importance to follow-up care. Several of its guidelines require that the sponsor explain its plans "for the provisions of additional care of the subjects once their participation in the trial has ended, where it differs from what is normally expected according to the subject's medical condition."[3125] Disclosure of follow-up plans are indeed a minimum standard.

Other guidelines do not go as far as the Helsinki Declaration in mandating follow-up health care.[3126] They simply urge investigators and sponsors to prepare and communicate in advance their plan as to how the benefits of the research will be shared. This is, in my view, an important principle. It allows ethics committees, subjects and the broader community to reach a decision as to participation based on a complete assess-

---

3116 *See* WMA (Clarification 30), *supra* note 3115, at 2.

3117 Paragraph 30 was indeed initially intended to prevent abuses in developing countries.

3118 *See* WMA (Clarification 30), *supra* note 3115, at 3.

3119 *Id.* at 5.

3120 *Id.* at 6.

3121 *See, e.g.,* Letter of Public Citizen to the WMA, (Aug. 28, 2003), *supra* note 1693 (commenting the proposed note of clarification of paragraph 30); letter of Public Citizen to the WMA (Mar. 1, 2004), at http://www.citizen.org/publications/print_release.cfm?ID=7303 (welcoming the WMA workgroup's recommendation to keep Paragraph 30 unchanged).

3122 *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 10 (commentary).

3123 "… there should be an obligation that the clinical trial benefits the community that contributed to the development of the drug. This can be e.g. to guarantee a supply of the drug at an affordable price for the community or under the form of capacity building. The protocol of clinical trials must specify who will benefit, how and for how long." EGE, *supra* note 110, at 18 (point 2.13). *See also* Shapiro & Meslin, *supra* note 245, at 141.

3124 *See* EGE, *supra* note 110, at 19 (point 2.10).

3125 E.U. Guidance (Ethics Committee), *supra* note 270, at 5 and also at 6.

3126 *See* WMA (Clarification 30), *supra* note 3115, at 9-14.

ment of the situation. On these grounds, the CIOMS guidelines contain the following principle:

> if an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the *subjects* after the conclusion of the study, and pending its approval by a drug regulatory authority. The sponsor is unlikely to be in a position to make a beneficial investigational intervention generally available to the *community* or population until some time after the conclusion of the study, as it may be in short supply and in any case cannot be made generally available before a drug regulatory authority has approved it ... In general, if there is good reason to believe that a product developed or knowledge generated by research is *unlikely to be reasonably available* to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community.[3127]

Finally, in October 2004, the WMA announced that it had reached a "consensus" position. A new note of clarification adds the following:

> The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.[3128]

In other words, two separate duties are stated. First, the protocol (or another similar document) must describe the treatments that the research subjects will be entitled to at the end of the trial. Second, this aspect of the protocol must be assessed by the ethics committee. Clearly, the requirements are not very demanding. Basically, the note of clarification only asks that people involved in the organization and oversight of the trial give some serious thoughts to the issue of post-trial treatment – but it does next to nothing to guide their thinking. The note does not even mention the expression "investigational treatment," so that it is unlikely that it could be invoked to make it mandatory for the sponsor to provide its yet-unapproved drug to former subjects.

8.6.3. Confidentiality and privacy

Research subjects are entitled to privacy and confidentiality. Confidentiality must be distinguished from privacy.[3129] Privacy refers to the ability or right of an individual to decide whether or not to communicate information to a given third party.[3130] When a subject decides to participate in a clinical trial, he knowingly lets the investigator enter his private sphere. He voluntarily allows the investigator to collect certain private in-

---

[3127] CIOMS, Comment to Guideline 10, *supra* note 103 (emphasis added).

[3128] *See, e.g.*, WMA's press release (Oct. 11, 2004), at http://www.wma.net/e/press/2004_24.htm.

[3129] *See* Goldman & Choy, *supra* note 491, at C-4 through C-5. Pursuant to paragraph 21 of the Helsinki Declaration, both privacy and confidentiality must be protected.

[3130] *See* BEAUCHAMP & CHILDRESS, *supra* note 16, at 294-297.

formation. Earlier, the subject signed the consent form explaining which medical procedures he will undergo and for what purpose.

Confidentiality refers to the right of an individual to limit *further disclosure* to third parties of confidential information that he has already provided to one person.[3131] Thus, the investigator infringes the subject's right to confidentiality – and not privacy – if she discloses anything confided to her by the subject to another person.

8.6.3.1. Under the LPTh and the OClin

8.6.3.1.1. The LPTh and the OClin

It is quite surprising that neither the LPTh nor the OClin set forth a general obligation to maintain confidentiality. In fact, the OClin does not even contain a separate clause on confidentiality. Confidentiality measures are only mentioned *indirectly* in Article 31.a OClin. This is startling considering the weight given to the issue by the medical and legal literature[3132] as well as by the ICH E6 guideline.[3133] By comparison, the former IOCM regulation contained an explicit provision on data protection.[3134]

Fortunately, other sets of rules can be invoked to protect subject's privacy and confidentiality.

8.6.3.1.2. ICH Guideline

According to the ICH E6 Guideline, the protocol should state the safety measures that will be taken to ensure that personal information disclosed by, or obtained through, research subjects is not further revealed to unauthorized persons.[3135] The principal measures to ensure subjects' confidentiality are the coding and safekeeping of data.[3136] Most data being collected are linked to the subject only by a code, and not by name. Thus, most researchers handling the data do not learn the identity of subjects. Only those in direct contact with subjects (e.g., nurses) are likely to know them by name. Personal data (i.e., data whereby the identity of the subject is apparent) should also be

---

3131 "[C]onfidentiality is a branch or subset of informational privacy – it prevents *redisclosure* of information that was originally disclosed within a confidential relationship." BEAUCHAMP & CHILDRESS, *supra* note 16, at 304, and also at 305-306.

3132 Similarly, it is one of the Principles (n°9) of the Council of Europe's Recommendation R(90)3 (*supra* note 115). *See also* Article 25 COE Research Protocol.
In the United States, see the Health Insurance Portability and Accountability Act ("HIPAA") of 1996, Pub. L. No. 104-191, at http://aspe.hhs.gov/admnsimp/pl104191.htm.
In the European Union, see Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, at
http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:31995L=46:EN:HTML
See, e.g., MANAÏ (CONTEMPORAINE), *supra* note 16, at 246.

3133 *See* sections 1.16, 1.21, 1,24, 2.11, 4.8.10.(n)&(o) of ICH E6.

3134 *See* Articles 4.3 of the former IOCM 1995 Regulation, and also Articles 1.9.h), 2.5.p) and the glossary (under confidentiality) of the accompanying Good Clinical Practices.

3135 *See* section 2.11. and 4.8.10.(n)&(o) of ICH E6. *See, e.g.,* University of Pennsylvania School of Medicine, Protocol Elements, chapter 9, http://www.med.upenn.edu/ohr/protocol/9.html.

3136 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 18 (commentary).

stored in a place where only authorized people can gain access.[3137] Access to personal data should be restricted to a "need-to-know" basis.

In most trials, the sponsor is one of the *unauthorized* persons, as only the investigator, her team, the ethics committee and the national drug agency are entitled to access such personal information.[3138] The position of the sponsor is particular. Although it finances the trial and generally drafts the protocol, it has no contact with subjects. It only receives (at the end of the trial or periodically) anonymous data from the investigator. These data refer to subjects only by number, not name[3139]. The sponsor does not have access to the table that matches subjects' numbers with their identity. On the contrary, the investigator must make sure that none of the information available to the sponsor allows it to identify a given subject. All identifiers (e.g., address, profession, socioeconomic status) must be removed before transmission to the sponsor.

The reason for this confidentiality towards the sponsor is not self-evident.[3140] While it is true that sensitive information could get lost or leaked within a large organization such as a pharmaceutical company, this does not explain it entirely. First, sponsors could be held to a confidentiality duty enforced through criminal sanctions.[3141] Second, pharmaceutical companies are rather secretive organizations that have an excellent record in keeping their secrets. Third, the investigator also may work in a large institution (e.g., a hospital) that is not necessarily best suited to protect the identity of subjects. Fourth, the law does not restrict trials in which the investigator also acts as sponsor, although there is no Chinese wall in this case.[3142] The best explanation is that the sponsor simply does not need to know the subject's identity.

8.6.3.1.3. Information to be provided

Subjects who agree to participate in a clinical trial unavoidably disclose many details about their personal life (e.g., their health habits).[3143] The tests conducted by the investigator's team will reveal further information. For example, a DNA analysis may divulge that the subject is at high risk for a given disease (e.g., Huntington disease). Some trials may focus on medical conditions that are viewed as sensitive (e.g., depression, AIDS, erectile dysfunction). Yet subjects do not surrender all rights to privacy and confidentiality. On the contrary, subjects should be told what losses of privacy and confidentiality to expect. This information is recapitulated in the consent form.

3137 *See generally* EFGCP Records Management and Archiving Working Party, Guidelines for Retention of Clinical Trial Records at Investigator Study Sites, at section 3.1, at page 3-4, at http://www.efgcp.org/webitems/guidelines_for_retention.pdf [hereinafter EFGCP (Records)].

3138 Monitors appointed by the sponsor occasionally get access to data incorporating subject identifiers, but this is the exception rather than the rule.

3139 *See e.g.,* Article 22.1 OClin (regarding the report by the investigator to the sponsor of serious adverse event); the European Union has a very similar provision at Article 16.1 of Directive 2001/20/EC. See *also* section 4.11.1 (p.19) of ICH E6; WHO (Operational Guidelines), *supra* note 1379, at point 9.3.b (p.17). In the United States, see 21 C.F.R. § 312.64(b).

3140 See, more generally and in a different context (manufacturer's right to access Swissmedic's file containing patient information obtained through pharmacovigilance), the decision of the Swiss federal appeal commission for therapeutic products, JAAC 67.59, *supra* note 1358.

3141 Article 321bis CP applies to sponsors.

3142 *See* Article 5.c last sentence OClin.

3143 *See* section 5.15.2 (p.25) of ICH E6.

In other words, subjects should know beforehand *what* kind of personal information will be requested or obtained from him.[3144] The subject should be told *who* will have access to or use his personal information. The subject should know that the ethics committee and the drug agency are entitled to conduct inspections and ask for information, including information that discloses the subject's identity.[3145] Similarly, the sponsor may appoint monitors or other committees which may access the subject's personal file.[3146] The U.S. National Cancer Institute points out that absolute confidentiality cannot be guaranteed in a clinical trial and that subjects should be made aware of this fact.[3147] At least in the United States, it may be necessary to inform the subjects of the extent to which the courts can legally compel release of medical records gathered in a clinical trial.[3148] The period during which the investigator and/or sponsor will retain records concerning the subject should be indicated. The fact that records may be sent abroad should be disclosed in advance.[3149]

Subjects should also be told whether information collected during the trial may be *re-used* by the same or by another group of researchers for another study.[3150] When further (non-research) use of information is unexpected, subjects should be informed (e.g., the information will be used to set up a new public prevention campaign aimed at groups considered to be more likely to transmit the HIV virus).[3151] If the clinical trial leads to a published study, the publication should not contain any reference to named subjects.[3152] Moreover, it should not be possible to infer the identity of subjects based on data contained in the publication (e.g., information pertaining to sex, age, ethnicity, profession, place of residence).[3153] While such disclosure almost never occurs in large phase III trials for common diseases, it may be inevitable in smaller trials of rare dis-

---

3144 *See* section 4.8.10(n) (p.17) of ICH E6. In the European Union, see E.U. Guidance (Ethics Committee), *supra* note 270, at 7.

3145 In the United States, see 21 C.F.R. § 50.25(a)(5). *See* NCI (Simplification), *supra* note 2444. *See* FDA (FAQ-IRB), *supra* note 1814, at question 38 ("FDA may inspect and copy clinical records to verify information submitted by a sponsor. FDA generally will not copy a subject's name during the inspection unless a more detailed study of the case is required or there is reason to believe that the records do not represent the actual cases studied or results obtained."); FDA (Interrelationship), *supra* note 1987; FDA (1981), *supra* note 260, at point 32. *See also* 21 C.F.R. § 312.68.

3146 Only in very rare cases will the sponsor itself have access to the subjects' records. See FDA (Interrelationship), *supra* note 1987.

3147 *See* NCI (Simplification), *supra* note 2444.

3148 *See, e.g.,* Farnsworth v. Procter & Gamble, 758 F.2d 1545 (11th Cir. 1985). In this case, Procter & Gamble was denied its request to access personal identification of women who had participated in a clinical trial which had bearing on the safety of the company's tampon products. The Court found that "even without an express guarantee of confidentiality there is still an expectation, not unjustified, that when highly personal and potentially embarrassing information is given for the sake of medical research, it will remain private." *Id.* at 1548.

3149 *See, e.g.*, COREC, *supra* note 1379, at point 9.16.f (p.26).
Information-sharing arrangements between the United States and the European Union, for example, foresee that the foreign agency may get access to confidential information pertaining to clinical trial inspections. The foreign agency must protect the confidentiality of the information. See letter of the FDA to European Commission and the EMEA, (Sept. 12, 2003), at
http://www.emea.eu.int/pdfs/general/direct/pr/Letter%20to%20EC%20and%20EMEA.pdf.

3150 *See* UCSF (Part X), *supra* note 2455. *See also* subsections 3.4.6.3. above and 8.6.7.2. below.

3151 Of course, the subject should expect that, in a drug trial with a commercial sponsor, the data will be used to support a drug marketing application.

3152 *See* section 4.8.10(o) (p.17) of ICH E6; ICMJE*, supra* note 945, at II.E.1.

3153 *See* Phil B. Fontanarosa & Richard M. Glass, *Informed consent for publication*, 278 JAMA 682 (Aug. 27, 1997).

eases. Exceptions to the general principle of confidentiality require the explicit consent of the subject whose identity is or may be disclosed. Subjects must be told *how* the article (containing the personal information) will be published when this has a bearing on who will have access to the information. Thus, for instance, publication on the Internet is different from publication in a paper-only medical journal. Nonetheless, subjects should be warned that once the article is published, it may no longer be possible to limit its dissemination through other media (e.g., TV).

8.6.3.2. Article 321 and 321bis CP

8.6.3.2.1. Applicability

Violation of the confidentiality obligation owed by doctors to patients is a criminal offense.

Under Article 321 of the Swiss Penal Code, the doctor who divulges any information acquired in the context of his relationship with a patient faces criminal sanctions. Article 321 CP protect secrets communicated by the patient to his doctor in the ordinary health care setting. The provision is intended to facilitate open discussions, thus allowing the doctor to deliver the best and most knowledgeable medical care to his patient.[3154] It does not apply to the investigator-subject relationship. Contrary to a classic patient-doctor relationship, a central objective in a clinical trial is precisely to obtain data from the subject. Thus, in a clinical trial, information derived from the subject is not provided with the same purpose: Above all, the investigator wants this information to satisfy the protocol, not to tailor the subject's individualized treatment. These data are then put to multiple uses and are accessible, by law, to many entities (e.g., Swissmedic). Clinical trials are characterized by the fact that the best therapeutic interest of the subject is not the investigator's only priority (see subsection 3.4. above). Hence, it is reasonable to argue that Article 321 CP does not extend to clinical trials.[3155]

Article 321bis CP was passed in 1993 to fill this gap in the penal legislation.[3156] It prohibits anyone from revealing a professional secret learned in connection with his medical or public health research activities. Article 321bis CP applies regardless of whether the person affected by the secret (here, the research subject) is dead or alive. Neither does the provision set any time limit for the duration of the protection.

3154 *See, e.g.,* Berney et al., *supra* note 2415, at 348 (on the reasons underlying the need for confidentiality).

3155 Article 321 CP does not apply either when the physician is using the information he collected from his patients (in the context of ordinary medical practice) for his own research activity, provided the information is not communicated to any third party.

3156 This provision entered into force on July 1, 1993; text in French at http://www.admin.ch/ch/f/rs/311_0/a321bis.html.
See also Article 35 of the Swiss Law on Data Protection ("LPD") (punishing intentional disclosure of sensitive information which constitutes part of a file under the LPD). *See also* note 3163 *infra*.

8.6.3.2.2. Exception to Article 321bis

Article 321bis.2 CP establishes a procedure allowing for lawful disclosure of medical secrets in order to conduct further research.[3157] Past clinical trials may contain the basis for further research conducted by persons other than the investigator and her team. If these other persons are not hired or employed by the investigator or, as the case may be, her institution, the investigator is not free to give them access to information naming or otherwise identifying subjects. Nonetheless, to enable such derivative research, Article 321bis.2&3 CP introduces an exception provided the public expert commission on professional secrecy has given its authorization.[3158] Three conditions must be met for the commission to grant its authorization.

First, the scientist filing the application must not be able to reach her research objectives by using anonymized data (i.e., data that do not incorporate, directly or indirectly, the subject's identity). Most studies do not necessitate the identity of subjects; however, when the scientist plans to match the clinical trial data with other information pertaining to the subject (e.g., matching data on clinical outcome of cancer patients with information about their income class obtained from another source), knowing his identity becomes necessary.[3159]

According to the second condition set forth in Article 321bis.3 CP, it must be either impossible or very difficult to obtain the subject's consent. If the subject explicitly authorizes the disclosure or use of his personal information, then Article 321bis.2 CP does not apply, since its purpose is to protect unauthorized disclosure. A subject can theoretically authorize the investigator to disclose his personal data to third parties. For example, the protocol may already anticipate that the investigator will transmit her files to another scientist for further research; in this case, the investigator will ask the subject's prior consent as part of the general consent process (see subsection 8.3.2.7. above). In theory, the consent form signed by the subject could contain a general authorization to disclose personal information to any researcher, whether related or not to the ongoing clinical trial (possibly with a country or time period limitation). In practice, ethics committees oppose excessively broad clauses deemed unfair since the subject is not in a position to anticipate what exactly he is consenting to. In Switzerland, excessively broad clause could also contravene Article 27 of the Swiss Civil Code (CC), which forbids excessive commitments. Nonetheless, middle-of-the-road arrangements can be implemented, under the supervision of ethics committees. It can be presaged that these arrangements will grow increasingly common as biomedical research explodes. Ethics committees should bear in mind that it is in the interests of all patients, research subjects included, that the best use be made of information already collected, instead of limiting its use to one investigator under a single protocol; such sharing can reduce the need for research subjects and the risks associated with clinical trials, while partly trimming duplicative research.

As mentioned above, Article 321bis.3.b CP allows for exceptions when obtaining subjects' consent is not impossible, but exceedingly difficult. When there is but few

---

3157 *See generally* Sprumont (De l'éthique), *supra* note 159, at 146-48.

3158 See the commission's website at http://www.admin.ch/ch/f/cf/ko/index_34.html.

3159 Epidemiologic research also may require identifiable data to make sure that an individual is not accidentally "counted" twice.

(e.g., a dozen) subjects enrolled whose data need to be disclosed, the difficulty is not enormous; in all other cases, there is a real difficulty. The main problem is that the party who has free access to the file, that is to say the initial investigator, has no reason to act as an intermediary between the other scientist and the former research subjects.[3160] The investigator's institution will accept that role only if that other scientist is affiliated with it.[3161] The public expert commission on professional secrecy does not engage in that sort of activities. Hence, the second scientist can explain that subjects' consent is impossible to obtain because she cannot have access to their names and that no one else is prepared to seek, on her behalf, their consent.

According to the third condition under Article 321bis.3.c CP, the interest of science, embodied in the new research project, must exceed the interest of subjects to remain anonymous and to protect their privacy. This appreciation, which is left to the public commission, is delicate. Is knowledge itself an interest worth protecting? Does the value of research depend on the significance of its results? Do significant results necessary mean the discovery of a new therapeutic product? If so, should the subject receive at least some benefit, for example because he will be able to use the future product? Similarly, it is difficult to quantify the subject's interest in protecting his medical information. Of course, if the subject was involved in a clinical trial studying a possible pharmaceutical cure against deviant sexual practice, the commission can surmise that the subject's interest is considerable. In addition, if the commission must really balance the two opposed interests, it should examine each subject's file to know if it contains sensitive information (e.g., patient X is alcoholic, patient Y has had three abortions). It appears from the (summary of) its decisions that the commission bestows a high priority to research.[3162]

8.6.3.3. Under the law on data protection

In Switzerland, confidentiality of personal records is governed by the Federal Law on data protection ("LPD").[3163] This law applies to files containing information linked with identified or identifiable individuals.[3164] Since the investigator does hold a file with the names of all subjects which is or can be linked with other personal and often sensitive information, the LPD applies.[3165] The LPD grants several rights to individuals (here the

---

[3160] Indeed, the investigator could track down all of its former human subjects in order to ask each of them whether he agrees to the disclosure of his data. However, the investigator has little incentive to undertake such a heavy task to help another scientist. Moreover, the latter cannot ask the question himself, since he would first need to know to the identity of subjects.

[3161] When the investigator is affiliated to a hospital or to a private clinic, the institution generally knows the identity of the subjects, notably because it keeps all the files generated by all clinical trials conducted within its facilities.

[3162] *See* Expert Commission, Report of activities for the years 1998 to 2000, at http://www.bag.admin.ch/themen/weitere/expkmedf/t_ber_f.pdf.

[3163] In French, "*Loi fédérale sur la protection des données*"; Federal Law on data protection; RS 235.1, of June 19, 1992, entered into force on July 1, 1993; text in French at http://www.admin.ch/ch/f/rs/2/235.1.fr.pdf. *See also* Ordinance regarding the LPD, of June 14, 1993; entered into force on July 1, 1993; RS 235.11; abbreviated (from the French): OLPD; text in French at http://www.admin.ch/ch/f/rs/2/235.11.fr.pdf.

[3164] As per Article 3.c.2. LPD, health information, hence also that obtained from a clinical trial, is deemed to be sensitive information.

[3165] *See* Articles 2.1, 3.a., 3.c.2 LPD.

subjects) whose data are contained in the file under the control of a third party (here the investigator); these are reviewed below.

8.6.3.3.1. Right to access the file

Pursuant to the LPD, a research subject has the right to access (i.e., read) his own file.[3166] Consequently, a research subject is entitled to ask the investigator, who is usually the "file master,"[3167] to see his own file; this file will normally contain all information collected about him throughout the clinical trial.

The problem is that this right is in conflict with the principle that the trial should remain blinded until its completion (see subsection 6.3.3.5. above).[3168] If the subject can peruse his entire file, he may determine whether he received the investigational drug or the control treatment. The LPD contains no exception for clinical trials.[3169] The solution could be to admit that an individual[3170] can temporarily (i.e., for the duration of the study) waive his right to access information that would lead to the breaking of the blind. However, explicit waivers are not a common feature of Swiss consent forms. The investigator could also invoke Article 9.3 LPD which allows for restrictions to the right to access when the file master's preponderant interests require and justify such restrictions. However, the application of this exception is not self-evident in this context. First, the balance of interests is not manifest, especially in the absence of a waiver by the concerned person. Moreover, the provision could also restrict all disclosure of subject information to third parties, including probably distinct entities such as the Data and Safety Monitoring Board.[3171]

Even if the subject waives his right to access the randomization code or similar information leading to his unblinding, the right to access the file remains hugely valuable. By regularly accessing his file (and, possibly, handing it to his usual doctor), the subject could continually verify that the treatment is really beneficial to his health. On the basis of this information, he could decide to withdraw from the trial once he realizes that the treatment is not or no longer medically helpful. Access to the file could also allow the subject to supervise the investigator, for example, by exposing departures from the protocol. The subject – if sufficiently educated and diligent – could almost do for himself what the ethics committees should periodically do for all subjects, that is supervise the clinical trial and the investigator.[3172] Finally, by holding on to his own case file, a

---

3166 *See* Article 8 LPD. *See also* MANAÏ (CONTEMPORAINE), *supra* note 16, at 247.

3167 *See* Article 3.i. LPD.

3168 *See* UCSF (Part X), *supra* note 2455.

3169 Other countries, in particular the United States and the European Union, admit a restriction of the privacy rights of research subjects during the course of the trial. Subjects can be refused access to their file during the trial so as to maintain the blinded randomization. They must be informed in advance of this restriction. Of course, at the end of the trial, research subjects recover full acces to their personnal data, including the right to know to which treatment group they were assigned. *See* Safe Harbor, Frequently Asked Questions, FAQ 14 – Pharmaceutical and Medical Products. Question 5, at http://www.export.gov/safeharbor/FAQ14PharmaFINAL.htm; HHS, Protecting Personal Health Information in Research: Understanding HIPAA Privacy Rule (03-5388) (April 2003), p.19, at http://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf.

3170 *See* Article 3.b. LPD.

3171 *See* Article 9.3 *in fine* LPD.

3172 In fact, the file that the subject is entitled to access is rarely read by ethics committees which often limit themselves to the broad-spectrum reports prepared by the investigator.

research subject is better able to monitor his health once the study ends. He will be in a position to explain to his subsequent doctors what treatments were administered to him and the procedures he underwent; these may have a long-lasting impact on his health and may influence later choice of treatment (e.g., it may explain drug resistance) (see subsection 8.6.2.2. above).

Yet, it seems that research subjects ignore their right to access the file. File access is fraught with so many practical difficulties, even in ordinary medical practice, than this right has received little, if any, attention in the clinical trial setting. It would be appropriate to consider more seriously the consequences of the application of the LPD to clinical trials. The LPD has extremely broad effects whose unwanted consequences are often neglected.

8.6.3.3.2. Right to restrict access

Pursuant to the LPD, the file master must take all precautions to avoid undue disclosure to unauthorized parties.[3173] Transfer of the file or file information to foreign countries is restricted.[3174] In particular, the transfer must be notified in advance to the Swiss Data Protection Commissioner.

This restriction may cause some problems when the sponsor (or other companies belonging to the same group as the sponsor) is located in a foreign country or when a foreign drug agency asks to see subjects' files in order to review a marketing application. The investigator would have to notify the Swiss authority first. It does not appear that this rule is strictly obeyed by investigators.

Although some exceptions or reliefs are stated in the LPD and in the OLPD,[3175] none apply perfectly to clinical trials. For instance, the exception of Article 7.2 OLPD cannot be invoked because clinical health data are deemed sensitive information. Subjects are apparently neither systematically informed that "their file" might be used abroad, nor are they asked to consent to possible transfers.

8.6.3.3.3. Right to correct mistakes

The third important prerogative granted by the LPD to individuals whose personal information is in a file is the right to ask that inaccurate information be corrected.[3176] To be subject to amendment, the information must truly be inaccurate, that is false, misleading or incomplete. An information that is simply disobliging or potentially damaging (e.g., the subject has used illegal narcotics) cannot be changed. Since one of the goals of clinical trials is precisely to gather clean and reliable data, the file should not include many mistakes. If there is one, the investigator will eagerly correct it.

3173 *See* Article 7 LPD and also Articles 8 and 9 OLPD. The investigator should be careful to keep records under restricted access facilities or in a safe. The code linking the references number with the subjects' identities should be especially protected against unauthorized access. The investigator should also decide what will happen to the files once she retires or leaves her institution.

3174 *See* Article 6 LPD and also Articles 5 to 7 OLPD.

3175 *See, e.g.*, Article 7 and Article 6.3 OLPD.

3176 *See* Article 5.2 LPD.

8.6.4. Payments to and by subjects

This subsection starts by discussing payments made to subjects. The second subsection focuses on costs that subjects are asked to bear.

8.6.4.1. Payments to subjects

8.6.4.1.1. Admissibility

Paying people to participate in research is an old practice.[3177] It became common in the United States in the 1920s and 1930s, partly as a consequence of the Great Depression;[3178] people would enroll in research projects to supplement their dwindling incomes.

Although most research subjects are interested in furthering the interest of science, this is rarely the only reason for them to participate in clinical trials. Yet, the concept of paying subjects is repugnant to many people.[3179] This relates to the general, yet somewhat controversial,[3180] principle that the human body or its parts should never be sold or used for profit.[3181] Civil law countries have a nearly absolute conception of this principle.[3182] Anglo-American countries hold a more flexible view.[3183]

Aside from this axiomatic ethical justification, people also fear that offering money may constitute undue inducement, in particular for poor people with no better financial prospects.[3184] It may also give rise to the impression, in either or both the investigator and the subject, that the former has "bought" the right to make use of the latter.[3185]

A minority considers that, on the contrary, making small payments helps clarify, in the mind of subjects, the fact that they are participating in research, and not receiving individualized treatment.[3186]

3177 *See also* LEDERER, *supra* note 54, at 115.

3178 *Id.* at 119-20.

3179 See the survey conducted among healthy *unpaid* Canadian volunteers by Margaret L. Russel et al., *Paying research subjects: participants' perspectives*, 26 J. MED. ETHICS 126-130 (2000) (whereby only 43% of respondents were in favor of payments), at http://jme.bmjjournals.com/cgi/content/full/26/2/126.

3180 *See* Carlo Foppa, *Le sujet, son corps, ses organes: un récent débat suisse*, [the subject, his body, his organs: a recent Swiss debate], 39(1) CAHIERS MEDICO-SOCIAUX 41 (1995) [my translation].

3181 For the Swiss Academy of Medical Sciences ("SAMS"), the principle should be gratuity, compensation for expenses, time and wages lost being the exception. *See* SAMS 1997 Guideline, *supra* note 110, at point D.11. at 11. *See also* Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 320. *See also generally* Article 21 of the Biomedicine Convention. *See also generally* COE draft Biological Report, *supra* note 493, at 8, para. 33.

3182 *See also* Article 19.2.e. of the Swiss Constitution (prohibiting that sperm donor be remunerated).

3183 For example, sperm is commonly sold in the United States.

3184 *See, e.g.,* the Federal Council's Message accompanying the LPTh, at FF 1999 3151, at 3230. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 7 (commentary).

3185 *See* LEDERER, *supra* note 54, at 121.

3186 *See* Neal Dickert & Christine Grady, *What's the Price of a Research Subject? Approaches to Payment for Research Participation?*, 341 NEW. ENG. J. MED. 198-203 (1999), at http://content.nejm.org/cgi/content/full/341/3/198 (discussing the advantages and disadvantages of three models of payments and ultimately recommending the wage-payment model); Miller & Rosenstein, *supra* note 1293.

Paying subjects is admissible under Swiss,[3187] European[3188] and U.S. laws.[3189] However, both legal and ethical principles impose many safeguards. The purpose of the compensation should never be to goad the subject into participating in the trial.[3190] On the contrary, subjects should decide freely whether or not to join the study, with financial considerations playing as little role as possible in their decision. Similarly, financial incentives should not be designed to push the subject into using the drug once it is available; coupons or rebates for the purchase of the drug are therefore not admissible.[3191]

8.6.4.1.2. Review by ethics committees

Ethics committees are to pay special attention to payments made to subjects.[3192]

First, they should check whether the amount received by subjects constitutes an undue inducement.[3193] Thus, for a poor subject, CHF 1'000.- might be an enticing amount of money, while, for a rich subject, it would hardly be worth considering. The same could be true for people living in different countries (wealthy v. poor countries).[3194] According to this argument, the protocol would have to set differentiated payments for each subject (or each class of subjects) depending on his income and wealth. Clearly, this would not only be unpractical, but would perpetuate inequalities, since the income gap between rich and poor subjects would be maintained. Swiss ethics committees have not debated about this issue and the current practice appears to favor only one amount (if any), regardless of the economic status of the subject.

Second, RECs require that any promised payment be clearly stated in the consent forms signed by the subjects.[3195] RECs should also make sure that payment is prorated, so that subjects are not forced to stay in the trial until the end to collect it.[3196] Subjects who withdraw from the study prematurely should still be entitled to a payment, although they may forfeit their completion bonus.[3197] According to the CIOMS, subjects who have to leave the study for health-related reasons should be given full payment.[3198]

3187 *See* Article 10.2.m OClin.

3188 *See* Article 6.3.(j) of E.U. Directive 2001/20/EC.

3189 *See* FDA (Recruiting), *supra* note 2038.

3190 *See e.g.,* Principe 13.1 of the Council of Europe's R(90)3 Recommendation, *supra* note 115. *See also* section 3.1.8 (p.10) of ICH E6.

3191 *See* ECRI (Guide), *supra* note 869, at 63.

3192 *See also* subsection 7.1.2.3. above. *See also* VanTx Report, *supra* note 148, at 20.

3193 PhRMA's recommendations states: "Payments should be based on research participants' time and/or reimbursement for reasonable expenses incurred during their participation in a clinical trial, such as parking, travel, and lodging expenses. The nature and amount of compensation or any other benefit should be consistent with the principle of voluntary informed consent." PhRMA (Principles on Clinical Trials), *supra* note 902, at 15-16.

3194 *See* VanTx Report, *supra* note 148, at 20.

3195 *See* sections 3.1.9 (p.10-11) and 4.8.10(k) of ICH E6.

3196 *See* sections 3.1.8 and 3.19 (p.10 and 11) of ICH E6; *See* FDA (Recruiting), *supra* note 2038 (However, "[u]nless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn.").

3197 Large bonus payments are not acceptable as they may create too strong an incentive for subjects to remain in the study. *See* FDA (Recruiting), *supra* note 2038.

3198 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 7 (commentary).

Third, RECs should verify that benefits offered to subjects are not misleading. For example, the FDA proscribes "coupon good for a discount on the purchase price of the product once it has been approved for marketing." The FDA rightly points out that such a coupon can delude subjects into thinking that the investigational treatment is particularly beneficial.

Ethics committees must pay special attention when payments/reimbursements are made to incompetent subjects, or worse, to their guardians. The risk is that the legal representative gives his consent on behalf of the subject only to receive the money, regardless of the harm possibly incurred by the subject. Therefore, many codes of ethics say that no payment should be made whenever incompetent persons are involved in clinical trials.[3199]

8.6.4.1.3. Amounts offered

Human research subjects often receive some sort of payment.[3200] The highest payments are typically made to phase I healthy volunteers, since their "love of science" does not suffice to win their consent.[3201] Based on a quick review of advertisements posted at the Geneva medical school, rates for healthy volunteers in this canton are about CHF 160.- per day.[3202] In the United States, GlaxoSmithKline used to indicate, on its website, that healthy volunteers in phase I studies can "earn a rate of $175 to $300 per study day."[3203]

In contrast, payments to phase III subjects are rarer and lower since they are receiving health care for their medical conditions. According to information obtained from the HUG-REC, subjects who are also patients do not receive payments.[3204] At best, they are reimbursed for their expenses (e.g., having to travel to the research site).

Little information is available on payments made to subjects. According to an American study:

> Of 32 [U.S. research] organizations [surveyed], 37.5% had written guidelines about paying subjects; all but 1 reported having rules of thumb. Few (18.8%) were able to provide a confident estimate of the proportion of studies that pay subjects. Organizations reported that investigators and institutional review boards make payment decisions and that both healthy and ill subjects in some studies are paid for their time (87%), for inconvenience (84%), for travel (68%), as incentive (58%) or for incurring risk (32%). Most organizations require that payment be prorated (84%) and described in the consent document (94%).[3205]

3199 An exception is generally tolerated for reimbursement of out-of-pocket expenses. *See id.* at Guideline 7 (commentary); Principle 13.2 of the Council of Europe's R(90)3 Recommendation, *supra* note 115.

3200 The word "payment" is to be preferred to the word "compensation," the latter generally referring to compensation for injuries resulting from participation in the clinical trial. See, *e.g.,* UCSF (Part X), *supra* note 2455.

3201 *See* Dickert & Grady, *supra* note 3186; FDA, Payment to Research Subjects, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators (1998 update), at http://www.fda.gov/oc/ohrt/irbs/toc4.html. *See also* VanTx Report, *supra* note 148, at 18.

3202 Advertisements viewed on November 25, 2003.

3203 Its website (previously at http://www.phillytrials.com) no longer exists.

3204 Interview with Bounameaux, *supra* note 1718.

3205 Neal Dickert et al., *Paying Research Subjects: An Analysis of Current Policies,* 136 ANNALS OF INTERNAL MEDICINE, at 368-373 (Mar. 5, 2002), at http://www.annals.org/cgi/reprint/136/5/368.pdf.

More helpful guidance in this area can be found on the website of the University of California at San Francisco (UCSF).[3206] For routine procedures entailing only limited risks, the University recommends paying an hourly compensation (presently between $15 and $20). For more painful and risky procedure, the hourly rate should be replaced by a per procedure payment that should not exceed $200-300.[3207] In addition, the University considers that the total payment for participation in the study should not exceed $1,000. However, it permits incident expenses to be reimbursed (e.g., travel arrangements, child care). The University also allows for payment of a small bonus (not more than 30% of the total) if the subject completes the study, while the main payments should be disbursed *pro rata* as the study advances. The University reports payments to the tax authority if they exceed $600 over a one-year period!

Other systems of remuneration may be based on the number of procedures. Thus, each blood sample may be paid some $10. Payments may also be based on the number of days or hours of gainful employment lost. Thus, when subjects are hospitalized and cannot carry out their normal lucrative activity, the sponsor's payment may make up this loss. Once again, the norm is an average sum, and not one directly calculated on the basis of the job's monthly, weekly or hourly wages.

Aside from cash payment, the sponsor may grant other types of remuneration. It may make arrangements to facilitate the life of subjects, for example by offering to pay a babysitter when the subject has to leave her children at home to visit the clinical facilities. Non-monetary compensation is subject to the same scrutiny as cash payments, since once again they may represent an irresistible temptation.

Finally, subjects may appreciate being acknowledged as participants in the research. Even when subjects enroll in order to gain access to a promising treatment, they feel that they are helping the progress of science. This is particularly true when they remain in a trial even though they are not deriving the expected therapeutic benefits. Hence, thanking subjects makes sense to foster this feeling of solidarity. Certain published studies now contain – and rightly so – an explicit acknowledgment of subjects' involvement.[3208]

8.6.4.2. Payments by subjects

8.6.4.2.1. Payment for the experimental product

Swiss law does not explicitly prohibit the sponsor from charging subjects for its unapproved investigational drug. Swissmedic does not formally oppose trials where subjects pay for the drugs, although this would certainly be frowned upon.[3209] Phase IV clinical

---

3206 UCSF, Guidelines for Payment of Research Subjects, (Apr. 12, 2000), at http://www.research.ucsf.edu/chr/Guide/chrPayment.asp.

3207 The University cautions that for blood taking procedures, the payment should not be proportionate to the amount of blood taken. *Id.*

3208 "The authors gratefully acknowledge the contributions of all the study site personnel and patients who participated in this study." K. Squires et al., *supra* note 577, at 319. In another study, not only are the subjects thanked, but also "their families who supported them." O'Connor et al., *supra* note 1576, at 1466.

3209 *See* Interview with Vital-Durand, *supra* note 484. It may however object to commercial trials whose scientific justification is woefully lacking.

trials sometimes do impose charges on subjects, especially if the drug is expensive and the trial is expected to last a long time.[3210]

Ethics committees are more wary of clauses whereby subjects must pay to participate in a trial. From their point of view, charging for an unapproved product is generally unethical, since the underlying principle of clinical trials is that subjects are acting altruistically by accepting the risks of the study to "help out" researchers. According to the President of HUG-REC, subjects are never charged for participating in a clinical trial.[3211]

Under certain restricted conditions, U.S. law allows the sponsor to charge subjects an amount equal to the cost of the investigational compound; sponsors are however barred from making any profit out of the operation. First, the sponsor can only recover the "costs associated with the manufacture, research, development and handling of the investigational drug."[3212] Second, the sponsor must obtain prior FDA approval by establishing that it is economically compelled to charge for its product.[3213] Third, IRBs scrutinize the ethical consequences of charging for the tested compound. In particular, low-income subjects should not be precluded from participating in a trial because of the cost charged by the sponsor. Subjects should be informed explicitly of the extra charges they incur because of their participation in the trial.[3214]

E.U. law is more restrictive and in principle does not allow the sponsor to charge for the investigational product.[3215] However, Member States can implement exceptions under clearly defined "exceptional circumstances."[3216] The E.U. Commission should be informed of the conditions governing these exceptions.[3217]

8.6.4.2.2. Payments for other health care costs

While the sponsor cannot charge for its product, it can – in theory – charge the subjects for the health care they are receiving. Subjects must be informed in advance of the costs they will have to bear.[3218]

Distinguishing between the general costs of health care and the cost related to investigational procedures is not always straightforward. Does the cost of the admini-

---

3210 *Id.*

3211 Interview with Bounameaux, *supra* note 1718. *See also* VanTx Report, *supra* note 148, at 20 (The VanTx Working Group wrote that, in principle, the investigational product must be provided free of charge.)

3212 *See* Quality Assurance, Charging for Investigational Products, at http://www.sqa.org/Committees/CSS/Infosheets/charging.html. *See also* 21 C.F.R 312.7(d)(3).

3213 *See* 21 C.F.R. § 312.7(d)(1). The sponsor must justify why "distribution of the drug to test subjects should not be considered part of the normal cost of doing business."
This requirement does not appear to be always strictly followed. Thus, the FDA issued a warning letter to the IRB of Irvine Regional Hospital and Medical Center, disapproving the fact that the investigator had been charging patients $15,000 for participating in the clinical trial, even though the FDA had not authorized any cost recovery. *See* FDA Warning Letter to Dan F. Ausman, *supra* note 1848.

3214 In the United States, see 21 C.F.R. § 50.25(b)(3).

3215 Article 19.2 of Directive 2001/20/EC. In addition, the sponsor cannot charge for the medical device used to administer the investigational drug.

3216 Article 19 of Directive 2001/20/EC.

3217 Article 19.3 of Directive 2001/20/EC.

3218 *See* section 4.8.10(l) (p.16) of ICH E6.

stration of the product by the investigator or her staff belong to the first or the second category? If the investigational drug must be administered while the patient is hospitalized or under narcosis, are the costs of hospitalization and anesthesia included in the cost of the drug?

Moreover, at least in Europe, ethical principles oppose such payments by subjects. This opposition is grounded in various reasons, notably that poor patients could end up excluded from clinical trials due to their inability to pay the required amounts. Indeed, a study of U.S. cancer patients found that 66% would have been interested in enrolling in a clinical trial if they did not have to bear the medical costs. Sixty percent of patients who did not enroll had feared that their insurance companies would not cover the related health care costs.[3219]

Hence, ethics committees should view with distrust all payments demanded from subjects, whether they are for the investigational product or for "more general" health care.

8.6.4.2.3. Insurance coverage

When subjects are asked to pay either for the investigational drug or for other health care services they receive during the clinical trial (e.g., cost of accompanying treatment delivered in hospital settings[3220]), the question that arises is whether health insurance companies have to foot the bill. Typically, health insurance companies only reimburse patients for medical treatments that are approved by the State (in Switzerland) or that are included in their formularies (in the United States). Experimental treatments are almost always excluded from reimbursement. Health services accompanying experimental treatments may be similarly excluded. The underlying justification is that investigational treatments are more expensive even though their efficacy is not guaranteed. Yet, a number of studies refute this rationale, showing that the overall cost of health care does not vary significantly depending on whether it is delivered in a clinical trial setting.[3221]

In Switzerland, the Federal Insurance Tribunal holds that insurance companies must reimburse methods of treatments when they are scientifically admitted. The basis for such recognition is the widely-shared opinion of researchers and practitioners, which must be in turn based on successful experiences with the method.[3222] In addition, the treatment must be cost-efficient.[3223] To my knowledge, the Federal Tribunal has never decided a case where the insured patient had participated in a clinical trial.[3224] When a treatment consists in the use of a drug which is not on the reimbursement list (List of Specialties), the drug will be reimbursed only if its use is closely linked to a

---

3219 *See* Vastag (Boost), *supra* note 901, at 1303.

3220 *See* GAO (Factors Affect), *supra* note 877, at 4.

3221 *See* National Cancer Institute ("NCI"), cancer.gov., Evidence Mounts that Clinical Trials Are not Costly, (2000), at http://www.nci.nih.gov/clinicaltrials/developments/notcostly0500.

3222 ATF 120 V 472, at 476-75, at point 4.a), case of *Supra* v. S (July 7, 1994); ATF 119 V 26, at 29, point 3.a), case of Asssura v. G. (Mar. 10, 1993); ATF 113 V 42, at 45, point 4.d)aa), case of L. against Helvetia (Feb. 2, 1987).

3223 ATF 119 V 26, at 32, point 4.c).

3224 In most cases decided by the Tribunal, the treatment, even though experimental, was delivered in the context of "ordinary medical care."

treatment or procedure which must be reimbursed. Applied to clinical trials, this rule leads to the conclusion that investigational drugs are not reimbursed by (basic social) sickness insurance. Indeed, the key aspect of clinical trials is experimentation on treatment methods whose efficacy is yet unresolved for the scientific community. Since this key aspect of the experimental treatment is not scientifically recognized and hence not reimbursed, the same consequence extends to all other ancillary treatments.

U.S. Courts apply similar principles.[3225] In general, insurance plans will not pay for experimental treatments.[3226] What constitutes experimental treatment in the eye of insurance companies varies. Lack of scientific consensus about the benefits of a given treatment is a common criterion. Often, the fact that a treatment is administered within a clinical trial setting (i.e., study conducted according to a protocol, signature of consent forms by subjects) can be enough to qualify the treatment as experimental. The status of the drug, whether FDA-approved or not, may also be taken into consideration.[3227]

There are some exceptions to the U.S. rule against coverage for experimental treatments. First, such treatments may be reimbursed where the language of the insurance policy subscribed by the patient is not sufficiently clear in excluding investigational treatments.[3228] Second, a number of States have enacted legislation forcing insurance companies to reimburse at least the "routine patient care costs" administered in the context of a clinical trial[3229]

Third, Medicare, the government-funded insurance program, has come to a turnaround resolving to pay for the portion of the costs that corresponds to standard care.[3230] Thus, Medicare covers the normal costs of administrating drugs as well as the

---

3225 *See e.g.*, Santucci v. Hyatt Corp., 955 F. Supp. 927 (N.D. Ill. 1997) (denial of coverage for experimental autologous stem cell replacement therapy against leukemia).

3226 GAO (Factors Affect), *supra* note 877, at 28. *See also* National Cancer Institute, cancer.gov., Clinical Trials and Insurance Coverage – A Resource Guide, (2002), at http://www.cancer.gov/clinicaltrials/understanding/insurance-coverage/page2.

3227 However, physicians in the United States have the right to prescribe drugs off-label and insurance companies generally do not even know whether the drug was prescribed for an unapproved therapeutic indication. *See also* subsection 3.4.4. above.

3228 *See, e.g.*, Glutzer v. Prudential Insurance Co., 183 F.R.D. 632 (N.D. Ill. 1999). In this case, the cancer patient was denied coverage for experimental autologous stem cell replacement therapy delivered outside the context of a clinical trial. The Court found the exclusionary language of the insurance policy to be unambiguous. *Id.* at 638. *See also* Harris v. Mutual of Omaha Co., 992 F.2d 706 (7th Cir. 1993) (coverage denied given the clear exclusionary language of the insurance contract); Hendricks v. Central Reserve Life Insurance Co., 39 F.3d 507 (4th Cir. 1994) (another denial of coverage for high-dose therapy with peripheral stem cell rescue); Vick v. Coventry Health Care, 2001 U.S. Dist. LEXIS 12198 (Kan. D.C. 2001); Zervos v. Verizon, 277 F.3d 635 (2d Cir. 2002) (coverage granted for high-dose chemotherapy treatment (HDCT) for breast cancer).
On the reimbursement of autologous bone-marrow stem cell transplants ("ABMT"), see BAZELL, *supra* note 673, at 92-96. On the clinical efficacy of high-dose chemotherapy with stem-cell transplant, *see* Sjoerd Rodenhuis, *High Dose Chemotherapy with Hematopoeitic Stem-Cell Rescue for High-Risk Breast Cancer*, 349 NEW. ENG. J. MED. 7-16 (July 3, 2003), at http://content.nejm.org/cgi/content/full/349/1/7 (finding the stem-cell therapy efficacious); M.S. Tallman et al., Conventional Adjuvant Chemotherapy with or without High-Dose Chemotherapy and Autologous Stem-Cell Transplantation in High-Risk Breast Cancer, 349 NEW. ENG. J. MED. 17-26 (July 3, 2003), at http://content.nejm.org/cgi/content/full/349/1/17 (finding that the therapy does not improve patients' outcome); Gerald J. Elfenbein, *Stem-Cell Transplantation for High-Risk Breast Cancer, Editorial*, 349 NEW. ENG. J. MED. 80-82 (July 3, 2003), at http://content.nejm.org/cgi/content/full/349/1/80 (trying to reconcile the two studies).

3229 *See* National Cancer Institute, cancer.gov., States That Require Health Plans to Cover Patient Care Costs in Clinical Trials (2003), at http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs.

3230 Centers for Medicare and Medicaid Services ("CMS"), Medicare Coverage – Clinical Trials, at http://cms.hhs.gov/coverage/8d2.asp.

costs of treating drug side effects, regardless of whether the drug is investigational or not. It does not cover, however, the cost of the drug itself, nor the cost of procedures related solely to data collection/analysis (e.g., blood taking for study purposes).[3231] Moreover, for coverage to apply, the trial must have a therapeutic purpose.

Fourth, a comprehensive survey conducted by the U.S. General Accounting Office (GAO) found that many U.S. insurers agree, on a case-by-case basis, to cover at least the "standard, nonexperimental care costs associated with a trial."[3232] However, even in such cases, the bureaucratic procedure necessary to obtain prior authorization of coverage by the insurer can discourage subjects.[3233] This procedure also creates a hurdle for investigators in charge of recruiting subjects, since they are often responsible for leading the negotiations with insurance companies.[3234] Subjects who can neither obtain insurance coverage nor pay out-of-pocket for an experimental treatment are often denied enrollment in clinical trials.[3235] Nevertheless, the GAO study conceded that these obstacles have not barred investigators from recruiting the desired number of subjects.[3236] Another study found that the additional health care costs generated by enrollment in a cancer clinical trial were not significant (only 6.5% higher).[3237]

8.6.5. Liability and compensation for damages

Liability is perhaps the most effective means to force compliance with legal and ethical requirements.[3238] Pharmaceutical companies sponsoring clinical trials refrain from actions (by themselves or by their investigators) that could result in damage awards and in negative publicity arising from the lawsuit. To minimize their liability risks, they strive to improve the organization of clinical trials.

3231 *Id.* A third exception pertains to "items and services customarily provided by the research sponsors free of charge for any enrollee in the trial."

3232 GAO (Factors), *supra* note 928, at 2, and also at 5-8. However, "insurers vary in how they define 'standard care'." *Id.* at 6 and also at 8. In deciding whether to grant coverage, insurance plans consider "the scientific merit of the trial and the anticipated costs" as well as the gravity of the insured patient's disease. *Id.* at 7. Out of 26 insurers surveyed, "[s]ixteen mentioned their preference for NIH-sponsored phase III trials, and six indicated that they would not approve requests to participate in commercial drug company trials." *Id.* Insurers admitted that public pressure can also influence their decision to award coverage. *Id.* at 8. According to another survey, "almost 80% of [cancer] trial participants did receive [insurance] coverage, and only 5% reported tedious wrangling with insurers." Vastag (Boost), *supra* note 901, at 1304.

3233 GAO (Factors), *supra* note 928.

3234 *Id.* at 2-3, and also at 10-11. "Paperwork requirements can be labor-intensive and time-consuming when staff physicians and nurses must document the necessity of enrolling each patient and negotiate the specific services and amounts to be paid as standard care." *Id.* at 3.

3235 In the above-mentioned Harris case, the cost of "High-Dosage Chemotherapy with Autologous Bone Marrow Transplants" was between $100,000 and $150,000 and the investigator required "pre-secured financing or pre-certification [of coverage] from a prospective patient's insurance company." *Id.* at 708.

3236 *Id.* at 10. This conclusion was criticized by the NIH. *Id.* at 17 and 31-34.

3237 Dana P. Goldman et al., *Incremental Treatment Costs in National Cancer Institute–Sponsored Clinical Trials*, 289 JAMA 2970-2977 (June 11, 2003), at http://jama.ama-assn.org/cgi/reprint/289/22/2970.pdf.

3238 *See* Angell (Publication), *supra* note 898, at 279.

Hence, the regulatory system would not run smoothly if it were not for the threat posed by research subjects willing and able to "police" trials.[3239] Neither the drug agencies nor the ethics committees have enough resources to monitor all clinical trials. They can only detect a fraction of unethical conducts. Their "rate of conviction" is even lower: Only few individuals and companies have ever been punished in courts for illegal actions in connection with medical research. On the other hand, subjects, acting individually or, where possible, in class actions, fare better in lawsuits and, certainly in settlement negotiations.[3240] Without tough liability clauses and courts willing to apply them, the system would almost be one of self-regulation depending primarily on the good faith and honesty of individual researchers and individual firms.

8.6.5.1. General principles of liability under Swiss law

In Switzerland, were it not for Article 7 OClin, investigators and sponsors would escape liability in many situations where a clinical trial causes injuries to subjects. Because the subject has been informed of the risks and has accepted them knowingly, most injuries related to these risks are difficult to compensate; the subject is even told that all risks are not yet known at this stage.

This result is no different from what would happen in "ordinary" medical setting: If a doctor tells his patient "I can give you drug X, but you need to be aware that it often causes the following side effects (e.g., nausea). Moreover, because this product has just been put on the market, it is quite possible that it will cause reactions that are yet unknown and therefore not listed on the drug's label," the doctor will not be found liable if the risks do occur.

Because this situation is unsatisfactory, the OClin offers a solution in the form of a specific liability clause applicable against the sponsor (see subsection 8.6.5.2. below).

3239 *See however* Palmer, *supra* note 212, at 623 (arguing that compensation may not be the most appropriate response to unethical research).

3240 Very few cases are decided on the merits by courts. In the United States, most cases are settled before reaching the courts. In Switzerland, claims get resolved even earlier, that is before an action has even been filed. *See also* subsection 8.6.5.4. below.
In France, nine years following the enactment of the Huriet Law on clinical research in 1988, there was still no Court decision on liability issues. *See Biomedical Research Faces its Judges*, 8(3) INTERN. J. OF BIOETH. 9 (1997).

8.6.5.1.1. The investigator's liability

In an action against the *investigator*, a subject can complain of the former's failure to satisfy her obligations as a physician[3241] or as an investigator.[3242] Liability as a *physician* (essentially a malpractice action for negligence) can be engaged for example because the wrong product was administered or a medical condition was incorrectly diagnosed.[3243] Liability as an *investigator* may arise, for example, because she failed to obtain valid consent,[3244] because she failed to follow the safety measures of the protocol, or because she enrolled subjects who were in fact ineligible to participate.[3245] In many cases, it is not necessary to distinguish whether the obligation owned to the subject derives from the defendant's role as a physician or as an investigator, because the two are congruent. For example, an investigator would violate both obligations if she persisted with a treatment once it became apparent that the subject was experiencing serious adverse reactions.[3246]

To the extent that the usual rules governing contractual or extracontractual liability apply, the investigator always has the opportunity to prove that she committed no fault not even negligent mistakes.[3247] If she succeeds, she escapes liability. Various guidelines and commentators have made clear that the "favorable approval" of the ethics com-

---

3241 See generally under Swiss law ATF 105 II 284. This case concerns liability arising in ordinary medical practice. The doctor, here a surgeon, is liable toward his patient if the latter can establish:
1. that the doctor failed to observe a medical standard (including the duty of information owed by the doctor to her patients);
2. that he, the patient, incurred a damage (including mental distress);
3. that there is a causal link between this failure and this damage.

Furthermore, the doctor can escape liability by proving that she committed no fault, because her failure to abide by the medical standard was neither intentional nor negligent.
See also ATF 108 II 59, at 61, at point 1 (a 1982 lawsuit by a patient against a surgeon who failed to provide complete information); ATF 113 II 429 = JdT 1988 I 180 (cosmetic surgery case); ATF 66 II 34, at 36 (an older and less relevant case where the standards were set very high for the injured plaintiff); ATF 119 II 456, at point 4 (on causality and hypothetic consent). *See also* GUILLOD, *supra* note 77, at 34, 71-73 (fault), 80-83 (causality).

3242 In the United States, the principles of medical malpractice are very similar whether the physician is an investigator dealing with research subjects or an ordinary doctor providing classic treatment to his patients. *See, e.g., Scott*, 606 F.2d 554 (Okl. 1979) (medical malpractice action for failure to secure the patient's informed consent).

3243 For a discussion (under U.S. law) of whether investigators have a duty of care towards subject similar to that of a physician toward his patient, *see* Jansson, *supra* note 192, at 238-44. In my mind, there is no doubt that clinical investigators have a concurrent obligation to provide health care to subjects (within the limits set forth in the consent form).

3244 In clinical trials, the investigator has the burden to prove that she obtained written consent; similarly, she must prove that the subject's consent was indeed informed. In practice, this proof is clearly facilitated by the use of written consent forms. If she fails to bring such proof, she may be held liable for any injury incurred by the subject, whether or not the investigator could have prevented it.
In my view, when consent has *not* been validly obtained, the investigator should not be allowed to establish that the subject would have enrolled in the trial anyway had he been correctly informed (i.e., hypothetical consent). In the context of clinical trials, the legislator has raised informed consent to the status of an absolute legal requirement.
Compare, in the context of "ordinary medical care," with GUILLOD, *supra* note 77, at 76-79 and 83-86; Manaï (procès), *supra* note 155, at 355-58. *See also* ATF 117 Ib 197, at point 5, p.206-210 = JdT 1992 I 214, at point 5, p.220-221.

3245 *See, e.g.*, the complaint filed by the U.S. firm of SSKR&P in the case of Steubing v. Korkak, (Mar. 2003), at http://www.sskrplaw.com/gene/steubing/.

3246 See, in the United States, *Vodopest*, 128 Wn.2d 840.

3247 If the liability is contractual, the fault is presumed.

mittee in no way relieves the investigator of her liability.[3248] The same is true for the "green light" of the drug agency.

The system of liability for fault may be perceived as unsatisfactory, particularly in nontherapeutic trials. The subject bears a significant risk without deriving a personal benefit from the research. Insurance coverage has been instituted precisely to correct this unfairness (see subsection 8.6.5.2. below).

8.6.5.1.2. The sponsor's liability under general legal principles

Under general tort principles (taking aside for the moment the specific regime set forth by Article 7 OClin[3249]), the sponsor is liable to a subject if it caused him or her harm through intentional or negligent actions. This may occur in rare situations, for example when the clinical trial was so badly designed that it caused a prejudice to subjects (e.g., the protocol called for a highly risky but totally unnecessary procedure). In most cases, the sponsor is not in a position to directly create a damage because it is not in contact with subjects.

An action against the sponsor can also be grounded in *product liability* law if the sponsor distributed a product that it knew was – or could have known to be – unsafe.[3250] The defect may pertain to a manufacturing problem (e.g., impurities in the product).[3251] Product liability may also encompass defects in the information accompanying the product (e.g., information found in the form given to subjects). But if the sponsor-manufacturer made its product properly and could not have known of the defect, it escapes liability.[3252]

Finally an action by the subject against the sponsor could have its basis in *criminal law*.[3253] For example, subjects in the United States have invoked sponsors' negligence in designing and supervising clinical trials. But subjects can also lay the blame on the sponsor for having initiated clinical trials when preclinical support for the drug's safety and/or efficacy was insufficient.

3248 *See, e.g.,* SAMS 1997 Guideline, *supra* note 110, at point D.4 at 9.
See however in the United States, Jansson, *supra* note 192, at 261-63 (holding that IRB approval "create[s] a rebuttable presumption of due care in research malpractice actions").

3249 The sponsor's liability under Article 7 OClin is examined at subsection 8.6.5.2. below.

3250 See the Swiss Federal Law on product liability of June 18, 1993; RS 221.112.944; entered into force on January 1, 1994; abbreviated (from the French): LRFP; text in French at http://www.admin.ch/ch/f/rs/2/221.112.944.fr.pdf.

3251 *See, e.g.*, the complaint in Robertson v. McGee, *supra* note 2068.

3252 *See* Article 5.1.e LRFP.
Compare, in the United States, with comment k to section 402A of the Restatement (Second) of Torts (text of comment k cited, for example, in Tansy v. Dacomed Corp., 890 P.2d 881 (Okl. 1994), at http://www.oscn.net/applications/oscn/DeliverDocument.asp?citeID=20346). Comment k calls for an exception to strict liability standards, whenever a therapeutic product was "properly prepared and accompanied by proper directions and warning." On the history of comment k and its underlying justification, see for instance Brown, 44 Cal. 3d at 1058-69. Section 402A has been remodeled by the Third Restatement of Torts.

3253 *See* SJ 2000 p.358 (whereby the Director of the Red Cross central laboratory was convicted of violation of Article 127 of the Swiss Penal Code for having exposed hemophiliacs to the AIDS virus).

8.6.5.1.3. Other liable parties

At least in the U.S., injured subjects are adding to the categories of possible defendants.[3254] REC members have become a tempting target.[3255] "Accordingly, bioethicists have begun to worry about the possibility of being found liable for the advice they give."[3256] Lawsuits against REC members raise the difficult issue of the intrusion of legal principles in bioethical analyses: Judges are invited to decide whether the REC's approval process was correct.[3257] To which extent can judges review how REC members applied ethical norms? Can these ethical norms be distinguished from legal rules?[3258] This issue brings us back to the difficult question of what is bioethics and how does it differ from legal analysis.

The explanatory report accompanying the draft additional protocol to Biomedicine Convention recommends that REC members be *insured* against civil liability. This insurance could be provided either by the institution to which the REC is affiliated (when this is the case), by the canton, or by the sponsor. According to the Steering Committee of the Council of Europe, such insurance would reinforce RECs' independence.[3259]

8.6.5.2. The OClin system of liability and insurance coverage

While liability requiring proof of fault (intentional or by negligence) is admissible for "ordinary medical care," it appears grossly unsatisfactory in the experimental setting. A subject is not a patient; he is incurring greater risks not just for his own benefit, but also in the interest of the investigator, the sponsor and, indirectly of patients and society at large. He deserves better protection.

Thus, justifiably, Swiss law compels sponsors to accept liability for damages incurred in connection with a clinical trial.[3260] This liability is made to rest with the *sponsor*

3254 In the European Union, see SPRUMONT, *supra* note 16, at 167 (for whom European ethics committees are not liable except if they intentionally inflicted damage).
In Switzerland, see Article 7.4 OClin which generally mentions the "other parties" against whom the sponsor can turn once he has indemnified injured subjects.

3255 Because ethics committees are not incorporated as a legal entity, an injured plaintiff can either sue individual REC members or sue the institution which oversees the committee (e.g., the Geneva University Hospitals). In Switzerland, another question would be whether the plaintiff can sue the canton where the REC was set up directly by the canton (and not affiliated to a given institution).

3256 *See* David N. Sontag, *Are Clinical Ethics Consultants in Danger? An Analysis of the Potential Legal Liability of Individual Clinical Ethicists*, 151 U. PA. L. REV. 667, at 668 (2002). *See, e.g.*, the complaint in Robertson v. McGee, *supra* note 2068. As for French law, see G. Memeteau, *Les principes ou le charbon? Incertitudes sur les comités consultatifs de protection des personnes dans la recherche biomédicale* (*loi du 20 décembre 1988)*, 4 (special issue) INTERN. J. OF BIOETH. 39-43 (Mar. 1993).

3257 *See* Mello et al., *supra* note 1873.

3258 "Although the focus of an IEC [institutional ethics committee] is primarily in relation to ethical approval of research project, this role embraces legal responsibilities. There is no precise boundary between ethical and legal responsibilities. … Ethical questions cannot be divorced from the legal framework in which they arise." Australian Health Ethics Committee, Report on Compensation, Insurance and Indemnity Arrangements for Institutional Ethics Committees, at 8 (Nov. 1994), at http://www.nhmrc.gov.au/publications/_files/withdrawn/e25.pdf (however this publication has been rescinded).

3259 *See* paragraph 45 of the COE Explanatory Report, *supra* note 417, at 9-10.

3260 Articles 54.1.a.5 and 54.1.b LPTh. *See also* Federal Council's Message FF 1999 3151, at 3229.
See also Article 31 COE Research Protocol.

because it is normally set to gain if the clinical trial brings about the approval of its product. By contrast, the *investigator* is an individual remunerated by the sponsor to conduct the trial; unless she has stock options or receives another kind of "contingency" fees (see subsection 5.3.2. above), she has no direct financial interest in the outcome of the trial.[3261] The investigator, being an individual and not a corporation, is also less capable of financially shouldering liability: It is the sponsor, not the investigator, that has the proverbial "deep pockets."

Yet the investigator is the party most exposed to the risk of committing mistakes, since she is in charge of actually performing the protocol, carrying out its procedures, and ensuring that subjects always receive appropriate health care. The investigator is legally accountable to the sponsor for any error made by her or by her staff. Under many sponsor-investigator contracts, the sponsor may turn against the investigator if she or her staff has seriously violated the protocol, intentionally harmed subjects, or shown gross negligence in the execution of her/their obligations. To lessen this uncertainty, the contract between the sponsor and the investigator, or as the case may be the contract between the sponsor and the investigator's institution, may contain language to solve future discords[3262]. A possible solution is for all parties to have the same insurance company.

Sponsors and investigators can decide to allocate liability between themselves as they see fit.[3263] Yet, subjects will typically direct their claims toward the sponsor and its insurance company.[3264] Allotment of responsibility decided between the sponsor and the investigator does not concern subjects. Apportionment of liability is settled during the later procedure opposing the sponsor to the investigator.

[3261] Of course, investigators prefer that "their" compound be successful in clinical trials. First, this is a natural feeling since everyone prefers to be professionally involved in thriving enterprises rather than failures. Second, if the trial yields exciting results, and preferably positive results, investigators will be able to publish them in scientific journals, and such publications are absolutely central to the advancement of a scientist's career.

[3262] Article 7.5 OClin allows sponsors and investigators to decide jointly on an agreeable key of repartition for their liability. However, this agreement should not affect subjects, who still can direct their claims exclusively against the sponsor. Indeed, it would be unfair to subjects if they had to divide their claims based on an agreement to which they are not party. *See also* Swissmedic, Essais cliniques de dispositifs médicaux, questions fréquentes, couverture des dommages [Clinical trials of medical devices, frequently asked questions, compensation for damages], point 1)b), (2003), at http://www.swissmedic.ch/md/pdf/vklin-schaden-f.pdf (although this guidance applies specifically to medical devices, and not drugs, it is still relevant because the applicable provisions of the OClin are essentially the same for medical devices and drugs) [hereinafter Swissmedic (FAQ – compensation)]. One should now refer to the document released in 2005 by Swissmedic on insurance coverage, at http://www.swissmedic.ch/files/pdf/Schaeden_Rahmenbedingungen-F.pdf.

[3263] Article 7.5 OClin.

[3264] However, the Geneva University Hospitals ("HUG") insists that subjects be given information about its own insurance policy, and not that of the pharmaceutical sponsor, because it considers having an excellent insurance coverage. Interview with Bounameaux, *supra* note 1718.

8.6.5.2.1. Scope of liability under the OClin

Unfortunately, Articles 54.1.a.5 and b LPTh and Article 7.1 OClin are exceedingly vague as to the scope of liability.[3265] The law does not state explicitly that the sponsor is liable for the acts of the investigator ("vicarious liability").[3266] Is the negligence of the investigator something that the sponsor can be blamed for? We are not told. In all likelihood, the answer is yes.

Nothing is said about the conditions that have to be met to admit liability. One does not even know whether the sponsor's main liability is grounded in *contract* or *tort law*. Yet, the legal consequences can be very different depending on the type retained, for instance with respect to the applicable statute of limitation.[3267]

The LPTh and the OClin do not specify either whether *causality* is a condition and whether it is up to the subject to prove it. While Article 54.1.a.5 LPTh may suggest a causality requirement,[3268] the other two provisions do not point to any causal link.[3269] Commentators have asserted that research subjects do *not* need to prove the exact cause of the injury;[3270] rather, the sponsor should have to rebut a presumption and convincingly show that the injury is attributable to a cause unrelated to the trial. For these commentators, if the study has worsened a pre-existing condition, the sponsor should also be held liable, unless the subject was asked about it and chose to hide it from the research team.

What about *intent*? That neither the LPTh nor the OClin mention this notion could speak either for or against imposing such a requirement.[3271] Under classic Swiss principles of liability law, some degree of fault is required. However, Article 54.1.b LPTh and Article 7.1 OClin seem to set forth a very general rule (which does not mention fault) and the reference to insurance could suggest that fault is not necessary. Once again, it is more congruent with ethical principles if subjects are allowed to claim damages even if

---

3265 *See* Jost Gross, *Staatshaftung und HeilmittelRecht*, LEGES 2003/1, at 137 ("*Die Auslegung dieser Bestimmung* [Article 54.1.a.5 LPTh] *ist nicht ganz einfach* …").
An excellent reference that can be used to fill up the blanks of Swiss law is the Australian Guidelines on sponsor's compensation. These Guidelines cover the key issues that arise when subjects incur injuries in a clinical trial and sue the sponsor. *See* Australian Pharmaceutical Manufacturers Association ("APMA"), Guidelines for the Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial, (Feb. 26, 1997), at http://www.medicinesaustralia.com.au/public/guidcomp.pdf.

3266 This can be an important issue since a claim against the investigator can normally be grounded in contract law with a longer statute of limitation. If the sponsor is made liable for the actions of the investigator, the same time bar should be applied.

3267 Under contract law, the statute of limitation is 10 years, while it is significantly shorter under tort law. Compare Article 127 CO with Article 60 CO.

3268 According to Article 54.1.a.5 LPTh, subjects must be informed of their right to compensation in case of injuries attributable to the trial.

3269 According to Article 54.1.b LPTh, subjects must be guaranteed "full and entire" coverage against injuries incurred within the framework of the clinical trial. According to Article 7.1 OClin, the sponsor answers for injuries incurred by a research subject within the framework of a clinical trial.

3270 *See* D. Sprumont et al., *Essais cliniques, responsabilité civile et contrats d'assurance*, 83 BULLETIN DES MÉDECINS SUISSES 2092, at 2092-93 (2002), at http://www.saez.ch/pdf/2002/2002-40/2002-40-881.PDF [hereinafter Sprumont (Assurance)].

3271 *See also* VanTx Report, *supra* note 148, at 21. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 19 (commentary).

neither the sponsor nor the medical team led by the investigator committed intentional or negligent wrongdoings.[3272]

The law places no restrictions as to the *type of damages* that can be compensated. Damages should thus extend to both direct and indirect losses.[3273] Liability should encompass both physical and moral harm, damage to physical property and loss of income. If the subject dies or suffers debilitating injuries, family members who depended on his income are entitled to compensation for loss of support.[3274] Compensable injuries may result from the investigational drug or from the comparator product.

Another issue is to distinguish damages caused by the investigational procedure from those due to *standard therapeutic treatment* or from the disease itself. Article 54.1.a.5 LPTh suggests – though this ought to have been made much clearer – that only damages *caused by the trial* are covered and that damages incurred in relation with the *standard* aspects of the treatment are not within the scope of the 2002 Federal Regulations.[3275] For instance, a patient may be hospitalized for advanced cancer and be treated by the institution's staff with chemotherapy, while at the same time he is enrolled in a clinical trial where he is prescribed an investigational compound to reduce the side effects of chemotherapy. Establishing the exact cause of an injury may be difficult. If the cause is an error in the administration of the chemotherapy, the hospital is – according to Swiss law – liable; if the cause resides in the investigational product, the victim has a claim against the sponsor.

It appears – although once again this is not entirely clear – that subjects can ask to be indemnified even for injuries which they could have *expected* based on the risk disclosure statement. The informed consent form does not act as waiver of liability for *known* risks. This result can however appear unsatisfying under some circumstances. If, for example, the consent form warns that the investigational compound may cause some subjects to loose all their hair, should a subject be allowed to sue if this risk materializes? Thus, the benefits obtained may need to be weighed against the risks incurred in order to determine whether liability is warranted.

Subjects must be entitled to direct their claims against the sponsor, without having to determine who was *at the origin* of the damage (see subsection 8.6.5.2. above). Thus, subjects do not need to distinguish between interventions from the investigator, her staff, or perhaps the sponsor.[3276]

Swiss law does not indicate which weight, if any, to give to *faults committed by subjects*, both with respect to the sponsor's liability and its insurance coverage. Under standard principles of Swiss law, such faults can be taken into account, usually to reduce

---

3272 *See also* Gross, *supra* note 3265, at 138.

3273 Article 541.b LPTh refers to a "*compensation pleine et entière*" (in German "*vollumfänglich entschädigt*," in Italian: "*indennizzate interamente*"). *See also* Interview with Vital-Durand, *supra* note 484.

3274 *See, e.g.,* Sprumont & Béguin, *supra* note 134, at 899 and 900.

3275 In contrast, the CIOMS Guidelines only require that injuries caused by "procedures performed solely to accomplish the purposes of research" be compensated. "Compensation and free medical treatment are generally not owed to research subjects who suffer expected or foreseen adverse reactions to investigational therapeutic, diagnostic or preventive interventions when such reactions are not different in kind from those known to be associated with established interventions in standard medical practice." CIOMS 2002 Guidelines, *supra* note 105, at Guideline 19 (commentary).

3276 *See also* subsection 8.6.5.2. above.

the sum awarded; an extremely serious fault can even interrupt the causal chain and exclude liability by the normally responsible party.[3277] There is no reason why these principles should not also apply to the area of clinical trials.[3278]

8.6.5.2.2. Sponsor's insurance coverage

Even the sponsor may not be affluent enough to face claims from possibly thousands of subjects. Therefore, the 2002 Federal Regulation requires that all sponsors "cover" their liability.[3279] This is generally achieved – though not necessarily so – by contracting an insurance policy. Indeed, the first sentence of Article 7.2 OClin states that the sponsor *must* guarantee its liability, whereas the second sentence only indicates that the sponsor *can* arrange for insurance coverage.[3280]

The insurance policy's *scope* may vary given that Swiss law does not state any minimum requirement.[3281] The language of the Article 7.2 OClin somewhat suggests that the insurance coverage should match the scope of the sponsor's liability.[3282] However, this is unlikely to be the case since insurance coverage is typically more limited than liability itself. For example, insurance policies limit payments to a certain amount, while the sponsor's liability has no monetary limits.

The insurance policy is normally contracted by and for the benefit of the sponsor.[3283] The law does not stipulate whether subjects are entitled to raise a claim directly against the insurance company or whether it is the sponsor that is to be reimbursed by the insurance for sums disbursed to subjects. In practice however, insurance policies allow subjects to direct their claims directly against the insurance company.

According to Article 7.3 OClin, the sponsor must either have its headquarters (or domicile in the rare case where the sponsor is a natural person) in Switzerland or des-

---

3277 *See, e.g.,* ATF 116 II 519, at point 4, p.523-25 = JdT 1991 I 634, at point 4, p.639-41.

3278 *See however* DuVal, *supra* note 1096, at 33 (according to whom, subjects' fault should only be admitted in case of a "serious and unreasonable departure from clear, research related instructions that directly cause the injury or harm").

3279 *See* Article 7.2 OClin. The LPTh does not mention this obligation. *See also* DHA (Ordinance Comments), *supra* note 522, at 44. The Winterthur insurance company appears to be well-positioned in this market segment. Telephone interview with Pascale Erbeia, lawyer and member of the Geneva outpatient ethics committee (Aug. 20, 2003).
Before the LPTh, sponsors were not legally obliged to subscribe any insurance to cover subject's injuries sustained during the clinical trial. *See* Dominique Sprumont et al. (Assurance), *supra* note 3270, at 2092-96 (observing that more than a third of clinical trials submitted for review between 1997 and 2000 to the Swiss central ethics commission (CES) did not mention any insurance). However, since 1981, the Swiss Medical Science Academy recommended that damages be covered by an insurance policy. See Article II.6. SAMS 1981 Guideline. *See* SPRUMONT, *supra* note 16, at 93-94 and at 219.

3280 In the French version "*doit garantir cette responsabilité*," "*peut conclure … une assurance*"; in the German version "*muss diese Verpflichtung sicherstellen*," " *kann … eine Versicherung abschliessen*"; in the Italian text "*deve garantire la copertura*," "*può stipulare un'assicurazione*."

3281 However, Swissmedic, in cooperation with the Swiss insurance trade association, prepared in 2004 a standard insurance policy. *See* Telephone Interview with Yves Chautems (Mar. 2004), *supra* note 170. The Swissmedic policy was finally issued in February 2005, too late to take it fully into account in this thesis (see note 3262).

3282 The first sentence of Article 7.2 OClin refers to the liability described at Article 7.1 OClin.

3283 *See* Swissmedic (FAQ – compensation), *supra* note 3262, at point 1)b) (confirming that the sponsor is the insured party).

ignate an agent residing in Switzerland.[3284] In this second hypothesis, subjects are entitled to direct their claims against this agent.[3285] Why this rule was established is not entirely clear. If the purpose is only to facilitate the exercise of legal claims by subjects, the same result could have been reached by introducing a mandatory forum/venue in Switzerland,[3286] for example at the Swiss domicile of subjects.[3287] In this hypothesis, even if the sponsor had its headquarters abroad, lawsuits could take place in Switzerland.

According to a survey of European insurance policies, maximum amounts covered for each subject varied between DM 500,000 and CHF 1 million,[3288] with the total coverage for the trial varying between CHF 1 million and DM 100 million.[3289] The average period of limitation was capped at five years.[3290] The premium for these policies fluctuated around CHF 30,000 and 50,000,[3291] a cost which can quickly become a financial stumbling block for non-commercial sponsors.[3292]

According to the Sprumont survey, the Swiss central ethics committee has found various weaknesses in current insurance policies. The most frequent are: the policy appears dubious; the amount covered is insufficient; the duration of coverage is insufficient; or there is no insurance coverage.[3293]

Swissmedic has come up with recommendations to improve and unify insurance policies. It has prepared a template to inform subjects of their rights to claim damages and get insurance coverage.[3294] In 2004, it negotiated a uniform policy with insurance companies and sponsors; its objective was to limit exclusionary clauses in these policies. In 2005, it released a template insurance contact titled "Insurance coverage of liability within the framework of clinical trials of therapeutic products, General conditions for

---

3284 When the sponsor designates an agent in Switzerland, Swissmedic asks to receive copy of the agreement binding them. *See* Swissmedic, Notification form for drug clinical trials, *supra* note 1636, at point 5b.

3285 Article 7.3 OClin. The European Union has a similar rule at Article 19 of Directive 2001/20/EC. The FDA requires that sponsors that neither reside nor have a place of business within the United States designate an authorized official in the United States. 21 C.F.R. § 312.23(a)(1)(ix).

3286 The application of Swiss domestic law is already implicitly mandatory, since the OClin applies to all trials occurring in Switzerland. *See also* Articles 133 and 135 of the Swiss law on International Private Law (SPIL) of Dec. 18, 1987; in French: "Loi fédérale sur le droit international privé"; RS 291; French text at http://www.admin.ch/ch/f/rs/2/291.fr.pdf.

3287 A third possibility would be to have the insurance company have either its headquarters or a branch in Switzerland.

3288 *See however* Amstad (Association), *supra* note 1860, at 5 (indicating that only very few RECs require a minimal insurance coverage *per patient*).

3289 *See* Sprumont (Assurance), *supra* note 3270, at 2095. *See also* Swissmedic (FAQ – compensation), *supra* note 3262, at point 1)b) (recommending that insurance coverage for clinical trials of medical devices be of CHF 1 to 3 million per subject).

3290 *See* Sprumont (Assurance), *supra* note 3270, at 2095. *See also* Swissmedic (FAQ – compensation), *supra* note 3262, at point 1)b) (recommending that insurance policies for clinical trials of medical devices be valid for more 3 years following the completion of the trial).

3291 *See* urgent question of MP Franco Cavalli, *supra* note 878.

3292 MP Cavalli raised the case of the Swiss Institute for Applied Cancer Research which could not afford to pay for its insurance coverage and therefore had to interrupt its clinical trials. *Id.*

3293 *See* Sprumont (Assurance), *supra* note 3270, at 2096.

3294 *See* Swissmedic, Text to be used in the information for trial subjects to explain their entitlement to claim damages in the event of harm caused by a clinical trial, at http://www.swissmedic.ch/md/pdf/vklin-schaden-f.pdf (p.5; although the document refers to medical devices, it also encompasses drug studies).

insurance policies."[3295] This document lists the conditions that the sponsor must follow starting no later than April 2005. The sponsor is allowed to depart from these conditions, but then faces the risk that Swissmedic will not give its clearance. Because of its late release in 2005, this guidance document has not been fully reviewed here.

8.6.5.3. Review by ethics committees

Ethics committees must review the indemnification provisions, including the insurance agreement, benefiting injured research subjects.[3296] The REC should verify that the sponsor has not imposed requirements, including procedural requirements, that would make it exceedingly difficult for subjects to be indemnified; deadlines to notify damages or statutes of limitations come under strict REC scrutiny.[3297]

Before the Swissmedic's template insurance agreement was released in 2005, Swiss law and Swissmedic had said very little about the insurance requirements. It was up to ethics committees to enforce what they considered fair. Their respective practices varied significantly.[3298] RECs rarely perused the entire insurance policy, a document that can be several pages long, but rather relied on a summary, also called the insurance certificate.[3299] The summary contains the key provisions of the insurance policy (e.g., maximum amount paid per subject and/or per study, duration of coverage).

The task of reviewing insurance policies typically fell to the jurist member of the REC. RECs placed great weight on the creditworthiness of the sponsor.[3300] If the sponsor is a well-established multinational pharmaceutical company, this fact alone represents a good guarantee.[3301] It is when the sponsor lacks these deep pockets that the precise content of the policy matters the most.[3302]

The template insurance policy released by Swissmedic in 2005 considerably simplifies the RECs' work. If sponsors confirm that their insurance contracts comply with this policy, RECs have no reason to review in details the actual contracts. The work of sponsors is also facilitated since they know in advance what is considered acceptable.

3295 Swissmedic, (Feb. 21, 2005), at http://www.swissmedic.ch/files/pdf/Schaeden-Rahmenbedingungen-E.pdf. The document sets a minimum indemnity of CHF 1 million per subject incurring physical harm, and CHF 50'000.- per subject incurring damage to his property. Punitive damages are specifically excluded. Confidentiality breaches can give rise to indemnification. Damages are normally covered by the insurance policy if they occur either during the trial or within 60 months of its end. Harms that were specifically announced to subjects (i.e. in the "risk section" of the consent form) as likely to be encountered are not covered. The document imposes a few obligations on subjects, such as the obligation to ask for the investigator's consent before undergoing treatments that are not part of the trial.

3296 Articles 9.2.f and 10.2.l OClin. *See also* Swissmedic (FAQ – compensation), *supra* note 3262, at point 1). *See* WHO (Operational Guidelines), *supra* note 1379, at points 5.3.13 (p.9) and 6.2.3.11&12 (p.12).

3297 *See* VanTx Report, *supra* note 148, at 21.

3298 *See* Amstad (Association), *supra* note 1860, at 5.

3299 Interview with Ciaroni, *supra* note 1338; Interview with Erbeia, *supra* note 3279. *See however* Swissmedic (FAQ – compensation), *supra* note 3262, at point 1)a) (advising ethics committees to review the entire policy).

3300 Telephone Interview with Erbeia, *supra* note 3279.

3301 *Id.*

3302 *Id. See also* VanTx Report, *supra* note 148, at 22.

8.6.5.4. Situation in the United States

It seems amazing, but under U.S. law, there is no specific obligation to indemnify subjects who sustain injuries in the course of clinical trials.[3303] Subjects must be told whether or not indemnification is to be provided.[3304] There is no obligation to subscribe insurance on behalf of subjects.

Thus, in the United States, subjects have to show that the defendant behaved *negligently*.[3305] If they do not succeed in bringing this proof, subjects may even be charged for health treatments made necessary by the *worsening* of their condition due to the experimental product.[3306] On the other hand, contract clauses that would waive researchers' liability for negligence are held void.[3307]

In practice, injured subjects manage to identify plausible claims against parties involved in one way or another in the clinical trial (see subsection 8.6.5.1.3. below). Regardless of whether negligence was duly proven, these actions tend to settle out of court.[3308] Research centers and pharmaceutical companies are not willing to risk their good repute if they can avoid it by paying a few hundred thousands dollars to a handful of injured subjects.

Nonetheless, U.S. bioethics bodies maintain that compensation for harm caused in the trial should be the rule.[3309] Their calls have not been heard so far.

In fact, international law has not (yet?) incorporated a strict requirement to indemnify subjects through either strict liability rules (i.e., no fault liability) or insurance provisions. For example, the Council of Europe's draft additional protocol on biomedical research does not mandate indemnification or insurance coverage.[3310]

3303 *See generally* LEVINE (1986), *supra* note 2550, at 155-59. *See, e.g.*, UCSF, Treatment and Compensation for Injury Statement, at http://www.research.ucsf.edu/chr/Guide/chrH_Injury.asp (offering only a very limited right to be treated and compensated for injuries resulting from participation in a clinical trial.). *See also* section 4.8.10(j) (p.16) of ICH E6 that only requires subjects to be informed of the availability of compensation; also chapter 5.8 (p.23) of ICH E6.

3304 In the United States, see 21 C.F.R. § 50.25(a)(6). *See also* FDA (FAQ-IRB), *supra* note 1814, at question 11.

3305 *See Whitlock*, 637 F. Supp. at 1463-72.

3306 *See, e.g.,* NCI (Simplification), *supra* note 2444.

3307 *See* 45 C.F.R. § 46.116. *See also Vodopest*, 128 Wn.2d at 854-56 ("Medical research using human subjects is one of those settings where public policy reasons for preserving an obligation of care owed by the researcher to the subject outweighs our traditional regard for freedom of contract." *Id.* at 856).

3308 See note 3240 above. *See also* SPRUMONT, *supra* note 16, at 94, n.135.

3309 *See, e.g.,* NBAC (Issues in Research), *supra* note 244, at 5 and at 17.

3310 *See* paragraph 60 of the COE Explanatory Report, *supra* note 417, at 11; also its paragraphs 145 and 146, at 24.

8.6.6. Waivers

8.6.6.1. Waivers of rights

As per general principles, subjects cannot be asked and cannot agree to waive any of the rights delineated in the above subsections.[3311] Any waiver, even in writing, is automatically void, and thus without any legal effect.[3312] For example, subjects cannot waive their right to sue for negligent acts committed by the investigator or her team.

Moreover, the consent form must not contain any *exculpatory language*, that is any clause that could give the impression that subjects are waiving a right.[3313] On the contrary, subjects should be clearly informed of their rights and be explained how to exercise them.

8.6.6.2. Biological material

As alluded to before, biological material has enormous value.[3314] It serves multiple purposes, most notably exploitation for commercial ends.[3315] For instance, therapeutic products and biotechnological tools can be crafted from human cell lines. Consent form often contain provisions according to which subjects waive any ownership rights as to biological material taken from their bodies. It is not absolutely clear whether subjects (or, for that matter, patients) maintain an ownership right to their biological material once removed from their bodies through a procedure for which they gave explicit consent. In such a situation, the subject or patient has agreed for the biological material to be removed. In the absence of any additional agreement, can the research team do with it what it sees fit without having to obtain additional authorization from the subject or patient? While the situation has not given rise to a decision under Swiss law, it has been decided under U.S. law.

The next subsection comments the best known decision on this topic, the U.S. *Moore* case. The following subsection tries to answer how Swiss courts would decide the issue of ownership of subject's biological material. The third subsection touches upon the moral principle of gratuity in health care.

3311 *See* section 4.8.4 (p.15) of ICH E6.

3312 *See* Articles 19.2 and 20.1 CO *cum* Article 27 CC.
In the United States, 45 C.F.R. § 46.116 and 21 C.F.R. § 50.20.
See in the United States, *Vodopest*, 128 Wn.2d 840 ("a preinjury agreement, which releases a medical researcher for liability for negligent conduct which occurs in the course of medical research, violates public policy" and is unenforceable. *Id.* at 862.).

3313 *See* section 4.8.4 (p.15) of ICH E6. In the United States, see 21 C.F.R. § 50.20. A review of FDA warning letters suggests that this requirement is not always strictly followed. *See* FDA warning letter to Matthias McGuire, *supra* note 1848. For examples of inadmissible and acceptable language, see Office for Protection from Research Risks (OPRR), "Exculpatory Language" in Informed Consent, (Nov. 15, 1996), at http://www.hhs.gov/ohrp/humansubjects/guidance/exculp.htm [hereinafter OPRR (Exculpatory)].

3314 *See* subsection 3.4.6.4.

3315 *See, e.g.,* Lori Andrews & Dorothy Nelkin, *Whose body is it anyway? Disputes over body tissue in a biotechnology age*, 351 LANCET 53-57 (1998).

8.6.6.2.1. The *Moore* case

In the U.S. *Moore* case of 1990 (see also subsection 8.3.2.5. above), the California Supreme Court had to tackle the novel issue of biological material ownership. Mr. Moore, the plaintiff, argued that he had maintained property of his cells after their removal, that he was entitled to dictate their proper use, and that he could profit from their commercialization once converted into a cell line.[3316]

The Court disagreed with Moore, finding instead that public interests were best served if medical teams are allowed to use and commercialize extracted biological material.[3317] It gave greater weight to the interests of researchers, including those of the then "infant biotechnology industry," than to those of patients.[3318] The fact that such material was already regularly used for research purposes without explicit additional consent was duly taken into account. Basically, the Court found that the interests of medical innovation by both public and commercial entities had to prevail over the more tenuous interests of the human donor who did not "expect to retain possession of his cells following their removal."[3319] Legal certainty is needed for research and business decisions to be made; such certainty would be impaired if researchers had to track down consent from each and every donor.[3320] The scientific and economic adverse consequences of modifying current research practices in the emerging field of biomedicine were deemed much too great given the ample protections already conferred to the patient by the general informed consent process.[3321] In that sense, the decision of the California Supreme Court was extremely pragmatic, and essentially devoid of a strict legal analysis.[3322] It can be assumed that the role of California in hosting some of the most important biotech firms was not lost on the Court.

A 1993 California Court of Appeal decision distinguished the *Moore* ruling in a case involving issues of ownership of deposited sperm.[3323] The donor had deposited his sperm in a sperm bank to be used by his girlfriend after his death. He left explicit instructions in that regard, both to the sperm bank and in his will; then he committed suicide. The Court of Appeal held that, "even if not governed by the general law of per-

---

[3316] Moore's claim was based on the notion of conversion, "a tort that protects against interference with possessory and ownership interests in personal property." *Moore*, 51 Cal.3d at 134.

[3317] *See id.* at 142-47. Three California Supreme Court judges filed one concur and two dissent opinions. See also for a comment of this decision, Michelle Bourianoff Bray, *Personalizing Property: Toward a Property Right in Human Bodies*, 69 TEX. L. REV. 209, at 236-39 (1990).

[3318] *See Moore*, 51 Cal.3d at 143.

[3319] *Id.* at 136.

[3320] *See id.* at 143. The Moore court referred extensively to the OTA Report on Ownership of Human Tissues and Cells, *supra* note 487, at 27.

[3321] "Liability based upon existing disclosure obligations, rather than an unprecedented extension of the conversion theory, protects patients' rights of privacy and autonomy without unnecessarily hindering research." *Id.* at 144. *See also id.* at 144 and at 147.

[3322] *See generally* NBAC, Research Involving Human Biological Materials: Ethical Issues and Policy Guidance, Report and Recommendations of the NBAC, at 51, (Aug. 1999), at http://www.georgetown.edu/research/nrcbl/nbac/hbm.pdf.

[3323] *See* Hecht v. Superior Court of Los Angeles County, 16 Cal. App. 4th 836, at 846-48 (Cal. Ct. App. 1993).

sonal property," the deceased had, at the time of his death, "an interest, *in the nature of ownership*, to the extent that he had decisionmaking authority as to sperm."[3324]

To summarize, under U.S. law, it appears that a patient has no property rights on his biological material once removed from his body; he is nevertheless entitled, should he wish to do so, to give instructions as to their use.[3325] This conclusion holds, even if – as in the *Moore* case – the patient did not give fully informed consent, because he was not told of the special economic and research interests of the medical team. This solution should encompass both patients receiving care in ordinary setting and subjects enrolled in clinical trials.[3326]

Despite the lack of property interest, the subject's consent is only fully valid if he was informed of the current or future research plans involving the use of his biological material.[3327] Consequently, researchers face liability claims if they did not secure a fully valid consent. Therefore, informed consent forms used in today's clinical trials generally include language regarding ownership and authorized uses of biological material.[3328] Such clauses may also turn up in separate documents.[3329] Typically, these clauses confirm that the research subject has no legal interest in his extracted biological material and/or that he "surrenders" all such interests.[3330] Subjects are informed of the possible uses to which the material may be put to, including the filing of patent applications and the development of commercial products. The European Union goes one

---

3324 *Id.* at 846. The Court further found that there was *no public interest* that could justify State interference with the deceased's will. Deborah Hecht, the girlfriend, was eventually allowed to receive the frozen sperm and use it for artificial insemination. *Id.* at 852-61.

3325 The request of the patient to retain possession of his biological material or his instructions to use it for a specific purpose must comply with regulations (if any) regarding biological hazards. *See Moore*, 51 Cal.3d at 137, n.20 and at 140-41. Moreover, for the California Supreme Court, the right to direct the use of excised biological material rests in "fiduciary-duty and informed-consent theories." *Id.* at 141.

3326 The Moore case was treated as a "patient" situation, and not as a clinical trial, because Mr. Moore was not informed that he was participating against his will in research. *See* subsection 8.3.2.5. above.

3327 *See* Article 22 Biomedicine Convention; CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary) (allowing an exception to informed consent on the use of biological material when the research only poses minimal risk and "is designed to answer an important question and would be unpracticable" otherwise).
In the United States, see however AMA, Commercial Use of Human Tissue, Policy E-2.08, at point (1), at http://www.ama-assn.org/ama/pub/category/8427.html (stating that "human tissue and its products may not be used for commercial purposes without the informed consent of the patient who provided the original cellular material").

3328 The Moore Court was not very optimistic as to the benefits of consent forms documenting the donor's consent to use his biological material. "[C]onsent forms do not come with guarantees of validity. As medical malpractice litigation shows, challenges to the validity and sufficiency of consent are not uncommon." *Moore*, 51 Cal.3d at 146.
The UCSF's website contains a model consent form intended specifically for removal of biological material for research purposes, at http://www.research.ucsf.edu/chr/HIPAA/CF-tissue-OK.doc

3329 *See, e.g.,* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 4 (commentary) (advising the use of a separate form when the use of biological material is not a necessary part of the clinical trial).

3330 However, since consent forms cannot waive any rights, words such as "surrender" or "donate" should be used. *See* FDA (FAQ-IRB), *supra* note 1814, at question 52. The OPRR suggests the following wording: "Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed. There are no plans to provide financial compensation to you should this occur," or "By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above." OPRR (Exculpatory), *supra* note 3313.

step further and asks that subjects be allowed to withdraw their consent as to the use and retention of their samples.[3331]

8.6.6.2.2. Biological material ownership under Swiss law

Under Swiss general legal principles, though the question has not been decided by courts or by statutes,[3332] people probably retain ownership of body parts, even after detachment.[3333]

The next question is whether relinquishing this ownership right necessarily implies explicit consent or if implicit consent can suffice.[3334] An *implicit* consent or surrender would first require the donor's awareness that the circumstances call for his consent; he must know that the medical team intends to gain ownership of his material. As long as the subject is not aware that his biological material may be re-used after removal, he cannot agree to surrender his property right.

It is therefore indispensable to provide subjects with sufficiently specific information. In my view, consent forms for further use of biological material (extracted as part of a clinical trial[3335]) should, at least, explicitly state:

i) which biological materials are going to be extracted (e.g., blood, skin biopsies or excised organ parts);

ii) which are going to be stored;

iii) where (e.g., at the research institution or overseas);

iv) by whom (e.g., the investigator or the sponsor);

v) who else may receive access to the material (e.g., commercial researchers outside the hospital);

vi) how (e.g., identifiable or anonymous samples);

vii) for how long (e.g., for two years or forever);

3331 *See* 15.2.i) draft COE Biological Instrument and paragraph 67 of the draft COE Biological Report, *supra* notes 492 and 493. *See generally* CPMP (3070/01), *supra* note 2298, at 3-4.

3332 The issue is on the Swiss agenda. In April 2004, the Tribune de Genève dedicated its first page to a story of alleged use of biological material without patient's knowledge or consent at the Geneva University Hospital (HUG). The HUG denied and explained that it had strict policies requiring informed consent for research use of patients' excised biological material. *See* Laurence Bézaguet, *Un médecin dénonce l'utilisation de tissus humains pour la recherche*, [A doctor exposes the use of human tissue in research], TRIBUNE DE GENÈVE, April 22, 2004, at 1 and at 19.

3333 See generally on the issue of detached body parts, ODILE PELET, ORGANES, TISSUS, CELLULES: LOIN DU CORPS, LOIN DE LA PERSONNE?, in particular at 128-29, 180, 178-79 (Staempfli 2002). This property right coexists with a personality right (Article 27 ff CC). *See also* Bray, *supra* note 3317, at 212-14 (1990) (discussing the different philosophical theories that recognize or deny a property right in body parts); SAMS, Position de la Commission Centrale d'éthique sur le prélèvement et l'usage des cellules souches humaines pour la recherche scientifique, point III.B. (Aug. 28, 2001), at http://www.samw.ch/content/Dokumente/f_Positionspapier.pdf.
An ownership right in body parts or biological material does not necessarily entail a right to sell them as commodities. Most authors are of the opinion that body parts and biological material should market-inalienable; according to this opinion, biological material can be given, but never sold. *See, e.g.,* Bray, *supra* note 3317, at 215. I touch upon this issue in subsection 8.6.7.2.3. below.

3334 *See* Federal Council's Message regarding the Biomedicine Convention, *supra* note 107, at 321 (admitting the possibility of implicit consent).

3335 Whether retrospective research projects require informed consent is an altogether different issue. *See* subsection 3.4.6.3. above.

viii) for which purpose(s) (e.g., better understanding of the subject's disease or developing commercial products); a general clause may warn the subject that his biological material may be used for other research projects and by other researchers which are *yet unknown at this stage*;

ix) and for whose benefit (e.g., commercial exploitation or use in publicly funded research).[3336]

Assuming that complete information has indeed been supplied, we can address the next question: Can researchers choose between an opt-in (i.e., explicit consent of the subject) or an opt-out clause (i.e., implicit consent unless the subject raises an objection)? Or, more to the point, is an opt-out system at all admissible?

While the law requires explicit informed consent for enrolling into research, it contains no similar clause for further research on stored samples. General legal principles are not precise enough to unequivocally impose *explicit* consent. Therefore, the question is best answered by balancing the interests in presence. An opt-out system serves the interests of research, those of future patients as well as those of the industry.[3337] What are the interests of the subject at stake? Commentators say that subjects may feel alienation and loss of identity if they cannot exercise full control over their excised biological material.[3338] These feelings are not rational,[3339] but rather appear tied to a religious, symbolic or emotional value of biological material.[3340] In my opinion, provided that the subject is given full information and the opportunity to opt-out, the predominant interest is that of research.[3341]

However, a majority of commentators hold the opposite view: Consent for further use of biological material should be *explicit*. Subjects should be allowed to decide exactly what is to be done with their biological material; they could agree to certain use by

---

3336 *See generally* Robert E. Weir, *The Ongoing Debate About Stored Tissue Samples, Research, and Informed Consent*, *in* RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE, VOLUME II (NBAC), at F-1 to F-21, at http://www.georgetown.edu/research/nrcbl/nbac/hbmII.pdf.

3337 The (U.S.) OTA Report gave great weight to the interests of scientists and the *Moore* Court adhered to its views. *See* OTA (Ownership), *supra* note 487, at 7-19.

3338 *See* Bray, *supra* note 3317, at 210 and at 240-44.

3339 In most cases, the subject cannot make any personal use of his excised biological material, which would simply be destroyed were it not used for further research projects.

3340 Since the subject has received detailed information, other interests related to trust in the treating physician and the ability to uncover medical abuses are no longer at stake.

3341 A more delicate question is whether this implicit consent compromises the general rule against subjects' waiver of rights (see subsection 8.6.7. above). If the subject has a strong property right in his biological material, any transfer of that right, even one under an explicit opt-in system, would amount to a waiver of right. *See also* OTA (Ownership), *supra* note 487, at 18. Obviously, this would not work and we need to adopt a more flexible approach to the waiver prohibition.
Another interesting question is whether a subject could be confronted to the choice between being enrolled in the trial and having to accept later re-use of his biological material or opting-out and being denied entry in the trial. This would be a form of coercion. But some similar forms of coercion are admitted. For example, subjects cannot refuse certain procedures stated in the protocol, even if they are not indispensable from a medical or a scientific point of view. They have to accept the entire protocol and cannot reject aspects that they do not like. One could argue that a clause on subsequent re-use of biological material is different because the subsequent research may be fully unconnected to the present protocol.

certain people, and refuse others. Subjects should also have the right to *revoke* their authorization.[3342]

8.6.6.2.3. Gratuity in research

The *Moore* case raises the more general issue of subjects' rights in the commercial exploitation of their biological materials. Many commentators, especially in Europe, consider that ethical principles *demand total gratuity*[3343] on the part of patients and subjects: People who give organs for transplant purposes should not be paid; subjects participating in clinical trials should not be remunerated; patients or subjects who give their biological material should not be compensated.[3344]

The first reason is that people could be swayed by financial considerations to make choices adverse to their health, for example selling an important organ. The second reason relates to the notion of justice: If organs, tissues or cells are sold, only rich people will be able to afford them. A third justification is that some donors are lucky to have a rare type of biological material (e.g., a rare blood type) and would derive an unfair profit compared to those with "normal" biological material. A fourth reason is that research would be impeded if scientists had to negotiate sales agreement with all donors. A fifth explanation amounts to a question of principles: Human beings should not be allowed to "sell themselves."[3345] In my opinion, this last ground disregards the fact that everyone else profits from research! Doctors get paid; companies sell their products; investors in these companies get dividends and stock price increase.[3346] Why should patients and subjects be the only ones not getting a piece of the pie? As a Swiss bioethicist, Carlo Foppa, said, "in reality, we all agree to sell our body for money."[3347] We work for money and we accept that, in the course of our work, we sometimes damage our body. What is the rationale behind allowing, say miners, boxers or prostitutes, to un-

---

[3342] The right to revoke authorization may lapse once the biological material has already been included in a new ongoing research project. Compare with Article 5.3 LRCS (regarding couples' withdrawal of their consent for research use of surplus embryos). *See also* Federal Council's Message, FF 2003 1065, at 1153.

[3343] The word "gratuity" is not widely used in English-speaking countries (although Canada uses it). In the United States, reference is made to the principle of altruistic and free donation. I nonetheless use the word "gratuity" for brevity's sake. Moreover, it translates better the French notion of "*gratuité*."

[3344] In the United States, the practice of paying subjects and donors is more acceptable. For example, women who agree to donate their eggs can earn up to $80,000.-, provided that they meet the strict eligibility criteria demanded by the future "parents" (e.g., height of 5'9 or higher, Caucasian, S.A.T. score around 1250, athletic, college student or graduate).

[3345] See more generally in the context of organ transplants, Olivier Guillod & Gabrielle Steffen, *Attribution d'organes en médecine de transplantation: Le choix préalable de la personne d'être donneur d'organes est-il un critère juridiquement admissible?*, in particular at 16 and at 18-19, at http://www.bag.admin.ch/transpla/gesetz/d/gutacht_guillod_2.pdf. *See also* PELET, *supra* note 3333, at 158-61 and at 462-63; Janet Radcliffe Richards, *Commentary. An ethical market in human organs*, 29 J. MED. ETHICS 139, at 140 (2003), at http://jme.bmjjournals.com/cgi/content/full/29/3/139.
See also Article 6.1 LTransplant; Federal Council's Message on the LTransplant, FF 2002 19, at 134; Article 4 of the LRCS and the accompanying Federal Council's Message, FF 2003 1065, at 1148-49.

[3346] *See also* PELET, *supra* note 3333, at 169-70 (regarding blood-related transactions); Charles A. Erin & John Harris, *An ethical market in human organs*, 29 J. MED. ETHICS 137-38 (2003), at http://jme.bmjjournals.com/cgi/content/full/29/3/137 (in the context of transplantation); Julian Savulescu, *Is the sale of body parts wrong?*, 29 J. MED. ETHICS 138-39 (2003), at http://jme.bmjjournals.com/cgi/reprint/29/3/138 (also in the context of transplantation).

[3347] *See* Foppa, *supra* note 3180 (my translation).

dertake notoriously dangerous activities, but refusing that subjects be paid to assume risks?

Once the key ethical objection is dismissed, all other objections (e.g., the risk of undue influence) can better be addressed by designing appropriate safeguards. Why do we allow healthy volunteers to receive payments for their time and the risks they incurred, but refuse them compensation for donated biological material? There is no logic in accepting that RECs can properly review payment schemes, but cannot be given jurisdiction over compensation for biological material.

8.7. Obligations of research subjects?

Swiss law does not explicitly impose any obligation on research subjects. The ICH is also very vague.[3348] There seems to be a consensus that subjects should not be burdened by any obligation. They should never have to fear lawsuits from the sponsor or the investigator. On the contrary, they should feel free to withdraw from a trial and, more generally, to behave as they wish. A minority of commentators has, however, taken the view that patients sometimes have a moral obligation to participate in clinical trials.[3349]

The next two subsections discuss two duties that could possibly be imposed to subjects.

8.7.1. Obligation to follow directions

Subjects are expected to follow the procedures indicated to them by the investigator or her staff. They should take their prescribed drug, come to the set appointments, fill out questionnaires and so on.[3350] If they fail to do so, they may endanger their own health as would any patient not heeding his doctor's advice.

Subjects who do not comply with the investigator's instructions can also be withdrawn from the study without their consent. This sanction is often specified in the protocol. Subjects should receive this warning during the informed consent process; a reminder should appear in the consent form.[3351] Their remuneration may also be reduced if this was made clear to subjects beforehand.[3352] Their insurance coverage may be restricted if the damage they incurred was caused by their lack of compliance.

3348 *See* section 4.8.10(e) (p.16) of ICH E6

3349 "Même si contribuer à la recherche peut être regardé comme un devoir de solidarité, la loi française ne rend pas cette solidarité obligatoire." [Even if participating in research may be viewed as a solidarity obligation, French law does not make such solidarity mandatory] *See* CCNE N°58, *supra* note 117, at 12. *See also* Michael Baum, *New approach for recruitment into randomised clinical trials*, 341 LANCET 812 (Mar. 27, 1993).

3350 *See, e.g.*, Stanford Sample Consent Form, *supra* note 2576.

3351 The Good Clinical Practices accompanying the former IOCM 1995 Regulation required that subjects be told under which circumstances they may have to cease their participation in the trial. Article 1.9.j) (former) GCP.

3352 *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 7 (commentary).

Evidence suggests that subjects do not always follow the directions they receive.[3353] Noncompliance creates problems for the investigator and the sponsor. Scientific results may be seriously distorted,[3354] with adverse consequences for the patients who, based on the misleading study, receive an inadequate drug or an inadequate dosage; it may take longer than expected to complete the trial. Some studies try to avoid this problem by introducing run-in periods at the beginning of the trial in order to sort out and withdraw from the study subjects who do not adhere to their treatment.[3355] Furthermore, technical tools may be incorporated in clinical trials to make sure that subjects have truly followed directions. For example, computer chip on bottles may record when exactly the subject opened it to take the pills.[3356] Additional analyses performed on the subjects may detect whether the latter truly ingested the prescribed treatment.[3357] Rates of patient compliance should be stated in study reports, whether in journals or in applications submitted to drug agencies.[3358]

8.7.2. Subjects' confidentiality obligations?

In the course of the clinical trial, subjects may have access to information or material protected by intellectual property ("IP"). For example, they are given pills whose ingredients, specific usefulness, or manufacturing process are protected by patent or by trade secrets. Unless otherwise agreed, subjects are, in my view, under no obligation to protect the IP rights of the sponsor or of the investigator.[3359] A subject could, for example, hand over the pill to a rival pharmaceutical company; he could have the pill analyzed and its chemical composition posted on the Internet. This conduct would destroy the patentability of the invention (if the patent application had not yet been filed) or put an end to trade secret protection (see subsection 4.1.6. above).[3360] Because there is no implicit obligation of confidentiality, only an explicit confidentiality undertaking subscribed by the subjects can protect the IP.

3353 *See* Michael McCarthy, *"Dumpers" may confound clinical trial results*, 356 LANCET 658 (Aug. 19, 2000).

3354 *See* Editorial, *Patient compliance in therapeutic trials*, 337 LANCET 823 (Apr. 6, 1991). *See also* ALBERT FANCHAMPS, LES ESSAIS DE MÉDICAMENTS CHEZ L'HOMME, 52 (Pharma Information 1984).

3355 This practice raises however some difficulties because it can lead to an exaggeration of the treatment's efficacy in real-life setting. *See* Pablos-Mendez et al., *supra* note 1533, at 222.

3356 *See Patient compliance*, *supra* note 3354.

3357 As an exception to the general rule, it is admitted that subjects are not to receive full information regarding the procedures implemented to check their compliance with the treatment regime. *See* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 6 (commentary).

3358 *See, e.g.*, K. Squires et al., *supra* note 577, at 314 ("Adherence to treatment was measured by using pill counts at each study visit, but pill counts were not formally analyzed and drug concentrations were not measured during routine study visits.").

3359 In the United States, see Upadhye, *supra* note 623, at 6.

3360 Since the subjects are under no obligation of confidentiality (absent specific agreement), it is unlikely that the sponsor can invoke the experimental use exception to the public use bar. *See id.* at 18-22 (going over the convoluted case law). Similarly, trade secret protection requires that active precautionary measures be implemented to constantly maintain the secrecy of the information.

9. Supervision of clinical trials

In this section, we follow the progress of a clinical trial and see how problems emerging during a trial are addressed. The first two subsections explain how clinical trials are supervised. The first one reviews the reporting obligations of the investigator and of the sponsor. The second one analyses the supervision powers of ethics committees and of Swissmedic. The third subsection recounts the most frequent violations encountered in the context of clinical trials.

9.1. Reporting obligations

The investigator bears the primary responsibility for complying with the protocol, with applicable regulations and with the sponsor's instructions. She must automatically report any deviations.[3361] The channels of communication follow the same pattern as for initial submission of research protocols: The investigator reports to the REC, whereas the sponsor reports to Swissmedic.

Surprisingly section 6 of the OClin nowhere mentions reports *to subjects*. This could imply that subjects do not need to be systematically informed of, say, protocol changes or adverse events. Accepting this interpretation would lead to unsatisfactory outcomes. Rather, it should be assumed that subjects must be told of protocol changes and adverse reactions, at any rate when these factors are relevant to their decision to maintain participation (see also subsection 8.3.3.11. above).

9.1.1. Changes to the clinical trial

During the course of the trial, the sponsor acting jointly with the investigator[3362] may decide to change one or several aspects of the study and, consequently, adapt the corresponding clauses of the protocol. All changes must give rise to a *protocol amendment*.[3363]

Reasons for changes may include identification of a better[3364] or more attractive[3365] treatment for the control arm of the study. Material changes are rare occurrences, be-

---

3361 *See* section 4.5.3 (p.14) of ICH E6. Deviations are also to be listed in the study report submitted to the drug agency. *See* chapter 10.2 (p.13) of the ICH E3. See also subsection 10.3 below.

3362 The investigator is not allowed to change unilaterally the protocol. If necessary to safeguard the health of subjects, she can infringe the protocol, but cannot make valid changes. She may however suggest changes to the sponsor, even though she had initially approved and signed the first protocol. The sponsor is free to approve or refuse the investigator's proposal. If the sponsor refuses the proposal, the investigator has the remedies (if any) that are set in her contract with the sponsor. Contracts passed between the sponsor and the investigator may not recognize the right of the latter to pull out freely from the clinical trial. However, subjects' safety must still always prevail over contract clauses.
See also Van Tx Report, *supra* note 148, at 23.

3363 *See, e.g.,* section 4.5 (p.20) of ICH E9.

3364 For example, in a study of high-dose chemotherapy with stem-cell transplant, the authors indicate that the protocol was changed (for the control arm) to administer five, instead of two years, of tamoxifen, since a longer period of treatment was discovered to be more efficacious. *See* Rodenhuis, *supra* note 3228.

cause mid-course modifications threaten the reliability of the trial. Changes in the conduct of the trial are viewed as a potential source of bias (see subsection 6.2.1.4. above). The sponsor, in particular, has an interest in keeping the protocol unmodified as this will facilitate the endorsement of the study by drug agencies. If feasible, the sponsor will prefer to anticipate alternative courses of action in the protocol itself, rather than to change the protocol. However, patient safety may render changes inevitable.

Formal changes are more frequent and pose fewer problems. For example, adding a co-investigator or changing monitors may require protocol amendments, since the document typically lists all persons involved in the trial. However, formal changes are sometimes indicative of a problem. For example, if monitors come and go too often, this could signal disputes between the involved parties.

9.1.1.1. Objectives of notification

Before the enactment of the LPTh, ethics committees deplored the fact that investigators failed to send protocol updates or changes systematically. Even though the 1995 IOCM Regulation compelled investigators to submit these changes, this duty was all too often infringed; the investigator would not submit them at all or would submit them after they had already been implemented.

The LPTh does not radically change applicable rules since Article 19 OClin resembles the former provisions of the IOCM.[3366] The fact that Swissmedic is a federal public entity may instinctively buttress its authority in the mind of investigators and sponsors. In addition, the LPTh contains criminal sanctions that did not exist under the intercantonal system. According to Article 86.1.g LPTh, anyone who performs or has another person perform on his behalf clinical trials that intentionally do not comply with the law will be sentenced to up to three years imprisonment and/or will be fined up to CHF 200,000.[3367] If there is no intention to endanger human health, the sentence is reduced to a prison sentence of up to three months or a fine of up to CHF 50,000[3368].

Does Article 86.1.g LPTh apply to all violations of the OClin, even if no provision of the LPTh is infringed ? Article 86.1.g LPTh only refers to violation of the "present law." The LPTh does not contain any provision explicitly requiring that investigators and sponsors submit changes to the protocol to their supervising authority (i.e., RECs and Swissmedic). However, the LPTh grants the Federal Council the power to enact ordinances and this delegation is fairly wide. The Federal Council can enact provisions[3369] on good clinical practices, on the sponsor's and the investigator's obligations, on the controls to which they are submitted,[3370] on the way the subjects' consent must be ob-

---

3365 BAZELL, *supra* note 673.

3366 *See* Articles 9.2.f) and 11.2.d) of the (former) IOCM 1995 Regulation, which do not distinguish between essential and minor protocol modifications; *see also* Articles 2.3.c) and Article 2.5.l) of the accompanying Good Clinical Practices.

3367 *See also* Laurent Moreillon, *La réglementation pénale de l'analyse génétique humaine et des cellules souches*, 3 RAPPORT IDS 23, at 30 (2003).

3368 Article 87.1.f LPTh.

3369 The following list is not exhaustive: Paragraphs 5 and 7 of Article 54 are other delegation clauses.

3370 Article 53.2 LPTh.

tained,[3371] on how clinical trials must be announced to Swissmedic,[3372] on the tasks of RECs and on the supervision procedure related to REC.[3373] Even though the LPTh does not govern changes to the protocol, it can be interpreted as prohibiting clinical trials that are not based on a protocol explicitly approved by the REC and Swissmedic. If a clinical trial is conducted according to a protocol which has not been submitted in its entirety to these two authorities, Article 54 LPTh is infringed. Article 54 LPTh is similarly breached if a study starts to follow a new or partly new protocol that has not been fully submitted to the REC or to Swissmedic. Therefore, both Article 86.1.g and Article 87.1.f LPTh can be applied if the investigator infringes Article 19 OClin by not reporting a change to her ethics committee. Similarly, the sponsor will be condemned if it breaches its reporting obligations to Swissmedic.

9.1.1.2. Essential changes

9.1.1.2.1. Scope of the changes

The OClin distinguishes between essential and minor changes in the study protocol.[3374] This distinction is founded on three criteria.[3375]

The first criterion is the most accurate: Any modification that may have an impact on the safety of subjects is deemed essential. For instance, an augmentation of the dosage of the investigational drug which was not initially forecasted will usually constitute an essential modification.[3376]

The second and third criteria are considerably vaguer.[3377] Any change that affects the interpretation of the fundamental documents on which the clinical trial is based is deemed essential; the same is true of any change that affects "other parameters evaluated by the ethics committee." The regulation does not explicitly say which documents are fundamental, while the list of parameters verified by the REC (Article 10.2 OClin) is

---

3371 Article 54.2 LPTh.

3372 Article 54.3 LPTh.

3373 Article 57.3 LPTh. This provision is not quite clear, since the terms "supervision procedure" could refer to either the supervision *of* RECs or the supervision *by* RECs.

3374 *See* Article 19.1&2 OClin. *See also* WHO (Operational Guidelines), *supra* note 1379, at point 9.3.a (p.17). There is in fact a third class of changes: Changes to a protocol involving genetic therapy or genetically modified micro-organisms. These changes undergo the full-scale authorization procedure (see subsection 7.2.4. above), whether or not they are essential; Article 19.6 OClin. This provision does not explicitly say that ethics committees must give a prior favorable opinion backing both the essential and/or *minor* changes; this however would make sense, since the sponsor's request to Swissmedic in support of such an authorization must – according to the second sentence of Article 19.6 OClin – include the changes that have been approved or that have not been opposed by the ethics committee.

3375 Article 19.2 OClin. These three criteria are in fact part of a non-exhaustive list.
See also section 4.5.2 (p.14) of ICH E6 (making a distinction between logistical and administrative changes, on the one hand, and other more important changes on the other hand). As compared to Article 19.2 OClin, section 4.5.2 requires a larger set of changes to be reported. See also in the United States, the more detailed regulations at 21 C.F.R. § 312.30(b)(1), which also lists examples of significant changes. The European Union has established an illustrative list of substantial amendments. *See* EU Guidance (Request), *supra* note 270, at 20 (Attachment 5).

3376 *See* Article 19.2.a OClin. *See also* UCSD-SOPP, *supra* note 485, at 88 (mentioning as examples of major modifications "escalation in the drug(s) dosage(s), the introduction of an additional drug(s), the addition of a new invasive procedure").

3377 Article 19.2.b&c OClin.

too comprehensive to be useful. The two criteria are in fact very similar. Article 19.2.b OClin refers to a change that affects, not the fundamental documents themselves, but their *interpretation*. Since the REC is charged with interpreting (i.e., assessing) these documents and since the other parameters it evaluates (i.e., assesses) are normally put down in writing in documents,[3378] letters b and c of Article 19.2 OClin mean about the same thing.

Another problem with Article 19.2 OClin is that the change is deemed essential even if the influence on subjects' safety, on the documents' interpretation, and on the REC's parameters is minor. In theory, the influence could even be positive; for instance, the safety of subjects is improved by repeating a medical check-up,[3379] an ambiguous clause of the protocol is rewritten to make it straightforward or the sponsor's CRO hires more staff to increase the frequency of its monitoring inspections.

A third problem is that Article 19.1 OClin mentions essential changes to the *protocol*.[3380] Changes in other important documents, for example the informed consent form,[3381] are not explicitly mentioned. Whereas Article 19.1 only refers to the protocol, Article 19.2 OClin appears to encompass changes to documents *other than* the protocol, notably changes to the fundamental documents.[3382] Because Article 19.2 OClin lists examples of essential changes, it should be understood as a clarification of Article 19.1 OClin. Indeed, it is absurd to restrict essential changes to the protocol exclusively. At Article 19.1 OClin, the drafter of the OClin should have added the words "or any other document" after the word "protocol." As a point of comparison, the ICH E6 Guideline requires that ethics committees be informed of changes in the brochure.[3383]

9.1.1.2.2. REC review

Essential changes are communicated to both the REC and Swissmedic; the investigator informs the former, while the sponsor is responsible for informing the latter.[3384]

Depending on the REC's internal procedures, it will either issue a new or confirm its previous favorable opinion.[3385] Once again, the REC must examine whether the ex-

---

3378 In theory, the REC could take into account parameters that are not put in writing (e.g. the good reputation of the investigator). However, for Article 19 OClin to apply, there must be a change to a written document. Thus, if the reputation of the investigator ceases to be good, but no document is changed, Article 19 OClin would not apply. In such a case, Article 12 OClin could apply instead.

3379 Article 19.2.a OClin refers to changes that can have an impact on the safety of subjects. By contrast, Article 20.1 OClin uses a clearer terminology with respect to facts that must be reported to Swissmedic and the REC, since it speaks of facts that may harm/jeopardize the safety of subjects (in French: "*risquent de porter préjudice à la sécurité des sujets de recherche*," as opposed to "*peuvent se répercuter sur la sécurité des sujets de recherche*").

3380 Article 19.5 OClin also speaks of changes to *the protocol*.

3381 In the European Union, changes to the informed consent are explicitly classified as substantial amendments. *See* E.U. Guidance (Request), *supra* note 270, at 20 (Attachment 5).

3382 *See* Article 19.2.b&c OClin.

3383 *See* section 4.4.2 (p.13) of ICH E6. Moreover, according to section 4.4.3 (p.13), "[d]uring the trial the investigator/institution should provide the IRB/IEC all documents subject to review." *See also* section 4.8.2 (p.15) (referring to new informed consent form and written information).

3384 Article 19.1 OClin; compare the French and the German version. See in the United States (for the investigator): 21 C.F.R. § 312.66. *See also* SAMS 1997 Guideline, *supra* note 110, at point C.4. at 8.

pected benefits exceed the risks and inconveniences borne by subjects; new facts that have come to light since the inception of the trial must be taken in consideration to the extent that they bear on this assessment. As was the case for the initial opinion, the REC has a 30-day deadline starting when it is in possession of the complete file.[3386] The REC usually does not need to receive the full file of Article 9.2 OClin again, but only the documents that are to be changed. Article 19.5 OClin does not repeat that the REC is allowed to ask – once more – for additional information or documents, or even an external expertise report; the provision stipulates instead that the deadline starts with the receipt of the proposed change. Yet, both Article 9.3 and Article 11.2 OClin should be applicable, at least by analogy. It would have been preferable to draft Article 9.3 OClin as a general and separate clause applicable at all times during the trial, whether or not the clinical trial's organization is altered. Similarly, the fact that Article 19.1 OClin requires that the sponsor explain to Swissmedic the reasons for the change while no similar obligation is imposed to the investigator is not very logical. Authors of the OClin may have thought that this obligation to motivate the change was self-evident in the case of the investigator, but needed to be confirmed explicitly in the case of the sponsor.

The assessment by Swissmedic follows the same lines as its initial "clearance." Unless it suspects that the change violates the law,[3387] Swissmedic only checks that it has received a full and duly updated file. Surprisingly, Article 19 OClin does not specify Swissmedic's deadline to give its clearance, or more accurately to raise objections; Article 15 OClin should certainly apply by analogy. It remains unclear whether the investigator must first receive the REC's favorable opinion before the sponsor can notify changes to Swissmedic or if both requests to the two authorities are to be made at the same time. Article 19.1 OClin rather suggests that the two requests are made concomitantly. Yet, it would make more sense if Swissmedic's decision to raise objections was based on the fully considered opinion of the REC.

9.1.1.3. Minor changes

Non-essential changes to the protocol (or to the clinical trial's organization, according to a better interpretation of Article 19 OClin) are called *minor* changes.[3388] These only have to be *notified* to the ethics committee; the REC is not supposed to issue a favorable opinion. However, if the REC deems that the change does not qualify as a minor one, it informs the investigator that the procedure of paragraphs 1 to 4 of Article 19 should be followed. Since REC decisions are generally unappealable, the investigator has to adhere to the REC's assessment. Pursuant to Article 19.5 OClin, Swissmedic is not notified of minor changes.

3385 If the REC does not give a favorable opinion, the sponsor and the investigator cannot implement the change in the clinical trial; the trial will continue in accordance with the previous protocol (or organization); Article 19.4.

3386 Article 19.3 OClin. In the European Union, ethics committees have a 35-day period; Article 10(a) of Directive 2001/20/EC.

3387 *See* subsection 7.2.3.1. above.

3388 Article 19.5 OClin. Under the OClin, there is no middle ground between essential and minor changes: A change is either essential or minor. In the European Union, see E.U. Guidance (Request), *supra* note 270, at 10.

9.1.2. Reporting obligations for adverse events

The adverse event reporting system for clinical trials is established by Articles 20, 22 and 23 OClin.[3389] It contains reporting obligations that point in three directions: from the investigator to the sponsor, from the investigator to her ethics committee, and from the sponsor to Swissmedic. The OClin apparently does not envisage the investigator reporting a problem directly to the drug agency, nor the sponsor entering into direct contact with the REC.[3390] Although clear lines of communication can be an advantage, there is no reason why investigators should not discuss problems directly with Swissmedic.[3391]

The reporting rules are spread out in the three above-mentioned provisions.[3392]. Article 12 OClin puts the last touches on this rather complex system. Facts that must be reported by the investigator to the REC and by the sponsor to Swissmedic encompass:

i) any *new fact* that may threaten subjects' safety;[3393]

ii) the *death* of a subject probably due to the drug;[3394]

iii) any deadly harm to the health of a subject probably due to the drug;[3395]

iv) any serious and unexpected adverse event probably due to the drug.[3396]

Although the OClin does not highlight this obligation, the sponsor and the investigator are responsible for analyzing the above-mentioned events.[3397] They must make sure that, despite these events, subjects can safely continue to participate in the trial. Hence, a sponsor cannot be absolved of its responsibility simply by notifying Swissmedic. It must also take spontaneously the necessary precautions to safeguard the interests of the subjects.

3389 In the United States, see 21 C.F.R. § 312.32.

3390 *See* Article 19.1, 20.2, 21.1, 22.3, 23.1&4 OClin *a contrario*.

3391 In the European Union, it is the sponsor that must report adverse reactions to ethics committees. E.U. Guidance (Adverse Reaction), *supra* note 270, at 6.

3392 Articles 22 and 23 OClin apply only to pharmaceuticals; Article 20 applies to all therapeutic products, while Article 24 OClin applies solely to medical devices.

3393 Article 20.2 OClin. See also sections 4.10.2 (p.19) and 5.16.2 (p.25-26) of ICH E6.

3394 Article 23.1 and Article 22.3 OClin.

3395 Article 23.1 OClin ("*atteinte mortelle à sa santé*," "*lebensbedrohende Gefährdung*," "*un pericolo mortale per la sua salute*").

3396 Article 23.2 OClin. Almost the same rule is stated at Article 17.1.(b) cum Article 2(o)&(p) of E.U. Directive 2001/20/EC. *See also supra* E.U. Guidance (Adverse Reaction), *supra* note 270, at 3. In the United States, see 21 C.F.R. §312.32(c)(A). See also FDA, form 3500A, at http://www.fda.gov/medwatch/safety/3500a.pdf. *See also* section 1.60 (p.8) and 5.17.1 (p.26) of ICH E6. See also, in the United States, 21 C.F.R. § 312.32(a) (defining "unexpected adverse drug experience").

3397 In the European Union, see E.U. Guidance (Adverse Reaction), *supra* note 270, at 4.

9.1.2.1. Adverse events and adverse reactions

Before we examine what must be reported, we should be familiar with the key terminology of pharmacovigilance. The reporting system distinguishes between adverse *events* and adverse *reactions*.[3398] Both adverse events and adverse reactions are occurrences that are detrimental to the health or well-being of subjects. Any change for the worse in the subject's condition (occurring after the beginning of the trial) must be considered as an adverse event.[3399] This includes abnormal laboratory results, even when the subject does not feel any different.[3400]

9.1.2.1.1. Causality

The difference between an *event* and a *reaction* hinges on *causality*. Adverse events form the broader category: They are not necessarily elicited by the investigational drug.[3401] Adverse reactions, a subset of adverse events, are those reasonably attributable to the tested drug. According to E.U. terminology, there must be a "reasonable suspected causal relationship" for an adverse event to be designated as an adverse *reaction*.[3402]

Pursuant to this definition, adverse events may be linked, for example, to the clinical trial directly (e.g., a mistake made by a nurse who administered a wrong product), to the treatments administered to the subjects[3403] (i.e., either the investigational compound or the reference product which can be either an active comparator or an inert placebo), or to a wholly external cause (e.g., the subject was killed in a car accident).

Determining with certainty the cause of an adverse event is often difficult. For example, the subject's accident may be due to the fact that he lost consciousness while driving because of the drug's soporific side effect. Or the subject may have been self-medicating so that the investigator cannot be certain if a side effect is due to the study's treatment, to another drug taken by the patient or to the interaction between the two products. Only in a few lucky cases can the investigator attribute with confidence an adverse event to a given and unique cause (e.g., the patient was crossing the street at the green light, and a drunk driver ran over him at 40 km above the speed limit). In most situations, the investigator can only make conjectures that will be verified, but only over time (e.g., a subsequent clinical trial will focus just on the interaction between the investigational drug and aspirin taken in self-medication). Because the regulatory system would not work if it had to wait (months or years) for all the corroborative testing to be completed, it is rooted instead in probabilities; the authorities want to be in-

---

3398 For a long time, the absence of a clear definition of events that required notification to the authority hampered the reporting process. A 1983 study by the U.S. GAO highlighted the lack of unambiguous definition to explain why reports were not filed and processed on time. GAO (Anticancer), *supra* note 1255, at 14.

3399 *Previously* observed medical conditions/problems do not qualify as adverse events, but cannot be used to lower the severity of an adverse event. Thus, an adverse event incurred by a subject who was already very sick at the beginning of the trial is to be recorded in the same way as the same event sustained by a comparatively healthy subject.

3400 *See* Annex 1 of E.U. Guidance (Adverse Reaction), *supra* note 270, at 12.

3401 Adverse event reporting starts with the first dose of the drug. Medical occurrences observed during an initial washout period are not adverse events.

3402 *See* E.U. Guidance (Adverse Reaction), *supra* note 270, at 4 and also at 12.

3403 *See, e.g.,* Article 2(m)&(n) of the European Union's Directive 2001/20/EC; see also sections 1.1 and 1.2 (p.2) of ICH E6.

formed of certain side effects that are *probably due* to the drug. If the investigator can exclude that the effect is due to the drug, there is no reason to inform the authorities. Yet to be on the safe side, the investigator should report effects possibly caused by the drug.[3404] It is mainly her responsibility to assess causality as she is in the best position to take all relevant circumstances into account. An E.U. guidance indicates however that the sponsor can submit its own distinct assessment of causality to the authority, if it rejects the conclusion reached by the investigator.[3405]

Grading systems are available to evaluate causality. A commonly used system goes from "not related" to "unlikely related," "possibly related," "probably related" and finally to "definitely related." An additional category "unclassifiable" can be used when the investigator is unable to assess causality. To categorize an experience as "not related," the investigator determines that another factor is clearly more likely and that available scientific knowledge makes causality implausible. A possibly related event is one "that follows a reasonable temporal sequence from administration of the study drug, [or that] follows a known or expected response pattern to the suspected drug."[3406] However, it is still possible to ascribe it to "a number of other factors."[3407]

The drug to which the OClin refers can be either the investigational compound or the active comparator.[3408] Indeed, since the investigator should not break the blind unless necessary to provide treatment to a subject,[3409] she may well ignore to which drug the side effect is due.

According to E.U. practice, adverse events *known* to be caused by the placebo (nocebo) effect do not qualify as adverse reactions, except when the side effect is due to the content of the placebo (e.g., its excipients).[3410] In practice, a large number of reported side effects are due to the placebo effect.

The language of Article 23 OClin could substantiate an even wider interpretation of the word "drug," that is one that would encompass any drug, and not just the investigational compound and its comparator product. Patients-subjects involved in clinical

---

3404 In the United States, the FDA regulations even contain a kind of liability disclaimer to confirm that the reporting of an adverse event does not constitute "admission that the drug caused or contributed to an adverse experience." 21 C.F.R. § 312.32 (e).

3405 *See* E.U. Guidance (Adverse Reaction), *supra* note 270, at 4.

3406 *See* University of Washington, General Clinical Research Center, Adverse Event Reporting guidelines for participants enrolled under CHRMC IRB approval, http://www.crc.washington.edu/CHRMC_Guidelines.htm [hereinafter Washington University (Adverse)].

3407 *Id.*

3408 See in the European Union, E.U. Guidance (Adverse Reaction), *supra* note 270, at 6. In case the adverse reaction was caused by the comparator drug product, the Guidance recommends that the clinical trial sponsor contact its marketing authorization holder. *Id.*

3409 If the blind is broken for a subject, the subject will usually not be allowed to reintegrate the study once he has recovered from the side effect. To avoid this and nonetheless provide adequate treatments to subjects, a third party can break the blind and provide medical treatment, without telling either the subject or the investigator. However, when the side effect is particularly serious, the investigator will want to break the blind to acquire as much knowledge as possible on its origins so as to prevent this side effect from affecting other subjects. *See also* E.U. Guidance (Adverse Reaction), *supra* note 270, at 8-9 (recommending that the sponsor break part of the blind for the subject having suffered an unexpected serious adverse reactions, while other study participants remain blinded).

3410 See E.U. Guidance (Adverse Reaction), *supra* note 270, at 6. However, the sponsor must report to investigators all serious adverse reactions, without distinguishing between subjects on the active drug and those on placebo, so as to maintain the investigators' blind. *Id.* at 11.

trials may receive many additional medications; they may also continue to take their former medicines (e.g., contraceptives for women). Yet, it would not be sensible to burden authorities with reports of side effects due to pharmaceuticals not directly under study. The objective of Article 23 OClin is to assess the risks pertaining to the clinical trial, not the risks attached to a standard and already approved medical treatment.[3411] Pharmacovigilance already serves this purpose. Therefore, the word "drug" must be understood as including the investigational treatment, the placebo (if the blind has not been broken) and, as the case may be, other drugs used to deliberately enhance the potency of the first treatment.

9.1.2.1.2. Foreseeability

Another distinction introduced by the OClin is based on the "foreseeability" of the effect. Effects that were anticipated are of less concern than unpredicted ones. If the effect was foreseeable, the authorities already know about it since it was – or in any case should have been – mentioned in the brochure or the protocol. Thus, the authorities have already taken it into consideration when they reached their decision that the clinical trial could proceed. Similarly, the investigator can take safety measures so as limit the consequences of the side effect (e.g., advise subjects against driving their car if the investigator knows that the drug has sleep-inducing effects). On the contrary, when the effect comes as a full surprise, it is cause for worry. It implies that the effect was detected by neither the preclinical safety studies nor the previous phases of clinical trials (if any). If this incapacity to detect it earlier was due to the faulty design or interpretation of the former studies, this is ominous. In practice, this incapacity frequently results from the low prevalence of the side effect (e.g., it affects only 1 patient in every 1,000).

Scales have been put forward to measure foreseeability. For example, a type A reaction is one that is predictable and depends on the dose administered (higher doses cause more important reactions), whereas type B reactions are unpredictable.[3412]

Aside from the clear-cut situation where the effect was either foreseeable or unexpected, there is a wide gray area. The existence of the side effect may have been known, but not its severity or its prevalence. Knowing that a drug will provoke depressive feelings in one patient out of every 500 is not the same as finding out that the drug in fact causes one patient out of every 100 to entertain suicidal thoughts. Even though the OClin does not underline this nuance, it should be interpreted as including wholly *and partly* unexpected side effects. This option offers the best protection to research subjects as it allows the authorities to exercise a more precise control over the clinical trial. This definition also matches that of the European Union.[3413] The European Guideline also adds that it is the sponsor (as opposed to the investigator) that must determine whether an adverse event is unexpected.[3414]

[3411] Of course, if the investigational drug creates adverse interaction with already approved drugs, this very important information must be communicated.

[3412] *See* Jeffrey K. Aronson & Robin E. Ferner, *Joining the DoTS: new approach to classifying adverse drug reactions*, 327 BMJ 1222 (Nov. 22, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7425/1222.pdf.

[3413] See E.U. Guidance (Adverse Reaction), *supra* note 270, at 5 and 12 (stressing that unexpectedness can relate to either the specificity or the severity of an adverse reaction).

[3414] *Id.*

9.1.2.1.3. Severity

A third distinction or grading scale concerns the *severity or seriousness*[3415] of the side effect. The OClin's scale has four degrees: death of a subject, deadly harm to his health, serious adverse event, non-serious adverse event. ICH's E6 guideline defines serious as "any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect."[3416]

U.S. clinical trials use a five point grading system. A grade 1 adverse event is of mild severity: It corresponds to "an experience that is usually transient, [and] requires no special treatment or intervention. The experience does not generally interfere with usual daily activities."[3417] A grade 2 adverse event is said to be moderate; it "is alleviated with simple therapeutic treatments [but still] impacts usual daily activities." A grade 3 event is severe as it "requires therapeutic intervention. The experience interrupts usual daily activities." However, hospitalization is not required. Grade 4 applies to life-threatening and disabling events, and 5 is for death. Grades 3 to 5 are included in the serious adverse events (SAEs) category. More detailed guidelines are available and contain lists of adverse events for each grade class.[3418]

9.1.2.1.4. Form of the report

Switzerland has not adopted standard forms to report adverse events occurring in a clinical trial, but those used for pharmacovigilance should be helpful.[3419] The reports should not identify the subject by name, but use only the subject's code number. This rule is stated in Article 22.1 OClin which pertains to reports exchanged between the investigator and the sponsor. However, it should also apply more broadly to reports made to the authorities, even though the latter have the right to ask for the subject's name.

[3415] The European Union highlights the distinction between serious and severe: Severe refers to the intensity of a reaction, while serious refers to the subject's outcome. *See* Annex 1 of E.U. Guidance (Adverse Reaction), *supra* note 270, at 12. See also the explanations from CACR (Dictionary), *supra* note 956, but at http://www.med.umich.edu/cacr/dictionary/R-S.htm ("Serious adverse events result in *death, disability, hospitalization* (or prolongation of a hospital stay), or birth defects," while a serious adverse event is any "event which causes *significant discomfort and requires treatment*, and which poses a *significant or permanent risk of harm* to the subject or requires in-patient hospitalization or prolongation of hospitalization." (emphasis added)).

[3416] Section 1.50 of ICH E6. The definition is the same as that of European Directive 2001/20/EC at Article 2(o). *See also* Annex 1 of E.U. Guidance (Adverse Reaction), *supra* note 270, at 12.

[3417] *See* Washington University (Adverse), *supra* note 3406.

[3418] *See* National Cancer Institutes, Common Terminology Criteria for Adverse Events (CTCAE) (Dec. 10, 2003), at http://ctep.cancer.gov/forms/CTCAEv3.pdf.

[3419] See Swissmedic, Annonce d'effets indésirables suspectés d'un médicament (EI) [form regarding suspected drug adverse reaction], (2003), at http://www.swissmedic.ch/files/formulare/B3.2.16-f.pdf.

9.1.2.2. New facts threatening subjects' safety

As we first read in subsection 9.1.2. above, four different types of circumstances need to be reported to the authorities. The first category, new facts threatening subjects' safety (point i) above[3420]) is the broadest. These new facts may have little to do with the observed effects of the drug on subjects. They may concern the facilities (e.g., a noxious virus is wreaking havoc in the hospital), or the medical team of the investigator (e.g., the investigator is delegating too many of her responsibilities to unqualified personnel). The origin of these facts may lie outside the relevant clinical trial (e.g., a nurse is "euthanasiating" subjects she finds too old or too sick). Or another scientific team (one with no affiliation with the investigator or the sponsor) has found that a close parent of the investigational compound or a close parent compound is carcinogenic if used for a period exceeding two years. According to the E.U. Guidance, adverse reactions related to another trial by the same sponsor or otherwise known to the sponsor (e.g., a preclinical study, an analysis of the literature, pharmacovigilance findings) must follow the same rules as adverse reactions detected by the clinical trial under consideration.[3421]

The two criteria set forth by Article 20.1 OClin are that the fact must be new and that it must pose a threat to the safety of subjects.[3422] Implicitly, "old" facts that compromise subjects' safety should have already been reported as part of the complete file submitted before the initiation of the clinical trial. A fact can be new even if it was foreseen by a party, but not previously reported to the authority (e.g., the sponsor has to admit that it will not be able to deliver sufficient quantities of the investigational product due to a manufacturing problem and the subject's treatment may have to be suspended for 24 hours).

The threat of a prejudice to subjects' health is a more delicate criterion.

First, the threat itself must be reported, even if it does not materialize, for instance because the investigator was able to take the adequate safety measures. Thus, an investigator should theoretically report her finding that a piece of equipment was not functioning properly even if it was repaired before it caused any prejudice to subjects. It is unclear whether the threat must still be reported once it has materialized and caused harm to a subject. There are arguments both in favor and against such a report. On the one hand, the ethics committee and Swissmedic have an interest in knowing what health prejudice subjects have suffered. This knowledge may help them evaluate whether the safety measures taken before by the investigator and the sponsor are sufficient to avert further injuries. If the investigator and sponsor have to report all harm caused to subject's safety, they may have to report even minor unexpected side effects in contradiction with Article 23 OClin, which requires only reporting of *serious* unexpected effects. The literal interpretation of Article 20.1 OClin also speaks in favor of applying Article 20.2 OClin only to potential threats.

3420 Article 20.2 OClin. See also in the United States, 21 C.F.R. § 312.31.

3421 *See* E.U. Guidance (Adverse Reaction), *supra* note 270, at 5.

3422 Compare with Article 10(b) of the European Union's Directive 2001/20/EC whereby the investigator and the sponsor must act when, "in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects." *See also* E.U. Guidance (Request), *supra* note 270, at 9-10.

Altogether, I believe it would be safer for subjects if both safety hazards and actual damages were reported. Article 23 OClin is not broad enough to cover all injuries suffered by patients, since it only deals with adverse effects caused by a drug; adverse effects that have another cause are not within the application scope of Article 23 OClin. Therefore, it would be advisable to include them in the scope of application of Article 20.2 OClin.

Second, the word "safety" is also open to speculation. Should it be understood as meaning "health" or should it be given a broader signification. For example, the inadvertent disclosure of sensitive information concerning the subject might be considered as a threat to his safety, if not his health. Here also, I would recommend a broad interpretation of the word "safety."

The "new fact" may have been uncovered by either the sponsor or the investigator. Both have the (implied) obligation to actively seek and investigate clues that may suggest the safety of the subjects is at risk.[3423] When the clinical trial is taking place at multiple sites, the sponsor or its designee (for example the monitor or the DSMB) must pool all reports received from the various investigators to check for emerging alarming patterns.

Although the OClin only mentions the duty of the investigator to take precautionary measures to protect subjects when new events warrant it,[3424] the investigator should have the right to stop the clinical trial and withdraw her participation when she feels that the study is not progressing properly, and in particular when she deems that subjects are incurring unacceptable risks. The contract signed with the sponsor should never force the investigator to pursue the trial if she believes that this would not be appropriate. On the contrary, the investigator should be recognized at least that measure of independence[3425].

9.1.2.3. Death of a subject

The second category of reportable situations, the death of a subject (point ii) above[3426]), is narrower. According to Article 23.1 OClin, a report is due when the death is presumably due to an adverse reaction to the drug.[3427] Since the report must be made both to the REC and to Swissmedic, the investigator and the sponsor should preferably agree beforehand as to whether such a conclusion can be drawn. The report must be sent as soon as possible but no later than seven days after death was known ("*la constatation*").

A possible question arises out of the confrontation of Article 23.1 and Article 22.3 OClin. The latter provision is also concerned about the death of a human research subject, but does not specify that this death must be (probably) attributable to a drug.[3428]

3423 See, with respect to U.S. sponsors, 21 C.F.R. § 312.32(b) and § 312.56(d).

3424 Article 20.1 OClin. See also the very similar provision at Article 10.(b) of the E.U. 2001/20/EC Directive. *See also* WHO (Operational Guidelines), *supra* note 1379, at point 9.3.c (p.17).

3425 *See e.g.*, Principle 12.2 of the Council of Europe's R(90)3 Recommendation, *supra* note 115.

3426 Article 23.1 OClin. See, in the United States, 21 C.F.R. § 312.32(c)(2).

3427 Compare with Article 17.1.(a) of E.U. Directive 2001/20/EC. *See also* E.U. Guidance (Adverse Reaction), *supra* note 270, at 6.

3428 Article 16.3 of E.U. Directive 2001/20/EC has a very similar rule.

On the contrary, Article 22.3 OClin obliges the investigator to prepare a report[3429] for each and every death. The purpose of this report is precisely to explain and discuss the cause of death. Thus, even if the death is due to a purely external cause (e.g., plane crash), a report must be submitted. The two recipients of this report are the sponsor and the ethics committee; Swissmedic is not mentioned as a recipient. The sponsor will exploit this report to ascertain beyond a doubt that the death was not linked to the drug. Its subsequent marketing application will normally reaffirm this analysis for each death that occurred during a trial. The ethics committee will also use the report to make sure that it is not due to any circumstances over which the investigator had or could have had control. Moreover, ethics committees have the – at least implicit – duty to uphold the trust of the public in research.[3430] Since any death, whatever its cause may be, has the potential to ruin this trust, ethics committees should be prepared to do "PR damage control." If the media want to unearth a scandal, ethics committees should have a ready answer for them. It makes therefore sense that any death be reported to the ethics committee. However, it would have made even more sense to inform Swissmedic of any death. The inconsistency between Article 22.3 and Article 23.1 OClin hence partly subsists.

9.1.2.4. Deadly harm

The third category of reportable occurrences relates to any deadly harm to a subject's health that is presumably caused by the drug (point iii) above).[3431] In this situation, the subject is not dead but dying. One can wonder whether the provision still applies if the harm is deadly only if left untreated. In other words, if the life of the subject was saved thanks to rapid medical intervention (e.g., a strong antibiotic drug is administered), must the authorities also be immediately notified? I would answer yes, although this answer influences only the notification deadline.[3432]

9.1.2.5. Serious and unexpected adverse reactions

The fourth category (point iv) above[3433]) is the residual one. The investigator must report to her REC, and the sponsor must report to Swissmedic, adverse reactions (probably due to a drug) that are *both* unexpected and serious. These are sometimes abbreviated SUSARs, for suspected unexpected serious adverse reactions.[3434] SUSARs must be reported no later than 15 days after they have been detected.

3429 Article 22.3 OClin does not use the word "report," but says instead that the investigator should submit all necessary supplement of information to the sponsor and to the REC (in French: "*remet … tous les compléments d'information nécessaires*"). See the almost identical provision at section 4.11.2 (p.19) of ICH E6.

3430 According to Article 2(k) of the European Union's Directive 2001/20/EC, ethics committees must, among other things, "provide public assurance of that protection" [of human subjects involved in a trial].

3431 Article 23.1 OClin. In French: "*atteinte mortelle à [la] santé [d'un sujet de recherche]*."

3432 The deadline under Article 23.1 OClin is 7 days, while it is 15 days for serious unexpected adverse events probably due to a drug; Article 23.2 OClin. The time limit starts running when the investigator first notices the triggering event.

3433 Article 23.2 OClin.

3434 On these notions, see generally subsection 9.1.2.1. above. *See also* E.U. Guidance (Adverse Reaction), *supra* note 270, at 5.

A contrario, adverse reactions that are unexpected but minor[3435], serious but expected,[3436] or both minor and expected must *not* be reported under Article 23.2 OClin. The fact that non-serious yet unexpected adverse effects need not be reported promptly is potentially problematic. For instance, if the majority of subjects suffer from repeated minor side effects (e.g., constipation), this increases the burden (i.e., inconvenience and pain) borne by subjects. If the expected benefits of the tested drug are also minor (e.g., a drug against acne), it is far from certain that the REC would have given its favorable opinion had it been aware of these side effects. Yet, if the REC is not informed of the frequency of these side effects, how can it revise its initial opinion? Similarly, a non-serious but unexpected reaction can be a warning sign for a subsequent serious reaction.[3437] Especially in early-phase trials, when little is known about the investigational compound, all unexpected reactions ought to be notified to the REC.

A solution could come from an interpretation of the word "serious" that would take into account the incidence of the effect. Thus, if one subject suffers from headaches once every month, the effect is minor, while the effect would be deemed serious if he suffers from the same headache every other day or if all subjects suffer from these headaches once a month. However, such an interpretation appears to me as stretching excessively far the classic definition of the expression "non-serious effect."

Another solution is to have these minor unexpected events come under Article 20.2 OClin, as new facts that can jeopardize the safety of subjects. The topic was discussed in subsection 9.1.2.2. above.

A third, but only partly effective solution is offered by Article 22.4 OClin.[3438] According to this provision, the sponsor must give Swissmedic access to its file of adverse events.[3439] This file records all adverse events that were reported to the sponsor by the investigator (see subsection below).[3440] In the United States, the annual report to the drug agency includes additional information;[3441] for instance, it indicates the number and characteristics of subjects who enrolled but dropped out;[3442] it also presents preliminary results[3443] and explains future study plans.[3444]

[3435] By minor, I mean here non-serious. Admittedly, there could be an intermediate level (e.g. mild) of severity. See however note 3388 above.

[3436] It can be assumed that the subject's death and the deadly harm to his health (both probably due to a drug) can never be expected, or else the ethics committee would not have given its prior favorable opinion.

[3437] Following the clinical trial that led to the death of Ellen Roche at the John Hopkins Medical School, the Internal Committee created to investigate the incident held that the investigator should have informed his IRB that a first subject had experienced coughing. *See* John Hopkins Internal Committee Report, *supra* note 378.

[3438] *See also* Article 16.4 of E.U. Directive 2001/20/EC.

[3439] Article 22.4 OClin. In the European Union, see E.U. Guidance (Adverse Reaction), *supra* note 270, at 4.

[3440] Article 23.4 OClin. In the European Union, Article 17.2 of Directive 2001/20/EC contains a similar rule. *See also* E.U. Guidance (Adverse Reaction), *supra* note 270, at 9-11 (listing the safety information that the sponsor must provide).

[3441] *See* 21 C.F.R. § 312.33, and also § 312.56(c).

[3442] *See id.* § 312.33(a)(2) and (b)(4).

[3443] *See id.* § 312.33(a)(3) and (b)(5).

[3444] See *id.* § 312.33(c).

9.1.2.6. The complete file of adverse events

Pursuant to Article 22.4 OClin, a complete file of all adverse events notified to the sponsor by the investigator must be kept. These adverse events are divided into three classes.

The first class of events must be notified immediately by the investigator to the sponsor.[3445] It includes all *serious* adverse events provided that i) it cannot be ruled out that the event was caused by the drug, and ii) it is not an event specifically excluded from the reporting obligation of the investigator pursuant to the protocol.

The deadline for reporting adverse events belonging to the second class is determined by the protocol.[3446] This second class is quite broad since it includes all adverse events, whether minor or serious, whether anticipated or unexpected.[3447] Also included are abnormal laboratory findings if deemed significant by the protocol to assess the safety (innocuousness) of the drug.[3448] Although this is not immediately apparent by reading Article 22.2 OClin, the limitation comes from the fact that the adverse event must be mentioned in the protocol. If the protocol does not mention this adverse event, either specifically or by a general clause, the investigator has no reporting duty, unless of course this event falls under another provision of section 6 of the OClin. In other words, Article 22.2 OClin does not prevent the protocol from stipulating that minor side effects should not be reported by the investigator or should only be reported once a year. The REC may have something to say against such a protocol, given that it can impose additional requirements that are rooted in ethics and not in the law. Moreover, in practice, the sponsor has an interest in receiving reports of adverse events that are both complete and prompt. Therefore, the sponsor is likely to incorporate strict rules on the reporting of adverse events in the protocol. Through such reporting, the sponsor can follow closely the progress of its trial; it can permanently evaluate the prospects of its investigational compound; it can decide to end the trial prematurely if the adverse effects, even minor, are so numerous that consumers cannot be expected to accept them.

The third class of adverse events reported to the sponsor and included in the complete file is a residual one: It includes any other adverse event that the investigator may spontaneously announce. The investigator may decide to report events that are not listed in the protocol as reportable events; she may also report events sooner than advised by the protocol. In practice, clinical trials are hard enough to manage for the investigator to shun excessive zeal and stick strictly to what is mandated by the protocol.

[3445] Article 22.1 OClin; in the European Union, see Article 16 of Directive 2001/20/EC. *See also* section 4.11.1 (p.19) of ICH E6.

[3446] Article 22.2 OClin. See the almost identical provision at section 4.11.2 (p.19) of ICH E6. See also the slightly different U.S. provision at 21 C.F.R.§ 312.32(c)(1)(i)(B).

[3447] In theory, Article 22.2 OClin also covers adverse events, whether or not they are due to the drug.

[3448] Article 22.2 OClin. In the European Union see Article 16.2. Directive 2001/20/EC; *see also* E.U. Guidance (Adverse Reaction), *supra* note 270, at 3.

9.1.2.7. Reporting obligations of the sponsor to the investigator

The sponsor may also have reporting duties toward the investigators, especially in multicentric trials. Investigators working for the sponsor under the same protocol do not communicate directly with each other.[3449] There may be one principal coordinating investigator charged with managing all other investigators; this person may concentrate the information collected from the various sub-investigators in order to submit it as a package to the sponsor. However, even in this case, sub-investigators do not automatically know what is happening at another sub-investigator's research site. In particular, an investigator is not automatically informed of the adverse events affecting subjects enrolled by another investigator. To forestall this detrimental situation, Article 23.3 OClin obliges the sponsor to circulate the information about serious adverse events among all investigators of a multicentric trial.[3450] More precisely, the sponsor must communicate to all its investigators any death of a subject, any deadly harm to his health, and any serious and unexpected adverse event, provided the effect is probably caused by a drug[3451]. Article 23.3 OClin does not set a deadline for this.

Article 23.3 OClin only refers to serious and unexpected adverse events that could have been caused by a drug (see Article 23.2). When there is no presumed causal link, or when the event is not deemed serious or unexpected, Article 23.3 does not apply and the OClin does not oblige the sponsor to pass the information on to other investigators. This represents a loophole, given that investigators in a multicentric trial have a clear interest in being informed of all adverse events.[3452]

This provision raises the question of whether an investigator in a multicentric trial who has received communication of an adverse effect involving a subject enrolled by another investigator must inform her own ethics committee. In my opinion, the answer should be clearly yes. The purpose of the notification obligation of the investigator towards her REC is to allow the REC to decide whether the risks borne by subjects are still as acceptable as they were when the REC gave its initial favorable opinion. The fact that an adverse event has affected another set of subjects studied by another investigator does not suppress the risks. If the drug causes a serious adverse effect, the risk exists for all patients, regardless of the location of the research site and regardless of the identity of the investigator. Under the present system, each REC has the right to take its decision independently as to whether its "portion" of the trial deserves a favorable opinion. Even though the law allows RECs to adopt a simplified procedure when a first REC has already given its favorable opinion, this is in no way compulsory (see subsection 7.1.2.2. above). For each REC to be in a position to assess the risks and benefits for its share of the trial, it is imperative that it receive complete information about all important side effects.

3449 *See however* section 5.23.5 (p.30) of ICH E6 (calling for facilitated communication between all investigators involved in a multicenter clinical trial).

3450 In the European Union, see E.U. Guidance (Adverse Reaction), *supra* note 270, at 11.

3451 Article 23.1 and 23.2 OClin.

3452 *See, e.g.,* Sprumont & Béguin, *supra* note 134, at 900.

9.1.2.8. Database of adverse reactions

The European Union asks that all suspected unexpected serious adverse reactions (SUSARs) be reported in its general database.[3453] The database lists all such reactions observed in clinical trials provided that at least one research site is located on the territory of a Member State.[3454] Thus, a SUSAR occurring at a Swiss site would have to be reported if the multicentric protocol is also being carried out in France. This database allows European authorities and Member States to gauge the safety of investigational medicines tested in clinical trials. Safety assessments are important first to protect human research subjects.[3455] The safety data can also be considered when the European Agency must decide on drug marketing applications. Switzerland does not maintain a specific database of adverse reactions detected during clinical trials.

9.1.2.9. Events that do not require reporting

Not all adverse occurrences need to be reported to Swissmedic and to ethics committees. A large number of such events are only notified by the investigator to the sponsor (see subsection above). For example, adverse reactions that are not serious or that are not unexpected (except for life-threatening ones) need not be reported specifically to the authorities. There is no reporting requirement either if an adverse occurrence seems unrelated to the administration of one of the drugs.[3456]

To minimize its own reporting burden and that of the investigator, the sponsor should regularly update the protocol and the brochure.[3457] Once they specify that the adverse event is a possible or likely risk, the occurrence should only be reported to the extent that these documents explicitly call for a report. For example, the brochure may state that there is no need for the investigator to make an advance report of a laboratory result within a certain range.

3453 Article 17.3 Directive 2001/20/EC. This same European database also contains reports of adverse reactions reported once the approved drug is marketed. *See* E.U. Guidance (SUSARs), *supra* note 270, at 2.

3454 *Id.* at 2.

3455 *Id.* at 4. Because the database can be searched using different criteria, it can also identify risks that are not related to the drug itself, but to other factors such as the conduct of a given sponsor.

3456 This rule corresponds to a recommendation of the VanTx Working Group. *See* VanTx Report, *supra* note 148, at 25.

3457 *See, e.g.*, Kessler (Regulation), *supra* note 447, at 283-84.

9.2. Oversight by the authorities

What is the role of the authorities once the clinical trial was allowed to begin? This subsection answers the question.

9.2.1. Oversight by RECs

9.2.1.1. Extent of the post-approval role of RECs under Swiss law

Read literally, the OClin seems to limit RECs' supervising role to the receipt of adverse event reports.[3458] Moreover, once the trial has received the initial favorable opinion, Swiss law calls for annual submission of an updated list of adverse events.[3459]

Yet, the ICH E6 Guideline goes much further, as it recommends that RECs "conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to subjects, but at least once per year."[3460] The former IOCM 1995 Regulation also contained provisions whereby investigators had to regularly report the progress made in the trial to their RECs.[3461] It is surprising that these clauses were not espoused by the OClin.[3462] Similarly, the European Directive makes no mention of annual review. In contrast, the United States has implemented this recommendation (see subsection below).

When asked whether they re-assess periodically approved clinical trials, two Geneva RECs answered that they do not.[3463] The HUG-REC requests investigators to return a yearly questionnaire, but the information contained therein does not serve to re-evaluate ongoing studies.[3464] Ethics committees throughout the world have proved unable to review effectively adverse event reports. The task can be overwhelming. The time constraints placed on RECs along with their militia organization render such involvement difficult (see subsection 7.1.4. above). Only few REC members have the ability, time, and dedication to do more than what the law requires of them. The risk is that Article 12 OClin remains a dead letter.[3465] If RECs only rely on periodic updates provided by the investigator, such as serious adverse event reports[3466], they may overlook important information that could have changed their view on the clinical trial. It is often regretted that investigators' reports come without any background information and are

---

3458 *See* Article 23.4 OClin.

3459 *See* Article 23.4 OClin. *See also* paragraph 13 Helsinki Declaration. *See* Ummel & Mandofia, *supra* note 39, at 60 (highlighting the same problem with respect to the former IOCM regulation).

3460 *See* sections 3.1.4 (p.10) and 4.10.1 (p.19) ICH E6. According to the paragraph 13 of the Helsinki Declaration, ethics committees have "the right to monitor ongoing trials." In the United States, see 21 C.F.R. § 56.109(f). *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2; WHO (Operational Guidelines), *supra* note 1379, at p.1 and at chapter 9 (p.16); Truniger et al., *supra* note 1337, at 2401.

3461 Article 11.2.e) of the (former) IOCM 1995 Regulation.

3462 For the overview of the situation in Switzerland before 1993, see SPRUMONT, *supra* note 16, at 97-98.

3463 Interview with Ciaroni, *supra* note 1338; interview with Bounameaux, *supra* note 1718.

3464 Interview with Bounameaux, *supra* note 1718.

3465 Similarly, in the United States, the obligation to conduct continuing review appears not to be always strictly followed. *See, e.g.*, FDA warning letter to Matthias McGuire, *supra* note 1848.

3466 Article 23.1&2 OClin.

consequently very difficult to interpret.[3467] If the investigator is not highlighting the significance of the reported event, the REC cannot really assess its impact on subject safety. Often it is the investigator herself who is not sure what to report and how. Clinical trial researchers often perceive this reporting system as imposing excessively bureaucratic obligations.[3468] It is therefore no surprise that the system is not operating efficiently at the REC level either.

Despite these hurdles, RECs should adopt a more proactive stance.[3469] For instance, at least one member should, from time to time, visit the research facilities. He should talk with subjects he encounters in order to hear about their impression. Their responses can be used to improve the ongoing trial or other subsequent trials.

9.2.1.2. IRBs' continuing review in the United States

The FDA requires that IRBs receive and consider periodical progress reports prepared by investigators.[3470] These reports should contain information about the number of subjects who have been enrolled and those who have dropped out, as well as about the drug's risks and benefits so far ascertained. This information should allow the IRB to review and update its initial risk/benefit analysis. The IRB should also verify that the documents used by the investigator, especially the consent forms, are current in that they match the more recently acquired knowledge regarding the drug. It should stop research that is not being conducted properly or that has caused unexpected serious harm to subjects.[3471]

A U.S. study by the Office of Inspector General (OIG) found that continued supervision of clinical trials by IRBs was seriously lacking.[3472] Provided there is enough time at the end of a session, IRBs will hastily go over documents sent by the investigator, focusing only on the most serious adverse events.[3473] As in Switzerland, U.S. IRBs find it impossible to sort between serious problems and inconsequential ones simply based on

---

3467 *See, e.g.,* GAO (Insufficient), *supra* note 893, at 9.

3468 In 2001, Ellen Roche, a healthy volunteer in an asthma study at the John Hopkins University, died. It was later found that the investigator delayed reporting to his IRB the side effects that another healthy volunteer had suffered (see note 3437 above). Moreover, the investigator had administered the investigational treatment to Roche before elucidating the cause of the adverse event incurred by that other patient. Further investigation at the University uncovered failures by affiliated IRBs to appropriately review protocols. See note 987 above. *See generally* NBAC (Issues in Research), *supra* note 244, at 16.

3469 *See however* COREC, *supra* note 1379, at point 7.33 (p.19).

3470 *See* FDA, Continuing Review After Study Approval, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators, (1998 update), at http://www.fda.gov/oc/ohrt/irbs/review.html. *See also* OIG (Reviewing), *supra* note 1187, at A-1; UCSD-SOPP, *supra* note 485, at 82-86.

3471 *See* 21 C.F.R. § 56.113. Suspensions and terminations decided by IRBs must not only be reported to the investigator, but also to the FDA. *Id.*

3472 *See* OIG (Reviewing), *supra* note 1187, at i.

3473 "For example, at one IRB meeting we observed, several annual reviews and amendments were approved within the last 15 minutes of the 2½ hour meeting. At another site, several members were visibly hurried to end the almost 6 hour meeting and the board relied mainly on the assessment of the primary reviewer for the annual re-reviews. One IRB member told us that he reviews the continuing review summaries during the board meeting to see if a patient has died. If no patient has died, then he generally will not raise questions." OIG (Reform), *supra* note 877, at 6. *See also* OIG (Reviewing), *supra* note 1187, at 7.

the stacks of documents they receive.[3474] The reports they receive can be so abstract that IRB members cannot fathom the impact on subjects' safety (see subsection 9.2.1.1. above).[3475] The continuing review is so riddled with problems that the OIG recommended to do away with the strict requirement of annual protocol review:

> On the basis of our review, this mandate generates substantial burdens on IRBs and does not have the intended effect. It compels IRBs to devote too much effort to routine, paperwork reviews at a time when the quantity of that paperwork is mounting. It impedes them from taking a more strategic approach – one that would enable them to concentrate on research involving substantial risks to human subjects …[3476]

9.2.1.3. Specific powers of RECs

Article 12 OClin allows RECs to withdraw their favorable opinion or to ask for a full reassessment of a clinical trial if the circumstances warrant it. Three hypotheses are contemplated. One relates to the serious adverse events that have been discussed in the previous subsection.[3477]

A second related hypothesis has to do with serious incidents referred to in Article 23.2 OClin (i.e., a subclass of serious adverse reactions).[3478] Therefore, the terms cannot be interpreted broadly to include any disturbing episode (e.g., the study nurse is mistreating subjects). This is regrettable as RECs would have had the use for a general clause allowing them to "police" clinical trials.

The third hypothesis is even broader and concerns new scientific facts, which would justify such a reappraisal;[3479] the reference to "new" facts could mean two things: new for the REC or new because they did not yet exist when the REC gave its previous favorable opinion. Of course, if a fact was deliberately hidden from the REC, neither the investigator nor the sponsor may complain if the REC acts upon it when it finds out. More generally, lies or misleading statements by the sponsor or the investigator should cause an immediate reassessment of the REC's favorable opinion, as well as harsher supervision measures (e.g., the presence of an external independent monitor). Even though the OClin does not deal with this issue, there should be sanctions against the sponsor and/or the investigator. But if the REC is to assume an active supervising role, it must have corresponding enforcement powers. Thus, if the REC detects violations of the GCP, but especially deviations from ethical principles (e.g., one nurse humiliates the

---

3474 "The IRB officials equate the review of AERs to that of looking for a needle in a haystack." OIG (Reviewing), *supra* note 1187, at 7.

3475 One IRB requires "investigators to fill out an accompanying adverse-event report form to assist the IRB in performing a risk assessment. These forms seek investigators' advice concerning the relationship of the adverse event to the intervention, whether or not a change in a protocol is necessary, and whether or not information about the adverse event is germane to consent and/or reconsent." OIG (Promising), *supra* note 1882, at 6-7.

3476 OIG (Reform), *supra* note 877, at 11.

3477 Article 12.1 and Article 23.1 OClin.

3478 Article 12.1 ("*incidents graves*," "*unerwünschte … Vorkommnisse*," "*eventi gravi*").

3479 Article 12.1 OClin ("*faits scientifiques nouveaux*," "*neue wissenschaftliche Erkenntnisse*," "*nuove scoperte della scienza*").

subjects), it should have effective reprimand measures at its disposal. Furthermore, the REC should disclose its findings to Swissmedic and to the canton hosting the trial.[3480]

A difficulty arises when the fact has not been intentionally concealed, but is nevertheless anterior to the REC's decision. Imagine the case where the REC learns belatedly of a Japanese research paper disclosing long-term safety risks related to the use of the compound. The REC might want to stop or suspend the phase III trial until the sponsor has carried out additional non-clinical or smaller clinical studies to evaluate these risks. Such an action would evidently be in the best interests of phase III human subjects. Clearly, it is only logical that it be permitted. If Article 12.1 OClin was interpreted as including only facts that did not exist at the time of the REC's approval, the REC still would not be able to act upon this finding, which would be shocking.

A more thorny question is whether the REC should be allowed to change its mind, if the circumstances have not changed. An *a contrario* interpretation of Article 12.1 OClin would lead to a negative answer. An abrupt turnaround by the REC could cause hefty financial damages to the sponsor, even if the trial is only suspended. However, the well-being of subjects should take precedence over set expectations. A possibility would be for the REC to make a greater use of the conditions and commitments it can impose on the investigator at the time of issuance of its favorable opinion. We have seen that the REC's opinion need not be unconditional, but on the contrary can include conditions or even restrictions (see subsection 7.1.2.7. above). Among the possible conditions "negotiated" between the REC and the investigator, there could be the pledge of the investigator to submit to occasional REC review based on on-site "inspections" and to comply with the REC's ensuing recommendations.

Under Article 12.2 OClin, the consequence of the withdrawal of the opinion is a notification to the investigator, to the canton and to Swissmedic. Does this withdrawal mean that the investigator must stop immediately her clinical trial? It is an implicit principle of the OClin that, at all times, clinical trials must "have" a REC's favorable opinion and Swissmedic's clearance. Yet, the OClin does not explicitly give RECs, but Swissmedic, the power to halt a trial.[3481] Therefore, it could be argued that the REC's withdrawal of its favorable opinion is not immediately effective, but becomes so only when "confirmed" or implemented by Swissmedic. Although this interpretation sticks to the letter of the OClin, it is not satisfying. What happens if Swissmedic fails to act promptly to stop the trial? It is true that, in practice, this situation should not occur often. Yet, it is appropriate to give more weight to RECs' decisions by recognizing that they have a direct and independent impact on clinical trials, regardless of Swissmedic's subsequent decision.

Aside from their power to withdraw their favorable opinion, Swiss RECs should be recognized the broad power to negotiate new conditions with the investigator. In comparison, U.S. IRBs are often granted additional rights. For example, IRBs at the University of California at San Diego can also impose "c) compliance audits; … e) restrictions on serving as an investigator on human subjects protocols; f) research privilege probation; g) suspension or termination of research privileges; h) requiring additional educa-

[3480] Article 12.2 OClin only applies to the withdrawal of the favorable opinion, but ought to be extended to all other sanctions decided by the REC.

[3481] *See* Article 27.2 OClin.

tion and training of the investigator or their research staff [sic]; i) embargo or retraction of publications; … k) or reclassification as possible scientific misconduct."[3482]

9.2.2. Supervision by the drug agency

In subsection 7.2., we noted that the role of Swissmedic at the onset of a clinical trial is relatively modest: It grants – almost automatically – clearance provided that the sponsor's file is complete and that there is no obvious ground to doubt compliance with existing regulations. Once the trial is underway, Swissmedic's role expands.

9.2.2.1. Trial suspensions

9.2.2.1.1. New information

Like the REC, Swissmedic has the power to act upon new facts. According to Article 27.2.b OClin, it can suspend, stop or submit to conditions a clinical trial if this is necessary in view of the new information. This new information must concern either "innocuousness" or "scientific basis."[3483] Innocuousness must be taken to refer to the safety of the investigational treatment, including possibly its comparator arm and the other medical procedures involved. The expression "scientific basis" is exceedingly vague:[3484] Why was the language of Article 12.1 OClin ("new scientific facts") not retained, at least for the sake of consistency? Which is broader: "scientific basis" or "scientific facts"?

Since Swissmedic normally does not analyze the risk/benefit ratio at the time of clearance, it is doubtful that it relies on a given "scientific basis" in order to take its decision. The expression "scientific basis" could instead refer to the basis for the clinical trial itself, in which case it would be equivalent to "scientific facts" since the latter also have to be relevant to the ongoing clinical trial.

Contrary to RECs at Article 12.1 OClin, Swissmedic is not constrained by the term "serious." A minor side effect can constitute "new information about innocuousness."

9.2.2.1.2. Objective reasons

According to Article 27.2 OClin, Swissmedic can also suspend, stop, or impose restrictions to a trial if objective reasons lead Swissmedic to believe i) that the conditions of the authorization are no longer satisfied; ii) that the sponsor's file has been modified with-

---

3482 UCSD-SOPP, *supra* note 485, at 112.

3483 *See* Article 27.2.b OClin ("*innocuité … bases scientifiques*," "*Unbedenklichkeit ... wissenschaftlichen Grundlage*," "*innocuità ... base scientifica*").

3484 The European Union's terminology refers to the amendments that are likely "to change the interpretation of the scientific documents in support of the conduct of the trial." Article 10(a) of Directive 2001/20/EC. Other grounds for compulsory notification to the Member State's authorities and to the ethics committee are substantial amendments that "are likely to have an impact on the safety of the trial subjects" or other significant amendments. *See also* E.U. Guidance (Request), *supra* note 270, at 8-9. The FDA has detailed regulations at 21 C.F.R. § 312.42.

out prior notification; or iii) that the clinical trial is not carried out in compliance with its file.[3485]

The mention – until the revision of 2004 – of "objective reasons" was startling.[3486] Are authorities inclined to apply the law without objective reasons? If the words had been deleted, could Swissmedic have concluded, *without any objective reason*, that the sponsor's file had been changed without prior notification? If these words are not to be taken as a sign of distrust of sponsors against Swissmedic, should they mean instead that some objective reasons are enough, even though Swissmedic does not have a definitive proof of misconduct. That interpretation too is a bit specious. Most administrative decisions are taken on the basis of objective reasons, and not necessarily on full-proof evidence. Moreover, pursuant to Article 27.3 OClin, Swissmedic is obliged to first let the sponsor express its position. Thus, the latter is given the opportunity to rebut these "objective reasons."[3487] Contrary to European law, no exception is made for urgent situations.[3488]

As for the three hypotheses of Article 27.2.a OClin mentioned above, they also give rise to a critical appreciation.

The first hypothesis (point i) above) consists in the conditions of authorization no longer being met. The problem is that, except for special clinical trials involving genetic somatic therapy and genetically modified micro-organisms, there is no authorization, but only a favorable opinion-clearance, process. Article 15.2 OClin – misleadingly – stipulates that Swissmedic *authorizes* the trial if it has no objection to raise. Yet, the intent of the legislator was to ground the clearance system in sponsors' notifications, and not to make it an authorization process. Nonetheless, from the December 2000 draft of the OClin,[3489] it can be inferred without a doubt that the word "authorization" at Article 27.2.a OClin must be construed as including both clearance and full-scale authorization. In that respect, Article 22.2 of the December 2000 *draft* OClin was clearer: It referred to the conditions of the said Ordinance being not or no longer satisfied. The 2004 revision of the OClin corrected this mistake.[3490]

The text of the 2000 proposal also allows us to deduce that the conditions underlying clearances (or authorizations) should be understood so as to *encompass all provisions* of the OClin. In other words, Article 27.2.a OClin should not be restricted to conditions over which Swissmedic has control, but should comprise the provisions applied or enforced by the REC. In particular, it should not be limited to the conditions referred to in

---

3485 I translate the French "*documentation*" by "file." The German and Italian versions of the OClin use respectively the term "*Dokumentation*," and "*documentazione*," consistently throughout the OClin, whereas this is not the case of the French OClin, which also refers to the "*dossier*."

3486 In the German, respectively Italian version: "*objektive Gründe*," "*motivi oggettivi*." The 2004 OClin revision removed the word "objective."

3487 The sponsor has one week to do so; the deadline is the same as in the European Union under Article 12.1 of Directive 2001/20/EC. Under U.S. law, there is no deadline when the FDA decides a clinical hold (see 21 C.F.R. § 312.43(c)); the deadline is 30 days if the FDA decides the termination (21 C.F.R. § 312.44(a) and (c)(1)).

3488 Compare with Article 12.1 of the Directive 2001/20/EC that contains an exception "where there is imminent risk." See also the similar exception under U.S. law at 21 C.F.R. §312.43(c) and §312.44(d).

3489 *See* Article 22.2 of the 2000 draft OClin.

3490 See the new Article 27.2.a OClin, which entered into force on September 1, 2004.

Article 54.4 LPTh, that is the conditions specifically imposed to the sponsor by Swissmedic along with the latter's clearance decision.

Certainly, establishing whether the ethical and slightly subjective conditions of section 3 OClin (i.e., the section on the REC's opinion) are met is more difficult. Swissmedic may have trouble determining, for instance, whether the information given by the investigator to bring subjects up to date is indeed adequate and complete (see Article 10.2.h OClin). The solution is *closer cooperation* between Swissmedic and ethics committees. Presently, this cooperation is limited. Swissmedic receives RECs' opinion on the investigators' applications; according to Articles 12.2 and 27.5.a OClin, RECs communicate to Swissmedic their decisions to withdraw their favorable opinions and vice versa for Swissmedic; under Article 29.3 OClin, Swissmedic provides specialized information to RECs members. Aside from that, there is no formal collaboration mechanism. For example, if a REC *suspects* serious incidents that would, if confirmed, warrant the withdrawal of the favorable opinion, there is no official channel (under the OClin) to pass its misgivings on to Swissmedic; it cannot invite Swissmedic to inspect the investigator's facilities. In fact, the REC is not even invited to attend inspections decided by the Agency.[3491] Ethics committees are informed only if the inspection leads to one of the measures of Article 27.2 OClin (i.e., interruption, prohibition, charges or commitments)[3492]. Undeniably, Swissmedic and RECs would have much to gain from a closer collaboration, since there is significant overlapping between their respective tasks.

The second hypothesis of Article 27.2.a OClin (point ii) above) appears straightforward. If the sponsor brings any change in the documentation (and not just the protocol) required at Article 14 OClin, without first notifying Swissmedic (see also subsection 9.1.1. above), the latter is entitled to stop the clinical trial, to suspend it or to impose conditions or commitments to the sponsor. Article 14.3 OClin obliges the sponsor to notify Swissmedic of any changes to the file ("*documentation*"); this notion refers to the documents of paragraphs 1 and 2 of Article 14 OClin. As for Article 19.1 OClin, it only mentions changes to the *protocol*, and not the other documents.[3493] The two provisions partly overlap.

The third hypothesis of Article 27.2.a OClin (point iii) above) concerns situations where the clinical trial is not conducted[3494] in conformity with the file ("*documentation*"). For instance, the investigator is not abiding by the protocol (e.g., she added new procedures or has modified the drug's dosage). Any intentional departure from the current protocol necessitates a change of the protocol. The main document that states how the trial must be conducted is – of course – the protocol. The other documents are not necessarily related to the conduct of the trial; for example, the brochure explains the characteristics of the investigational product, but these characteristics by themselves are not directly linked to *how* the trial is *conducted*. The word "conduct" seems to imply tangible or physical actions. Thus, for instance, if the sponsor terminates its insurance policy, it is

---

3491 Swissmedic decided in 2004 to notify RECs of inspections and to provide them with a copy of the inspection report. Interview with Chautems (Mar. 2004), *supra* note 170.

3492 Article 27.5.a OClin. The REC is not automatically given copies of the inspection reports prepared by Swissmedic. Compare with Article 15.2 of Directive 2001/20/EC, according to which ethics committees can make a "reasoned request" to receive inspection reports.

3493 However, as we saw in subsection 9.1.1.2. above, Article 19.1 must be interpreted as including at least all fundamental documents. Therefore, the two provisions at least partly overlap.

3494 Article 27.2.a OClin ("*conduit*," "*durchgeführt*," "*eseguita*").

not self-evident whether this action has to do with the conduct of the clinical trial. Yet, it is – once again – in the best interests of subjects to construe broadly the legal text.

With this objective in mind, can the reference to "*documentation*" be extended to good clinical practices of ICH's E6 guideline? All drug clinical trials must conform to these principles.[3495] Generally, the documentation submitted contains at least a reference to GCP or to ICH's guideline; often, it states explicitly that the trial is conducted according to ICH E6.[3496] In this case, it could be argued that Article 27.2.a OClin is also applicable to GCP compliance. From a practical perspective, the problem is moot since a violation of GCP would automatically fall within the first hypothesis of Article 27.2.a OClin (i.e., the conditions of the authorization are no longer met).

As written above, the Agency cannot take a decision under Article 27.2 OClin without having first heard the sponsor.[3497] The latter has one week to issue its comments.[3498] It is noteworthy that this obligation be mentioned here. By contrast, there does not appear to be a right to be heard when the REC decides to withdraw or reassess its favorable opinion.[3499] There is no such explicit right when Swissmedic decides to raise objections against a trial. Yet, it is a general administrative principle that public authorities should not take a decision that could adversely affect a party's interests before having given that party a chance to express his or her viewpoint. The right to be heard is legally guaranteed by Articles 29 and 30 of the Federal Law on administrative procedure[3500] (applicable pursuant to Article 84.1 LPTh).

9.2.2.2. Remedial plans

Besides the power to stop, suspend or submit a clinical trial to conditions, Swissmedic holds another power which partly overlaps with Article 27.2 OClin. According to Article 27.4 OClin, if the Agency notices that the sponsor, the investigator or any other person participating in a clinical does not fulfill the legal conditions, it establishes a remedial action plan.[3501] It is unclear which of paragraph 2 and paragraph 4 is applicable and when. If the sponsor does not satisfy the legal provisions (Article 27.4 OClin), then it is hard to imagine how the conditions of the authorization can still be satisfied (Article 27.2 OClin). A possible explanation could be that Article 27.4 OClin refers to personal conditions (i.e., required characteristics of "the sponsor, the investigator or any other party participating in the trial"); for example, Article 8.2 OClin requires that the investigator be a licensed physician: This condition is strictly "personal." Yet, this explanation does not hold very well, since there is no "personal" condition for the sponsor.

3495 Article 4.1 OClin.

3496 *See also* subsection 6.2.1.1. above.

3497 Article 27.3 OClin. This is not necessarily an oral hearing.

3498 *Id.*

3499 Article 12 OClin.

3500 *See* Federal Law on administrative procedure of December 20, 1968; in French: "*Loi fédérale sur la procédure administrative*"; RS 172.021; French text at http://www.admin.ch/ch/f/rs/172_021/.

3501 In French, German and Italian, respectively: "*plan d'action visant à remédier à cet état de fait*," "*einen Aktionsplan zur Behebung der bemängelten Situation*," "*un piano d'azione per ovviare alle lacune*." Article 27.4 OClin takes after Article 12.2 of the 2001/20/EC Directive. *See also* E.U. Guidance (Request), *supra* note 270, at 10.

It would rather appear that Article 27.4 OClin represents a sub-category of penalties. When Swissmedic deems that interrupting a clinical trial is not the best solution to remedy the failure of one party to adhere to the regulations, it can apply paragraph 4 instead. However, it could be argued that the conditions and commitments which can be imposed at Article 27.2 OClin are not fundamentally different from the action plan of Article 27.4 OClin, and therefore that the same result can be achieved either way. Perhaps, the expression "remedial action plan" refers to a more complex scheme, with longer-term obligations. In addition, the plan could plausibly involve persons other than the sponsor, the investigator and the trial team; for example, Swissmedic could ask that certain monitors be replaced. Finally, the remedial plan could be imposed even once the trial is stopped or has ended: Even though the clearance is "permanently" withdrawn,[3502] Swissmedic could impose its action plan.

It is not clear whether Swissmedic has the power to disbar the investigator and prohibit her to take part in any further clinical trial. The OClin contains no explicit provision on disbarment. This is surprising since the VanTx affair plainly raised that particular issue. In contrast, the FDA can inflict an array of sanctions, the most serious being investigator disbarment or disqualification.[3503] Disbarred investigators can no longer participate in clinical trials. Their names are made public.[3504]

9.2.2.3. Inspections in Switzerland

The third power of the Agency is the power to make inspections.[3505] These inspections can be useful to reveal circumstances that will then lead to the application of paragraphs 2 and/or 4 of Article 27 OClin. Swissmedic can inspect – or have someone inspect – research sites, facilities and laboratories. By mentioning these three places, paragraph 1 of Article 27 OClin tries to cover everything, even though there is no clear-cut difference between a research site, a facility or a laboratory. The 2004 revision of the OClin added the possibility to inspect sponsors and CROs.[3506] The 2004 revision of the OClin added the possibility to inspect sponsors and CRO.

Swissmedic's inspections encompass both the physical premises in which the clinical trial takes place and the records. These physical premises should include any place in which the clinical team is working, and not only those in which subjects are being hosted. Swissmedic must also be able to inspect the physical premises used by the sponsor if some of the work in relation with the clinical trial is conducted there (e.g., documentation regarding the trial is kept there). Similarly, if there is a CRO or another

---

3502 A sponsor cannot be prevented from re-submitting a request for clearance. Thus, no withdrawal is absolutely permanent.

3503 *See* 21 C.F.R. § 312.70(a) and (b). *See also* OIG (FDA Oversight), *supra* note 95, at 7, 14-15 and 16-17. According to the OIG survey, "fraud was the main reason that disqualification proceedings are initiated against a clinical investigator. … If violations first noted in an initial site visit are found again in a second inspection, the clinical investigator will likely have disqualification proceedings initiated against him." *Id.* at 14.

3504 *See* OIG (FDA Oversight), *supra* note 95, at 8.

3505 Article 27.1 OClin. Compare with the more detailed Article 15 of E.U. Directive 2001/20/EC. See also in the United States, 21 C.F.R. § 312.58 and § 312.68.

3506 See the new Article 27.1 OClin which entered into force on September 1, 2004.

entity participating in the trial, Swissmedic must be able to inspect its facilities too.[3507] However, Swissmedic cannot inspect ethics committees, since these are under the supervision of the cantons;[3508] it can however inspect their records.[3509]

The inspection of records consists of the right to read and take copies of documents generated in the context of the trial. It is not limited to the records that the sponsor must store in the archives in accordance with Article 25 OClin. Case report forms (CRFs) constitute perhaps the most important records, since their analysis allows Swissmedic to verify if the investigator has correctly transcribed all her observations of subjects and has duly reported adverse events. Swissmedic can conduct random cross checks to verify that CRFs were correctly filled. Inaccuracies in CRFs occur frequently; CRFs are sometimes "doctored" (e.g., the subject had a fever of 39.4 C, but 39.0 was recorded instead). In the VanTx affair, it appeared that data reported on CRFs had been mixed up.[3510]

As a complement to the examination of physical locations and documents, Swissmedic can also, as part of its inspection, interrogate staff members. The investigator, in particular, answers questions asked by Swissmedic's agents. Questions need not necessarily relate to past observations (of facilities or records). Swissmedic can also inquire about other circumstances, such as the economic dependence of the investigator towards the sponsor.

According to information obtained from Swissmedic, about 20 inspections take place annually; they concern sponsors, investigators and CROs.[3511] This is not much. Already in 2000, the VanTx Working Group expressed regrets that the IOCM lacked funds and personnel to carry out regular inspections of investigators and research sites.[3512] It appears that other European countries are in a similar situation and do not conduct enough inspections.[3513] Lack of funding for inspections is regularly highlighted as a barrier to effective enforcement.[3514]

9.2.2.4. Disqualification of data

The former intercantonal regulation stipulated that clinical data obtained in violation of the existing rules could be disqualified, that is deliberately not taken into consideration by the drug agency in its review of the drug's application for marketing authoriza-

---

3507 The European Union defines "inspection" so as to include the inspection of facilities other than that of the trial site, such as "the sponsor's and/or contract research organisation's facilities, or … other establishments which the competent authority sees fit to inspect." Article 2.I of Directive 2001/20/EC.

3508 *See* subsection 7.1.5. above. *See also* Article 57.4 LPTh. Compare with Article 12.2 of the (former) IOCM 1995 Regulation (according to which, the IOCM could inspect ethics committees).

3509 *See* Article 33.2 OClin.

3510 *See* VanTx Report, *supra* note 148, at 9.

3511 *See* Telephone Interview with Chautems (Mar. 2004), *supra* note 170.

3512 *See* VanTx Report, *supra* note 148, at 7, 30 and 38.

3513 *Id.* at 9.

3514 *See* Amstad et al. (Lieux), *supra* note 800, at 2452-53.

tion.[3515] Swissmedic applies the same rule, although there is no longer an explicit legal basis.[3516]

Such a sanction has a dramatic impact on the sponsor. The latter's investment in the clinical trial is essentially lost. The sponsor has to repeat the tainted study.[3517] The IOCM used this prerogative in the VanTx affair, although no drug was ultimately withdrawn. The penalty can be applied even though the sponsor was not personally guilty. It could be applied even if the validity of the data is not at issue, because the violation concerned a different aspect of the trial (e.g., the protection of research subjects, a delay in a notification). Admittedly, such sanctions can have damaging consequences that affect parties other than the sponsor. Patients may be deprived – at least momentarily – of a life-saving and perfectly effective treatment because the sponsor or the investigator made mistakes that did not affect the validity of the scientific results. Thus, many ethical guidelines call for caution before handing out such a severe punishment.[3518]

9.2.2.5. Inspections in the United States

The death of Jesse Gelsinger, a young subject enrolled in a gene therapy trial, represented a watershed event for clinical trials.[3519] It spawned a series of trial inspections by the FDA, [3520] which unearthed a score of reporting violations.[3521] Many academic clinical trials had to be temporarily halted.

In 2002, the FDA inspected 276 American clinical investigators, but only 30 foreign investigators.[3522] Inspections of sponsors, monitors and CROs were even less common, with only 15 during 2002. The agency selects the investigators it inspects mainly on the

---

3515 *See* Article 15.1 of the (former) IOCM 1995 Regulation. In the United States, see 21 C.F.R. § 312.70(c) and (d). *See also* OIG (FDA Oversight), *supra* note 95, at 8.

3516 For instance, Swissmedic has reviewed the drugs approved based on studies performed by VanTx to verify whether these drugs were truly safe and effective. *See* Press Release, Swissmedic, Swissmedic a identifié les études VanTx [Swissmedic has identified the VanTx studies], (Mar. 14, 2003), at http://www.swissmedic.ch/Archiv/VanTx_nicht_Generika-F.pdf. *See also* Telephone Interview with Chautems (Mar. 2004), *supra* note 170.

3517 *See* 21 C.F.R. § 56.103(b). At least under U.S. law, if the violation is discovered after the drug has received its marketing approval, the drug may still be withdrawn from the market, pending new confirmation of its safety and efficacy. *See* 21 C.F.R. § 312.70(e).

3518 *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).

3519 *See* Charles Marwick, *Failure to inform public is undermining confidence in clinical trials*, 325 BMJ 356 (Aug. 17, 2002), at http://bmj.com/cgi/content/full/325/7360/356/e. See also the list of articles relating to Gelsinger's death posted on the website of the U.S. law firm that represented his family against the University. SSKR&P, Gelsinger v. University of Pennsylvania, at http://www.sskrplaw.com/gene/gelsinger.html.

3520 Many other academic or public research centers were found to be in violation of their obligations. These include "the Veterans Affairs Medical Center in West Los Angeles, California; …; Duke University in Chapel Hill, North California; the University of Illinois in Chicago; the University of Colorado; John Hopkins University in Baltimore, Maryland; and Fred Hutchinson Cancer Center in Seattle, Washington." ECRI (Guide), *supra* note 869, at 11.

3521 Baram, *supra* note 253, at 256.

3522 FDA 2002 Report to the Nation, *supra* note 1803, at 23. In fiscal year 1999, the FDA inspected "468 clinical investigators of nearly 14,000 clinical investigators potentially involved in clinical trials." OIG (FDA Oversight), *supra* note 95, at 11. *See also* OIG (Globalization), *supra* note 786, at i and 7 ("FDA inspections of foreign clinical investigators conducting drug research have also increased dramatically, from just 22 in 1990 to 64 in 1999." *Id.* at i).

basis of size: Bigger research centers (sometimes referred to as "pivotal" sites) are more likely to be inspected.[3523] However, a significant percentage of inspections is motivated by suspicion of compliance problems or by past compliance violations.[3524]

FDA inspections are generally *retrospective* in that they take place once the study is completed and has been submitted as part of a marketing application.[3525] For this reason, inspections represent only an indirect form of protection for subjects: They discourage future violations, but cannot detect violations as they occur. Moreover, since inspections take place while the deadline for FDA review of the marketing application is running, they must be conducted rapidly.[3526] Finally FDA inspections of investigators are centered on document review.[3527] While there are regular exchanges of written questions (from the FDA) and written answers (from the investigator) during and following inspections,[3528] the FDA does not interact with subjects.[3529]

9.2.2.6. Criminal inquiries

As mentioned in subsection 9.1.1.1., Article 86.1.g. LPTh punishes by imprisonment or a fine anyone conducting or sponsoring clinical trials which do not abide by the LPTh. Swissmedic leads the inquiry, provided that the Confederation itself (and not the canton) has jurisdiction on the underlying activity.[3530]

9.2.2.7. Appeals

According to Article 85 LPTh, parties can appeal decisions by Swissmedic.[3531] The Agency has confirmed that its pronouncements involving clinical trials (e.g., refusal of a notified trial, suspension of a trial) are decisions and hence are appealable.[3532] Appeals are however infrequent because parties prefer to negotiate an amiable solution with Swissmedic.[3533]

3523 *See also* OIG (FDA Oversight), *supra* note 95, at 12. The OIG notes that "under a data validation focus this [inspection predominantly of larger centers] is appropriate, as smaller sites contribute proportionately less to the overall data. This could be problematic in a protocol or human subjects protection sense, as smaller sites may be no more or less likely to conduct studies correctly than sites with more subjects." *Id.* at 12-13. *See also* OIG (Globalization), *supra* note 786, at 7.

3524 *See also* OIG (FDA Oversight), *supra* note 95, at 11-12 and 13. Complaints filed with the agency, for example by a disgruntled research subject, do not automatically trigger inspections. *Id.* at 16.

3525 *Id.* at 15. This is also true of the EMEA. See EMEA, Ethical considerations in clinical trials, EMEA Workshop (Nov. 26, 2001), at 38, at http://www.emea.eu.int/pdfs/human/regaffair/415802en.pdf.

3526 *See* OIG (FDA Oversight), *supra* note 95, at 18.

3527 *Id.* at 15.

3528 *See, e.g.*, FDA (Operations), *supra* note 259; OIG (FDA Oversight), *supra* note 95, at 6 ("The inspection involves interviews with the clinical investigator and study staff and a review of the clinical investigator's processes, records, data and documentation.").

3529 *See* OIG (FDA Oversight), *supra* note 95, at 2.

3530 Article 90 LPTh.

3531 The OClin contains no specific provision on appeals.

3532 *See* Interview with Vital-Durand, *supra* note 484.

3533 Under U.S. law, the sponsor can ask that the decision to order a clinical hold be reconsidered. *See* 21 C.F.R. § 312.42(f). Additionally, the FDA offers the service of an ombudsman to mediate disputes. See 21 C.F.R.

9.2.3. Supervision of a clinical trial by the investigator's institution

When the investigator is affiliated with an institution, for example when she works as a physician in a public university hospital, she has to follow the institution's own internal regulations, in addition to the LPTh and the OClin. These internal regulations may have significant impact on her research activities. They may mandate the approval of the clinical study by the investigator's hierarchical superior; they may also implement monitoring mechanisms over and above those required by the law or set up by the sponsor.

In Switzerland, the role of the institution has not yet been properly recognized in the legislation.[3534] In contrast, in the United States, there is a trend to recognize more weight to institutions' role in biomedical research. Placing the entire burden on the investigator without any internal control can easily lead to abuses that ultimately tarnish the entire institution's reputation. This occurred for example when two patients died in two distinct clinical trials taking place at prestigious university research hospitals. Therefore, the institution, both in its own interest and in the interest of subjects, should supervise research activities by its employees and collaborators[3535].

9.2.4. Supervision of a clinical trial by the canton

Under the LPTh system, cantons have lost many of their prerogatives regarding the organization and supervision of clinical trials.[3536] They do supervise the cantonal ethics committees, but the OClin does not compel RECs to inform cantons. Cantonal law can introduce an obligation to inform, provided that it does not affect RECs' autonomy[3537].

Cantons are also entitled to receive certain information from Swissmedic. According to Article 28 OClin, the Agency must inform the canton in which a trial takes place of the type of clinical trial underway, the beginning date of the trial, the opinion given by the REC, the name of the research site, the name of the investigator,[3538] the date on which the trial ended. The provision does not set any deadline for this notification.

---

§ 312.48. The FDA has in fact two ombudsmen. *See* FDA, CDER, Role and Procedures of the CDER Ombudsman, Manual of Policies and Procedures (MAPP 4150.1) (Oct. 10, 2002), at http://www.fda.gov/cder/mapp/4150.1.pdf; website of the CDER Ombudsman, at http://www.fda.gov/cder/ombud/default.htm; website of the FDA Ombudsman, at http://www.fda.gov/oc/ombudsman/homepage.htm.

3534 *See also* subsection 5.2.7. above.

3535 Donna Shalala, former secretary of the HHS, said that "[p]rotecting patient safety, and ensuring informed consent, is a shared responsibility. I want to urge university presidents, leaders of our academic centers, and others involved in biomedical research to take a hard look at oversight of clinical trials … Research institutions such as academic health centers and universities have the ultimate responsibility to ensure that clinical investigators adhere to this informed consent process." *See* Press Release, HHS, Secretary Shalala Bolsters Protections for Human Research Subjects, (Mar. 23, 2000), at http://www.os.dhhs.gov/news/press/2000pres/20000523.html.

3536 For a description of the cantonal powers with respect to clinical trials before 2002, see Marinette Ummel & Jean-Pierre Restellini, *Contrôle de l'expérimentation humaine: rôle des autorités sanitaires cantonales*, 39(2) CMS 155-60 (1995).

3537 Article 31.c OClin.

3538 The sponsor is not mentioned at Article 28 OClin.

In addition, Swissmedic has to inform the canton when it inspects a site on its territory; the information must be given sufficiently early so that the canton can send its agents to attend the inspection.[3539]

Swissmedic must also inform the canton if it forbids or suspends a clinical trial or if it imposes conditions or commitments. If the end of a trial is due to the withdrawal of the REC's favorable opinion, Swissmedic does not need to inform the canton since the REC has already done it.[3540]

9.2.5. Supervision by foreign agencies

Since clinical trials in one country generate results which are then submitted to drug agencies throughout the word, the latter have an interest in ensuring that these results are reliable and, correspondingly, that the trials were correctly conducted (see subsection 4.3. above). When citizens of one country enroll in a trial conducted in another country, authorities of the first country also have an interest in making sure that rules protecting their citizens are properly followed. These interests should theoretically lead to close collaboration between drug agencies and, quite possibly, to joint inspections. However, this is not observed in practice. Drug agencies do not cooperate much on the broad issues related to the conduct of clinical trials.[3541]

Although Switzerland has mutual recognition agreements ("MRA") with the European Union and with the United States, these agreements do not directly relate to Good Clinical Practices. They concern Good Laboratory Practices ("GLP") and Good Manufacturing Practices ("GMP").[3542] Nonetheless, Switzerland does allow foreign inspectors to conduct inspections of Swiss research sites.[3543] Similarly, Swissmedic conducts GCP inspections abroad.[3544]

9.2.6. Supervision by other entities

The price of a publicly listed company's stock is heavily affected by the results of each of its clinical trials. Investment firms keep a close tag on those results and update their neutral-buy-sell recommendations whenever the company has new clinical trial results.

3539 Articles 28.f and 27.1 OClin.

3540 Articles 28.g and 12.2 OClin.

3541 *See* VanTx Report, *supra* note 148, at 34.

3542 *See* Memorandum of Understanding between the Federal Office for Foreign Economic Affairs of the Swiss Confederation and the FDA, (1985), (FDA Agreement No. 225-85-8401), at http://www.fda.gov/oia/Agreements/swicon.htm (which concerns GLP); letter of the U.S. Secretary of State to the Swiss Ambassador, (Oct. 28, 1968) (FDA Agreement No.225-75-4058), at http://www.fda.gov/oia/Agreements/swisos.htm (regarding drug inspection for bulk drugs). *See* Agreement between the European Community and the Swiss Confederation on mutual recognition in relation to conformity assessment, O.J. L 114 p.369 (30.4.2002), in particular at chapters 14 and 15 of Annex 1, at http://pharmacos.eudra.org/F2/mra/doc/mra_eu_ch_gen_en.pdf.

3543 Swissmedic accompanies these foreign inspectors and receives a copy of their reports. *See* Telephone Interview with Yves Chautems, Swissmedic clinical trial division, Apr. 14, 2004.

3544 The Swiss inspection reports are also communicated to the host agency. *Id.*

The stock market is interested in new information about almost all ongoing clinical trials. Of course, clinical trial information affects the stock prices of small biotech firms more than that of large pharmaceutical firms. However, even for the latter, bad news regarding a late stage clinical trial will bring down their stock price.[3545]

Moreover, publicly quoted firms have a duty to keep the investor community informed of any new and important development. For example, the N.Y. Stock Exchange requires its listed firms to release any information which "might reasonably be expected to materially affect the market [price]."[3546] Companies are also prohibited from disclosing information selectively (e.g., only the good news and never the bad ones). Hence, pharmaceutical and biotech companies keep investment firms abreast of all developments concerning clinical trials.[3547] Investment firms receive crucial information (e.g., approval of a new product) only a few hours after the company itself has got hold of it. This relationship between pharmaceutical firms, investment firms and the capital markets calls for appropriate caution in the conduct and reporting of clinical trials.

Worse, companies that deliberately mislead investors in their reports of clinical trials can face lawsuits from disgruntled investors. Decrease in stock price because of inaccurate or untimely reports by the company may well lead to lawsuits.[3548] In the United States, these lawsuits are particularly feared as they often take the form of stockholders' securities fraud class actions. Given that these class actions group numerous plaintiffs, their claim for money damages can be very high. The U.S. Securities and Exchange Commission ("SEC") has also decided to cooperate with the FDA to better investigate faulty reporting of clinical trials by commercial sponsors.[3549]

9.3. Frequent shortcomings of clinical trials

Swissmedic does not publish reports of its inspections. Thus, after the VanTx scandal, the authority (at the time the IOCM) appointed a special commission to investigate the affair. Only a summary of the commission's report was made publicly available.[3550]

3545 *See, e.g.*, PharmaTimes, S-P [Schering-Plough] ends Sarasar trial, (Feb. 9, 2004), at http://www.pharmatimes.com/news/090204c.asp ("[I]nvestors are very sensitive to late-stage product failures, and sent S-P's shares down more than 2% on the New York Stock Exchange on Friday").

3546 New York Stock Exchange 202.05, entitled "Timely Disclosure of Material News Developments," at http://www.nyse.com/lcm/1078416930743.html?archive=no.

3547 *See, e.g.,* Press Release, Serono, Serono Announces Positive Results For Onercept In Psoriasis And Psoriatic Arthritis In Phase II Trials, (June 22, 2003), at http://www.serono.com/media/stories2003/20030622_en.jsp?major=4&minor=1. For further information on reporting obligations of listed companies, see my article: *Les devoirs d'information des sociétés cotées envers leurs investisseurs dans le secteur pharmaceutique*, 7 SEMAINE JUDICIAIRE 175-215 (2005), at http://www.pharmalaw.org/Article%Semaine%20Judiciaire.pdf.

3548 The recent case in point is of course the year 2001 ImClone scandal involving the cancer drug Erbitux. *See* complaint of the SEC against Samuel D. Waksal, former CEO of ImClone (Mar. 11, 2003), at http://www.sec.gov/litigation/complaints/comp18026.htm. See also the decision in United States v. Snyder, 291 F.3d 1291 (11th Cir. 2002). For more detailed background on the ImClone case, read ALEX PRUD'HOMME, THE CELL GAME (HarperBusiness 2004).

3549 See Kerry Dooley & Robert Schmidt, *Talk of drugs' approval at issue,* Two U.S. agencies want to speed investigations in cases where investors may have been misled, PHILADELPHIA INQUIRER, Jan. 7, 2004; Susan Warner, SEC and FDA Join Forces Against Biotech, 18 THE SCIENTIST 48 (July 19, 2004).

3550 *See supra* note 189.

On the contrary, the FDA makes its warning letters available on the Internet.[3551] These letters include warnings addressed to sponsors, investigators, and IRBs. Moreover, the FDA decided in July 2003 to also post the responses it receives on the web.[3552] Together, they provide a remarkable perspective of the type of inspections conducted by the FDA and of the most frequent violations observed. About 3% of FDA inspections lead to the identification of serious problems.[3553] The FDA has listed the most common violations, among which: "failure to follow the protocol," falsification of data, problems with informed consent, "failure to report adverse event."[3554]

Much more serious frauds include complete invention of research subjects based, for example, on obituaries or former patients ![3555] A famous case of fraud was uncovered in 1999. An investigator named Robert Fiddes had for years fabricated subjects and data for countless pharmaceutical companies;[3556] he was involved in over 170 studies. Patients of Dr. Fiddes were apparently coerced into participating in clinical trials;[3557] ineligible patients were routinely enrolled, their ineligibility situation hidden from monitors and sponsors. The FDA and the public then realized to which extent the clinical trial system remains dependent on sheer trust. Despite early accusations directed against Fiddes, the FDA was slow to crack down on his medical practice. The agency was apparently reluctant to confront this well-established figure of the research community.[3558] While errors can be easily ascertained, fraud is hard to detect.[3559] Similarly, monitors found it difficult to confront the highly regarded investigator, as sponsors

---

3551 *See* FDA, CDER, Warning Letters and Notice of Violation Letters to Pharmaceutical Companies, at http://www.fda.gov/cder/warn/.

3552 The responses (about 25 so far) can be searched from http://www.accessdata.fda.gov/scripts/wlcfm/searchwl.cfm.

3553 *See* OIG (Globalization), *supra* note 786, at 24. See also for earlier reports, Lynne Mctaggart, *Putting Drug Testers to the Test*, N.Y. TIMES, Dec. 7, 1980, at 174 (In a broad review of physician-investigator compliance with regulations, the FDA found that "[o]f 409 doctors who underwent routine, spot-check audits, one-third had no evidence to show that their patients had given informed consent and one-fifth had failed to keep accurate or adequate records."); Lawrence K. Altman, *The Doctor's World, Flawed Study Raises Questions on U.S. Research*, N.Y. TIMES, Mar. 15, 1994, at C14 (reporting fraud in a breast cancer trial).

3554 Other violations included: "qualifications of persons performing the physicals (27), inadequate records (25), failure to get IRB approval, report changes in research (20), failure of follow FDA regulations (13), charging for the test article (9), drug accountability (7), no active IND (7), violations of GLP [regulations] (7), misleading advertisements (5), blinding (3), no [form] 1572 (2), monitoring practices (2), IRB shopping (1)." Stan W. Woollen & Antoine El Hage, *Scientific Misconduct, the "F" word*, FDA, (Oct. 2001), at http://www.fda.gov/oc/gcp/slideshows/misconduct2001/misconduct.html. *See also* OIG (FDA Oversight), *supra* note 95, at 15 and 22-23. "Eighty-five percent of all the [FDA] official actions highlighted problems with documentation. Sixty percent of all warning letters mention missing documentation. Other documentation problems include missing data in submitted documents, discrepancies between documents, missing correspondence, documentation that has been altered, falsification of data and inconsistent or poor data collection. … Both CDER and CBER noted protocol violations in 88 percent of their official actions to clinical investigators." *Id.* at 22. *See also* OIG (Globalization), *supra* note 786, at 25.

3555 *See* Woollen & El Hage, *supra* note 3554.

3556 It was referred to as "one of the most corrupt research enterprises discovered by law enforcement." Kurt Eichenwald & Gina Kolata, *A Doctor's Drug Trials Turn into Fraud*, N.Y. TIMES, May 17, 1999, at A1.

3557 *Id.*

3558 *Id.*

3559 *Id.*

were more disposed to rally with the investigator than with the monitor.[3560] The affair also highlighted the threat to integrity posed – once again – by financial incentives.[3561]

An important question that arises in connection with substandard clinical trials is whether subjects should be informed of the investigators' failings (see already subsection 8.3.3.11. above).[3562] For example, when an investigator strays from the protocol, should all subjects be automatically notified or only those likely to have been injured? While Swiss law does not answer this question, ethical principles call for broad dissemination of information.[3563] Posting warning letters on Swissmedic's website would be a first step.

[3560] For example, "Pfizer said that the company replaced monitors if there seemed to be a conflict." *Id.*

[3561] *See also* subsection 5.3. above.

[3562] *See* Heather Goodare, *Commentary: Of course patients should be told*, 324 BMJ 420 (Feb. 16, 2002), at http://bmj.com/cgi/reprint/324/7334/419.

[3563] *See, e.g.*, Tony Sheldon, *Trial halted because effects not reported to ethics committee*, 327 BMJ 1010 (Nov. 1, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7422/1010-e (where the university which decided to stop the trial informed both the public (through the Internet) and the enrolled subjects).

10. End of clinical trials

This section explains how clinical trials end and what happens after their completion.

10.1. Common reasons for ending a clinical trial

10.1.1. Normal termination

Clinical trials end either at their normal completion date or prematurely. The protocol gives the expected date of completion[3564] and describes the last medical procedures to take place.[3565] The normal date of completion can nonetheless be postponed due to delays (e.g., subject recruitment is taking more time than anticipated). The trial's end does not categorically rule out follow-up interventions. On the contrary, subjects may, for example, be asked to complete a questionnaire some time after the end of the study to assess whether the treatment has long-lasting therapeutic effects. Similarly, follow-up medical visits can occur after the end of the trial, provided that no investigational substance is administered and that only traditional medical procedures are performed. If the visit involves riskier procedures that go beyond what is necessary to monitor the health of the subject, these must be integrated to the protocol. Likewise, if these procedures have a primary research objective, they should only be carried out as part of the clinical study.[3566]

10.1.2. Early termination

Early termination occurs when the sponsor,[3567] the investigator,[3568] the ethics committee[3569] or Swissmedic[3570] so decides. Many possible reasons can explain early trial termination.

The sponsor can stop its trial because it is not yielding the anticipated results. For example, the drug is not as safe or as efficacious as projected[3571]. If the early signs of benefits do not outweigh the discovered side effects, the sponsor must decide whether

---

3564 *See* E.U. Guidance (Request), *supra* note 270, at 11 (also stating that a change in the definition of the ending date is considered a substantial change of protocol).

3565 For instance, it can stipulate that the trial ends after 6 weeks of administration of the investigational substance and 6 weeks of observation with no treatment.

3566 In practice, drawing the line may not be that easy.

3567 *See* section 4.12.2 (p.20) of ICH E6.

3568 *See* section 4.12.1 (p.19) of ICH E6.

3569 *See* section 4.12.3 (p.20) of ICH E6.

3570 Article 27.2 OClin.

3571 *See, e.g.*, Writing Group for Women's Health Initiative Investigators, *Risks and benefits of estrogen and progestin in healthy postmenopausal women: principal results from the women's health initiative randomised controlled trial*, 288 JAMA 321-33 (2002), at http://jama.ama-assn.org/cgi/reprint/288/3/321.pdf?ijkey=0e9e7578febfbe248e0268bbe2f433cb8b0a6a76.

continuing the trial until its normal completion date could reverse this preliminary trend; if there is no clear sign that such a reversal is possible, the sponsor must stop the trial or implement other precautions to safeguard the health of subjects (e.g., lowering the drug dosage). [3572] It should not wait for the decision of the ethics committee or that of Swissmedic, even if both authorities have been informed of the situation.[3573]

A trial may also be terminated prematurely because information originating from *other studies* has shown the treatment not to be safe or efficacious.[3574] In that case, the practical difficulty consists in obtaining this outside information early enough, particularly if the other study was performed in a foreign country. National drug agencies do not cooperate to automatically share with each other negative findings arising from trials conducted on their territory.

Conversely, the sponsor may decide to end the clinical trial early because its investigational drug appears *particularly effective*. In such a hypothesis, ethical principles require that all subjects be switched to the most effective treatment.[3575] Since the 1990s, several important and large studies have been terminated early for this reason,[3576] most notably several AIDS treatments. Provided that there is one, the data and safety monitoring committee is involved in the decision to terminate the trial (see subsection 5.8. above). As alluded to before, this is a hard decision to take as the sponsor must balance ethical issues with economic and scientific concerns. If a trial is interrupted too early, it may not support the drug's marketing application; prolonging the study may also yield a better understanding of side effects.[3577]

Are sponsors entirely *free to decide* to put a unilateral end to a trial?[3578] Can a sponsor end a trial, for example, out of fear that its comparative study will not demonstrate superiority of its own product? Can a sponsor end a trial because of disagreements with the investigator? What about terminating a trial in order to allocate scarce resources to another research avenue whose market is viewed as more important? A merger between two pharmaceutical companies may also result in stopping one study to avoid

---

3572 *See* Article 20 OClin; Article 10 of the Nuremberg Code.

3573 For instance, in the Elan's and Wyeth Pharmaceuticals' Alzheimer vaccine Phase II trial, the sponsors decided to stop the study when more than 10 of the 375 enrolled subjects experienced serious side effects, in that their medical symptoms of Alzheimer worsened; Douglas Steinberg, *Companies Halt First Alzheimer Vaccine Trial*, 16[7] THE SCIENTIST 22, (Apr. 1, 2002), at http://www.the-scientist.com/yr2002/apr/steinberg_p22_020401.html.

3574 *See* Peter Brocklehurst et al., *Role of external evidence in monitoring clinical trials: experience from a perinatal trial*, 320 BMJ 995-998 (Apr. 8, 2000), at http://bmj.com/cgi/reprint/320/7240/995; A. Fletcher et al., *supra* note 1714, at 653.

3575 On the role of the DSMB in the decision to stop a trial early, see subsection 5.8. above.

3576 For example, in August 1989, a study of 3,200 AIDS patients was ended when AZT was shown to produce goods results. See ARNO AND FEIDEN, *supra* note 125, at 131. In March 2003, a large multi-year long study of finasteride was ended, after having enrolled over 18,000 subjects. *See* Abigail Zuger, *A Big Study Yields Big Questions*, 349 NEW. ENG. J. MED. 213-214 (July 17, 2003), at http://content.nejm.org/cgi/content/full/349/3/213.

3577 *See, e.g.,* Scott Gottlieb, *Experts regret early cessation of anticancer drug trial*, 327 BMJ 885 (Oct. 18, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7420/885?etoc.

3578 *See* Bruce M. Psaty & Drummond Rennie, *Stopping Medical Research to Save Money*, 289 JAMA 2128-30 (Apr. 23/30, 2003), at http://jama.ama-assn.org/cgi/reprint/289/16/2128.pdf (criticizing the pharmaceutical sponsor for stopping – for undisclosed business reasons – the CONVINCE trial); Editorial, *A curious stopping rule from Hoechst Marion Roussel*, 350 LANCET 155 (July 19, 1997) [hereinafter Editorial (curious)] (criticizing Hoechst for stopping a trial following its acquisition of the Marion Merrell Dow company). See also the follow-up letters in 350 LANCET 890-991 (Sept. 20, 1997).

cannibalization between products now sold by the same entity. A company could stop a trial when it realizes that the drug under study is about to lose its patent protection.

The interests of research subjects are at risk whenever a clinical trial is abruptly ended. Subjects agree to enroll in clinical trials also out of a desire to advance science. If sponsors can end a study before any conclusive result is reached, this reasonable expectation is defeated.[3579] In addition, changing subjects' treatment regimen may take time and jeopardize their health.[3580] Finally, subjects should at least be told the true reason for ending the trial.[3581] If the sponsor can anticipate reasons for which the trial may be terminated in the future, it should inform subjects during the informed consent process.[3582]

Investigators' expectations are also threatened by early discontinuation of a clinical study. Scientists and physicians invest time and efforts in understanding the protocol, recruiting patients and following the prescribed procedures.[3583] They do so out of motivations that go beyond the mere monetary compensation offered by the sponsor. Moreover, with the early discontinuation of the clinical trial, they lose the opportunity to publish scientific papers. They may also lose credibility in the eyes of their subjects/patients if the trial that they praised finally does not take place as announced.

Such issues were raised in the Olivieri-Apotex case (see subsection 5.3.3.1. above). The review panel reached the conclusion that the sponsor should not have brusquely ended the trial.[3584] Medical journals have also sounded the alarm bell and criticized commercial sponsors that pull the plug on their clinical trials.[3585] They have protested that "clinical trials should not be discontinued before the results of the first interim analysis are available unless there are sound and pressing reasons."[3586] Most commentators agree that ethics committees and data monitoring boards ought to be contacted prior to discontinuation.[3587]

Under the present law, there is no legal mechanism to force a sponsor to continue a clinical trial that it wants to end. However, RECs could force the sponsor to consult with them (and with the DSMB, if there is one), by introducing this as a condition of their favorable opinion.[3588] However, discussions with Geneva REC members suggest that RECs do not think they hold such a power.[3589] The remaining alternative is public

---

3579 Michel Lièvre et al., *Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility*, 322 BMJ 603, at 604 (Mar. 10, 2001), at http://bmj.com/cgi/reprint/322/7286/603 (speaking of a "moral contract" between investigators, sponsors and subjects to "help medical research and future patients with the same condition.").

3580 In all cases, the investigator must arrange for subjects to receive appropriate follow-up care. *See* section 4.12 (p.19) of ICH E6.

3581 *See, e.g.*, the complaint in Robertson v. McGee, *supra* note 2068.

3582 In the United States, see 21 C.F.R. § 50.25(b)(2).

3583 *See* Lièvre, *supra* note 3579, at 604.

3584 *See* Olivieri Report, *supra* note 1084, at 26 and 27 ("Apotex showed disregard for the interests and concerns of patients when, without prior notice, it terminated both trials and stopped supplying its drug L1 in May 1996.").

3585 *See* Editorial (curious), *supra* note 3578, at 155.

3586 *See* Lièvre et al., *supra* note 3579, at 603.

3587 *See id.* at 605.

3588 *See further* DuVal, *supra* note 1096, at 33.

3589 Interview with Bounameaux, *supra* note 1718; Interview with Ciaroni, *supra* note 1338.

pressure: A sponsor may yield to it. A safer bet would be to amend the OClin so as to limit the discretion of sponsors in that respect.

10.2. Notifying authorities

If the trial ends at its normal anticipated date, the sponsor and the investigator have 90 days to inform Swissmedic and the REC.[3590] If the trial ends early for any reason, whether or not foreseen by the protocol, the deadline is 15 days.[3591] The underlying reason for termination (e.g., the investigational new drug clearly lacks efficacy) needs to be reported.[3592] Yet, when a trial is stopped for *safety* reasons, Article 20.2 OClin should prevail over the above-mentioned rules of Article 21.2 OClin and both Swissmedic and the REC should be informed immediately.

10.3. Preparing the study report

Once the trial is finished, the sponsor, the investigator, or both, prepare the study report.[3593] Clinical trials generate heaps of data that must be organized and analyzed to prove or refute the underlying scientific hypothesis. It is not uncommon that, for each subject, twenty thousand different pieces of data have been accumulated.[3594]

Preparing a study report is strongly recommended even if the trial ended prematurely or its results are disappointing (see subsection 10.1. above).[3595] Unfortunately, in these two cases, study reports are too often neglected.[3596] While the initial version of the LPTh and the OClin did not impose the preparation of study reports, the 2004 revision made them mandatory. The new Article 21.3 requires that the final report be sent to Swissmedic within six months following the trial's end.[3597] This deadline starts running

---

3590 Article 21.1 OClin. Generally, the deadline starts running with the last medical intervention on the last subject. See also the very similar E.U. provision at Article 10(c) of Directive 2001/20/EC; E.U. Guidance (Request), *supra* note 270, at 10-11. E.U. sponsors must fill out a form to notify the end of a clinical trial. *See* Declaration of the end of trial form, available as Annex 3, at 38. *See also* E.U. Guidance (Ethics Committee), *supra* note 270, at 10-11. *See also* section 4.13 (p.20) and 5.21 (p.30) of ICH E6. *See also* 21 C.F.R. § 312.38(a) and (b).

3591 Article 21.2 OClin. In the United States, 21 C.F.R. § 312.38(c); FDA (FAQ-IRB), *supra* note 1814, at question 19 (requiring investigators to notify their IRB of the end of the clinical trial).

3592 Article 21.2 OClin. See also section 4.11.1&2 (p.19-20) and 5.5.9 (p.22) of ICH E6. In the European Union, Article 10(c) of the Directive 2001/20/EC sets a quite similar rule. *See also* E.U. Guideline (Request), *supra* note 270, at 11 (indicating the kind of information that has to be supplied).

3593 The main investigator should normally sign the study report. See, in the United States, 21 C.F.R. § 312.64(c).

3594 BAZELL, *supra* note 673, at 175.

3595 *See* section 5.22 (p.30) of ICH E6, which refers to the ICH E3 Guideline for Structure and Content of Clinical Study Reports. The European Union refers explicitly to this ICH E3 Guideline. *See* E.U. Guideline (Request), *supra* note 270, at 11.

3596 *See generally* Truniger et al., *supra* note 1337, at 2402 (noting that many of the clinical trials approved by the former central ethics committee had not resulted in a study report).

3597 *See* the new Article 21.3 OClin, which entered into force on September 1, 2004. This obligation existed under the previous intercantonal system. *See* Article 2.3.i) of the GCPs accompanying the (former) IOCM 1995 Regulation.

either from the normal completion date of the trial or from its premature stop.[3598] Moreover drug agencies also receive the study report as part of the application for marketing authorization if the sponsor does file an application relying on its trial.[3599] In this case, Swissmedic will have plenty of opportunity to peruse the report and its accompanying data.[3600]

Furthermore, the ICH requires that the investigator submit a "summary of the trial's outcome" to its REC.[3601] A summary is however not sufficient; a better rule would require the full report as well as all ensuing publications in medical journals to be submitted.[3602] This would imply, in turn, that RECs demonstrate their ability to absorb these additional data. As we saw, RECs seem to be overwhelmed by what they already receive.

The ICH E3 Guideline explains in great details how the study report must be written.[3603] The ICH's purpose is to facilitate and accelerate the marketing authorization process by allowing the submission of a substantially similar file to the different regulatory authorities of all ICH regions.[3604] Information specific to a given region is to be filed as an appendix to the core report.[3605] Additional appendices contain the protocol, a sample case report form (CRF), information and publications regarding the investigational product.[3606] The main text of the report is produced by integrating the protocol, the clinical findings and their statistical analysis.[3607] The goal is to have a report which is "complete, free from ambiguity, well organised and easy to review."[3608] When these conditions are met, the drug agency should have enough information to allow for replication of the trial's critical analysis.[3609] The report must pay special consideration to adverse events observed during the trial. It should discuss limitations of the study design (e.g., use of active control instead of placebo, lack of blinding) and of the study findings (e.g., recruitment of a fewer subjects, significant rate of drop-outs).[3610] The report should discuss whether safety and/or efficacy are affected by subjects' characteris-

---

3598 Compare with E.U. Guideline (Request), *supra* note 270, at 11 (setting a one-year deadline). Also the form announcing the end of the trial contains the signed commitment of the sponsor to "prepare the clinical trial report and submit a summary to the competent authority and ethics committee concerned as soon as available." *See* Declaration of the end of trial form, available as Annex 3 to the E.U. Guidance (Request), *supra* note 270, at 39.

3599 The European Union uses the term "dossier."

3600 *See* section 4.9.1 (p.18) of ICH E6.

3601 *See* section 4.13 (p.20) of ICH E6. Similarly, according to WHO Guidelines, a copy of the study report, or at least its summary, should be presented to the ethics committee. *See also* WHO (Operational Guidelines), *supra* note 1379, at points 9.5 (p.17) and 9.7 (p.18). British ethics committees affiliated with the NHS must also receive a final report within 3 months of completion of the clinical trial. *See* COREC, *supra* note 1379, at point 7.26 (p.19).

3602 *See* Lo Verso, *supra* note 793.

3603 ICH E3.

3604 See the introduction to the ICH E3 Guideline, at p.1.

3605 *See id.* at 1.

3606 *See id.*

3607 *See id.* at 1 and 2.

3608 *Id.* at 1.

3609 *See id.* The Guideline could have specified what these "critical analyses" are, since this is not made immediately clear.

3610 *See, e.g., id.* at chapter 9.2 (p.6) and 9.4.6 (p.9).

tics such as age, sex, race, weight, disease stage.[3611] Data are to be presented in tables that break down results for various subgroups.

10.4. Publication and publicity

Clinical trials benefit the medical community and society in general only to the extent they are made *publicly available*. The usefulness of a trial is a function of how well its results are reported. Hence, the importance of accurate, complete, and timely publication is never to be overlooked.

This subsection is divided into two main parts. The first one is about publication of scientific articles mainly in *medical journals*. The second one looks into measures taken by authorities to promote *transparency* in clinical trials.

10.4.1. Publication by the investigator or the sponsor

As mentioned earlier, investigators want to participate in clinical trials to advance both science and their own careers by publishing their clinical findings. This prospect is particularly enticing to investigators affiliated with universities,[3612] since the traditional academic motto is "publish or perish." Hence, the protocol or the contract between the sponsor and the investigator should specify how the results of the trial are to be published.[3613] The sponsor may want to postpone publication so as to apply for additional patent rights (see also subsection 4.1.6.1. above).[3614] It can also ask to receive a copy of the investigator's manuscript before publication. Often, some of the sponsor's employees are mentioned as co-authors, but publication guidelines now require that these people be awarded the status of "author" only if their intellectual contribution extended beyond the traditional tasks of a sponsor.[3615]

10.4.1.1. Publishing both good and bad

Commercial sponsors support investigators' ambition to publish to the extent that the article will help promote their products. Published articles can be used in marketing campaigns targeted to doctors; papers also generate interest from investors contemplating acquisition of the company's stock (see subsection 4.1.8. above). But when what investigators have to say about the sponsor's drug is not positive (e.g., lack of efficacy),

---

3611 *See id.* at 2.

3612 According to Brazell, "[i]n trials, the rule is that the doctor whose institution enrolls the most volunteers wins the right to be senior author of the published paper explaining the results." *supra* note 673, at 61.

3613 Under the previous intercantonal regulatory system, the sponsor was required to agree with the investigator on a publication policy. *See* Articles 2.3.k) and 2.5.e) of the GCPs accompanying the (former) IOCM 1995 Regulation. This is indeed good policy.

3614 The editors of the most prominent medical journals have stated that the grant of short delays (between 30 and 60 days) can be tolerated; sponsors should not, however, be allowed to delay investigators' submission of manuscripts for publication for longer periods. *See* Davidoff et al., *supra* note 603, at 826.

3615 *See id.*

sponsors have an incentive to hinder the release of adverse information.[3616] Alternatively, they may downplay the importance of the information.[3617] This has occurred frequently.[3618] Sometimes, the investigator is an accomplice, and not just a victim of the sponsor's unscrupulous strategy.[3619]

It has been found that clinical trials which are sponsored by pharmaceutical companies tend to *report* results favorable to the companies' drugs.[3620] The quality of privately financed trials is not contested per se;[3621] commercial clinical trials are often better conducted than publicly funded studies.[3622] A better explanation is that pharmaceutical firms launch clinical trials only when they can reasonably expect the trials to confirm the safety and efficacy of their drug candidates.[3623] In other words, firms avoid investing in clinical trials if the odds do not appear to favor their products. A more alarming reason resides in incorrect or misleading interpretation of study results. The evidence is presented in such a way that the favorable aspects are heavily stressed, while the negative ones are omitted from discussion.[3624] A third and widely accepted explanation is that pharmaceutical sponsors arrange for flattering studies to be published, if possible several times,[3625] while negative findings are simply not disclosed. The overall effect is to exaggerate the efficacy of pharmaceutical products. Pharmaceutical firms have thus been criticized for citing only the evidence in their favor, and disregarding, or worse hiding, adverse evidence.[3626]

3616 *See* Academic Freedom in Clinical Research, Editorial, 347 NEW. ENG. J. MED. 1368-1371 (2002), at http://content.nejm.org/cgi/content/full/347/17/1368. See *also* Olivieri Report, *supra* note 1084.

3617 For instance, the pharmaceutical company Wyeth has been accused of minimizing the implications of adverse studies regarding side effects of hormone replacement therapies ("HRT"). *See, e.g.,* Ray Moynihan, *Drug company secretly briefed medical societies on HRT*, 326 BMJ 1161 (31 May 2003), at http://bmj.com/cgi/content/full/326/7400/1161.

3618 *See e.g.,* Hywel C Williams, *Evening primrose oil for atopic dermatitis*, 327 BMJ 1358-59 (Dec. 13, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7428/1358.pdf.

3619 See the harsh accusations made by Peter Jüni and others, against the authors of the CLASS study, *in Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs?*, 324 BMJ 1287-88 (June 1, 2002), at http://bmj.bmjjournals.com/cgi/reprint/324/7349/1287.pdf. See also the rapid responses published by BMJ, at http://bmj.bmjjournals.com/cgi/eletters/324/7349/1287.

3620 *See, e.g.,* Bodil Als-Nielsen et al., *supra* note 867, at 921-28 ("Conclusions were significantly more favorable toward experimental drugs in trials funded by for-profit organizations compared with those of trials funded by other sources" *Id.* at 924); Joel Lexchin et al., *Pharmaceutical industry sponsorship and research outcome and quality: systematic review*, 326 BMJ 1167-1170 (31 May 2003), at http://bmj.com/cgi/content/full/326/7400/1167.

3621 *See, e.g.*, Bodil Als-Nielsen et al., *supra* note 867, at 924 ("Funding by for-profit organizations alone or by for-profit and nonprofit organizations was associated with more complete reporting of adverse events, more adverse events in the experiment group, more frequent report of adequate allocation concealment and double blinding, and more frequent use of placebo or no treatment as control intervention … with a larger sample size and publication in high-impact journals.").

3622 Commercial sponsors need to gather clinical evidence that will support a marketing application. Hence, they generally require that their investigators collect a greater amount of data.

3623 *See, e.g.,* Bodil Als-Nielsen et al., *supra* note 867, at 926.

3624 *See, e.g.,* David Spurgeon, *GlaxoSmithKline staff told not to publicize ineffectiveness of its drug*, 328 BMJ 442 (Feb. 21, 2004), at http://bmj.bmjjournals.com/cgi/reprint/328/7437/422-a.pdf.

3625 *See* Rennie (Fair Conduct)*, supra* note 2056, at 1766.

3626 This reproach has also been leveled at trade associations, such as the European Federation of Pharmaceutical Companies ("EFPIA"). *See* Alessandro Liberati & Nicola Magrini, *Information from drug companies and opinion leaders, Double standards in information for medical journals and practitioners should go*, 326 BMJ 1156-1157 (31 May 2003) at http://bmj.com/cgi/content/full/326/7400/1156.

Studies have revealed that many clinical trial findings are never made publicly available.[3627] In a British study of 100 submitted protocols, 21 studies (out of a subset of 71 clinical trials that had been completed) were simply not published. Only 19 were published in books or journals. A U.S. 2003 study found that 26% of large phase III randomized cancer trials had not been published 5 years following completion.[3628] Studies whose results are not statistically significant ($p > .05$) are less likely to be published;[3629] somewhat surprisingly given what has just been written, trials sponsored by the pharmaceutical industry were more – not less – likely to be published.[3630]

Owing to mounting criticism, several initiatives have tackled the problem of publication bias. The Helsinki Declaration requires that both negative and positive clinical results be published.[3631] The FDA now requires that "negative trial findings" be mentioned in the drug's label (intended for physicians).[3632]

PhRMA, the U.S. pharmaceutical industry trade association, has committed "to timely communication of meaningful results" of clinical trials "regardless to outcome."[3633] While sponsors have the right to review the investigator's paper before its publication, they undertake to do so rapidly and not to censor the paper's content.[3634] Reasonable delays may be inevitable to allow for the filing of patent applications when the article is to disclose an invention for which no patent has yet been applied.[3635] The PhRMA statement is however limited to products "that are approved for marketing."[3636] For PhRMA, sponsors do not have to divulge clinical trials of investigational compound that ultimately do not receive marketing approval.[3637] This represents a sig-

---

3627 *See* Wise & Drury, *supra* note 1999; Terry P. Klassen et al., *Abstracts of Randomized Controlled Trials Presented at the Society for Pediatric Research Meeting: An Example of Publication Bias*, 156 ARCH PEDIATR ADOLESC MED 474-479 (2002) (finding that about 40% of randomized pediatric trials initially submitted as abstracts are not subsequently published; results favoring the tested treatment are more likely to be published).

3628 Monika K. Krzyzanowska et al., *Factors Associated With Failure to Publish Large Randomized Trials Presented at an Oncology Meeting*, 290 JAMA 495-501 (July 23, 2003), at http://jama.ama-assn.org/cgi/reprint/290/4/495.pdf.

3629 See id. at 498. See also Hans Melander et al., *Evidence b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications*, 326 BMJ 1171-1173 (31 May 2003), at http://bmj.com/cgi/content/full/326/7400/1171.

3630 Krzyzanowska et al., *supra* note 3628, at 498. *But see* Joel Lexchin et al., *supra* note 3620, ("Research funded by drug companies was less likely to be published than research funded by other sources.").

3631 *See* paragraph 27 Helsinki Declaration. *See also* ICMJE, *supra* note 945, at III.A. (observing however that "many studies that purport to be negative are, in fact, inconclusive; publication of inconclusive studies is problematic, since they add little to biomedical knowledge and consume journal resources.").
In Switzerland, see Kleist (Abhängigkeit), *supra* note 800, at 2349.

3632 *See* ASCO/FDA, *supra* note 572, at 8.

3633 PhRMA (Principles on Clinical Trials), *supra* note 902, at 21.

3634 *Id.* at 23.

3635 *Id.* at 23.

3636 *Id.*

3637 *Id.* at 28 ("If the product never reaches the market and the results are only informative with regard to the specific product being studied, the results are likely not of significant medical importance and need not be communicated. However, if the results are thought to be of significant medical importance, the sponsor should work with the investigators to communicate the results of the trial.").
See however in the European Union, point (7) of the Introduction and general principles of Annex I to Directive 2001/83/EC, as modified by Directive 2003/63/EC (requiring that information, including negative information, regarding therapeutic indications *not* covered by the marketing application be also provided to the drug agency).

nificant limitation to the principles of open science. Also, PhRMA members retain the option not to publish early exploratory studies (e.g., phase I).[3638]

Many scientists have spoken enthusiastically in favor of *public registers* of clinical trials, including trial reports.[3639] As we saw in subsection 8.1.2.4., many government agencies have set up clinical trial databases, mainly with the view of speeding the recruitment process. In Switzerland, the SAMS advocates the creation of a central register of clinical trials which would be accessible to the public.[3640] Apart from facilitating the recruitment of human subjects, such registers would solve the publication bias problem.[3641]

Publication of clinical trials and their results should be encouraged, if necessary by mandatory measures taken by the authorities.[3642] Publication is a reasonable expectation of the public. First, considerable research leading to new drugs is funded by taxpayers. In return, taxpayers should know how their money is invested. Second, many members of the public participate in clinical trials as subjects. In exchange, they should know how their participation contributed to the progress of medicine.[3643] Third, waste of resources should be avoided by making sure that trials are not repeated out of ignorance of previous research on the same topic. Conversely, knowing what is being currently studied allows scientists to focus their own efforts in untapped areas of endeavor. Fourth, publishing all clinical study reports minimizes the publication bias, making sure that medical decisions are taken on the basis of all existing evidence, and not just the data most favorable to the industry. Openness should be promoted for the public to perceive research in a favorable light.[3644]

3638 PhRMA (Principles on Clinical Trials), *supra* note 902, at 20-21, and also at 29. Attacking this restriction on access, Steinbrook (Registration), *supra* note 2369, at 315.

3639 *See id.* (discussing how scientists' calls for a register is increasingly being heard by governments). For an update on recent developments regarding access to clinical trial information, see my article on transparency to be posted at: http://www.pharmalaw.org/Articles_support.htm.

3640 The SAMS 1997 Guidelines ask that results be made available to the public either through publication or through registry filings. *See* SAMS 1997 Guideline, *supra* note 110, at point D.10. at 11; also the added comment to point D.9, *id.* at 12. *See also* Lüscher, *supra* note 943, at 2143. SAMS (Collaboration), *supra* note 1075, at point I.3. The Canton of Ticino has started an optional Internet register of clinical studies. *See* Comitato etico cantonale, Repertorio delle sperimentazioni cliniche in Ticino, at http://www.ti.ch/DSS/DSP/SezS/ComEC/Ricerca/obiettivi.htm.

3641 The Cochrane Library partly assumes this much needed function. Its collection of clinical trials is quite exhaustive as it also includes trials published in language others than in English. The Cochrane Collaboration has a register of over 300,000 studies. It prepares comprehensive reviews of given drugs or medical conditions. *See* Ray Moynihan, *Cochrane at crossroads over drug company sponsorship*, 327 BMJ 924, at 925 (Oct. 18, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7420/924.pdf. See also the Cochrane's website at http://www.cochrane.org/reviews/clibintro.htm.

3642 Compare in Switzerland with 9.2.b and 13.2.b.2 LRCS (requiring that researchers doing research on embryos and embryonic stem cells make publicly available a summary of their research results). See also the Federal Council's Message accompanying the LRCS, FF 2003 1065, at 1151. In addition, according to Article 18 LRCS, the FOPH holds a public register listing all existing embryonic stem cell lines as well as all corresponding research projects.
See also Alexa McCray, *Better Access to Information about Clinical Trials*, 133 ANN. INTERN. MED. 609-614 (Oct. 17, 2003), at http://www.annals.org/cgi/reprint/133/8/609.pdf.

3643 *See also* Krzyzanowska et al., *supra* note 3628, at 500 (observing that some 47,000 subjects participated in large phase III randomised trials whose results were *not* published).

3644 *See supra* note 367 above.

10.4.1.2. Publishing without delays

When a clinical trial has yielded important findings, these results should be published as soon as possible because they have the potential to alter medical practice. In the early days of AIDS research, it took three years for the key study of the drug AZT to be published.[3645] In the meantime, doctors, especially those in small and rural private practices, did not know about this new life-saving treatment; had they known, they could have improved significantly the treatment of their patients.[3646]

On the other hand, publishing papers rapidly increases the risk of committing errors. When scientists realize that their published paper contain mistakes, the custom is to publish a corrective statement in the same journal. This happens from time to time. For instance, in 2003, German researchers had to withdraw a Nature Medicine paper regarding a cancer vaccine clinical trial.[3647] When the error impinges on the validity of the results, the authors must retract their paper. It is still debated whether reasonable or small errors require full retraction of the entire study or if a corrective statement is sufficient.[3648] In practice, however, proving deliberate fraud is extremely difficult: Whistleblowers face uphill battles. Some have complained that journal editors are far more worried of lawsuits for libel (initiated by researchers whose papers are being questioned), than of publishing wrong and misleading scientific results.[3649]

10.4.1.3. Providing supporting documents

Published articles allow physicians to adapt their medical practice (see subsection 4.1.3. above). However, these articles may not contain sufficiently detailed information to allow researchers to build on these results; for example, a scientist may not be able to replicate a clinical study based on the information available in the published study report.

To address this problem, commentators have called for the *protocols* of published studies to be made public, for example on the Internet.[3650] Being able to refer to the protocol allows to make an independent verification of the study methods. While some journal editing guidelines require detailed explanation about study methods,[3651] published articles may still not provide sufficient information to make a critical assessment of the trial results. For example, the article may not reveal all subject exclusion criteria

---

3645 *See* ARNO AND FEIDEN, *supra* note 125, at 132-33 and also at 191-192 (mentioning a review study of steroids against AIDS whose publication was delayed for several months). *See also* SPRUMONT, *supra* note 16, at 102.

3646 *See* ARNO AND FEIDEN, *supra* note 125, at 187.

3647 *See* Annette Tuffs, *German scientists withdraw research paper on cancer vaccine*, 327 BMJ 637 (Sept. 20, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7416/637-a?etoc. *See also* JUDY SARASOHN, SCIENCE ON TRIAL (St.Martin's Press New York 1993) (telling the story of a controversial non-clinical study published by a Nobel Prize winner in Cell Magazine).

3648 *See* Richard Smith, *When to Retract?* Editorial, 327 BMJ 883-884 (Oct. 18, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7420/883?etoc (proposing to reserve retraction for scientific misconduct and severe errors that are not directly apparent). *See also* ICMJE, *supra* note 945, at III.B.

3649 *See* Annabel Ferriman, *Have editors got their priorities right?* 327 BMJ 1113 (Nov. 8, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7423/1113.pdf?ck=nck.

3650 *See* Curtis L. Meinert, *Beyond CONSORT: need for improved reporting standards for clinical trials*, 279 JAMA 1487 (May 13, 1998), at http://jama.ama-assn.org/cgi/reprint/279/18/1487.pdf.

3651 *See* subsection 10.4.1.5. below.

(e.g., potential subjects suffering from severe depression were excluded). If the doctor does not have this information, he may prescribe a drug to all her patients, without thinking about asking about depression. Access to the protocol is therefore necessary to acquire a more complete understanding of the published study results. The Helsinki Declaration sides with such a plea and recommends that "[t]he designs of all studies should be publicly available."[3652] The Swiss Academy of Medical Sciences (SAMS) invites researchers to make available any information and material necessary to third parties wishing to replicate and verify the duly completed clinical trial.[3653]

PhRMA however is *not* prepared to oblige. It will only lend journals a synopsis of the protocol, but not the full text version.[3654] The pharmaceutical industry argues – not persuasively – that protocols are intrinsically confidential;[3655] it has never demonstrated exactly what information is so sensitive.

10.4.1.4. Not publishing unethical studies

Many published articles contain a statement confirming that the clinical trial was conducted in accordance with ethical principles.[3656] The Helsinki Declaration is customarily mentioned as the ethical foundation.[3657] Editors are to verify whether the clinical study they plan to publish was done in compliance with basic ethical principles, in particular approval by an ethics committee.[3658] This should also be confirmed in the article itself.[3659]

Conversely, studies done in violation of ethical principles are banned from publication, even if they do advance science.[3660] This harsh rule was deemed necessary to goad researchers into abiding strictly to ethical principles.[3661] However, a 1997 study found that the rule was still not thoroughly applied.[3662] Angell describes the possible reasons for editors' reluctance in applying this rule.

3652 Paragraph 16 Helsinki Declaration.

3653 *See also* SAMS (Integrity), *supra* note 1075, at point 2.4. This obligation comes into effect once the initial project is completed and its results have been published.

3654 PhRMA (Principles on Clinical Trials), *supra* note 902, at 24. For PhRMA, even the synopsis is confidential and should be returned to the sponsor.

3655 *See* Burls & Sandercock, *supra* note 789, at 1446.

3656 *See* ICMJE, *supra* note 945, at II.F. *See however* Michael A Weingarten et al., *Assessing ethics of trials in systematic reviews*, 328 BMJ 1013-1014 (Apr. 24, 2004), at http://bmj.bmjjournals.com/cgi/reprint/328/7446/1013.pdf.

3657 *See also* Human & Fluss, *supra* note 72, at 3.

3658 *See* Richard Smith, *Draft code of conduct for medical editors*, 327 BMJ 1010 (Nov. 1, 2003), at http://bmj.bmjjournals.com/cgi/content/full/327/7422/1010-c.

3659 *See* Veronica Yank & Drummond Renie, *Reporting of Informed Consent and Ethics Committee Approval in Clinical Trials*, 287 JAMA 2835-38 (June 5, 2001), at http://jama.ama-assn.org/cgi/reprint/287/21/2835.pdf.

3660 *See* Paragraph 27 Helsinki Declaration. *See also* CIOMS 2002 Guidelines, *supra* note 105, at Guideline 2 (commentary).

3661 *See* SPRUMONT, *supra* note 16, at 101-102 (proposing that unethical studies be published accompanied by the editor's explicit statement that the studies were done in violation of ethics standards).

3662 *See* Yank & Rennie, *supra* note 3659 (finding that "roughly 30% of articles published before 1997 did not report informed consent, and another 30% did not report ethics committee approval." After 1997, there were still 9% of studies that reported neither informed consent nor ethics committee approval.").

> First, editors are reluctant to accept responsibility for evaluating the ethics of a study; there is a tacit assumption that this is the job of the institution where the research was done. … Furthermore, the growing importance of publication to the success of a researcher increased the reluctance of editors to deny it on so "soft" a ground as questionable ethics. Moreover, with the completed manuscript in hand, editors are influenced by the importance of the results. If the study is of great practical significance – that is, if it might save lives – it is difficult to deny publication.[3663]

The disadvantage of a complete publication ban is that the same research may be duplicated unknowingly because the medical community has not been informed of the previous results.[3664] However, this problem could be addressed by mandating the release of the results on a public database dedicated to unethical clinical projects. Thus, the results would be available, but the researchers would not profit from their unethical conduct.[3665]

10.4.1.5. The Consort Guidelines

For clinical trial results to be taken seriously, they must be publicized in a convincing manner. Badly reported studies may be *a priori* dismissed even though their findings were entirely accurate.[3666] This is an unfortunate and wasteful result: The investment in the clinical trial is needlessly squandered.

Nowadays, articles in medical journals must follow precise rules set forth by the editors. Publications in medical journals typically follow the CONSORT guidelines.[3667] The guidelines' purpose is to guarantee transparency and the correct interpretation of clinical trials results. Readers should understand both the trial's strengths and its weaknesses.[3668] Customary sections of a published article include its title, abstract, introduction, methods, results and discussion.[3669] Having a uniform publication format facilitates the reading and the analysis of medical articles. Readers can skim through a great number of articles and focus immediately on the aspects that interest them most.

3663 Angell (Publication), *supra* note 898, at 281.

3664 *See* SPRUMONT, *supra* note 16, at 101.

3665 The benefits of publication are tied to the prestige of the medical journal accepting the article. Publication in an "infamous" database would have more drawbacks than advantages.

3666 See generally Heloisa P. Soares et al., *Bad reporting does not mean bad methods for randomised trials: observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group*, 328 BMJ 22-24 (Jan. 3, 2004), at http://bmj.bmjjournals.com/cgi/reprint/328/7430/22.pdf.

3667 *See* Colin Begg et al., *Improving the quality of reporting of randomized controlled trials: the CONSORT statement*, 276 JAMA 637 (Aug. 28, 1996) (going over the history behind the first CONSORT guidelines); C. L. Meinert, *supra* note 3650, at 1487; David Moher, et al., *The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials*, 357 Lancet 1191-1194, (Apr. 14, 2001), at http://www.consort-statement.org/Statement/lancet.pdf [hereinafter Moher (CONSORT)].
The Swiss Academy of Medical Science (SAMS) urges compliance with the CONSORT Statement. *See* SAMS (Integrity), *supra* note 1075, at point 2.5.

3668 *See* Moher (CONSORT), *supra* note 3667, at 1191.

3669 *Id.* The "Methods" section is further divided in: participants, interventions, objectives, outcomes, sample size, randomization, blinding, statistical methods. The "Results" section is divided into: participant flow, recruitment, baseline data, numbers analyzed, outcomes and estimation, ancillary analysis, adverse events. *Id.* at 1192. *See also* ICMJE, *supra* note 945, at IV.A.1. to IV.A.14. (discussing the so-called "IMRAD" structure).

10.4.2. Information available from drug agencies

10.4.2.1. In Switzerland

Article 54.7 LPTh grants authority to the Federal Council to decide whether to make information about notified and authorized clinical trials publicly available.[3670] This provision was put forward by a parliamentary commission, for the purpose of reducing publication bias. As we have just seen, transparency benefits physicians by giving them the information necessary to make informed decisions; it puts pressure on firms and clinical trial participants to comply strictly with all legal requirements. Furthermore, the commission wanted the public to be kept abreast of health risks posed by new experimental treatments. It alluded to Gelsinger's death and to the fact that the Swiss population was kept ignorant that a similar gene study was stopped in Switzerland.

A minority of Parliament members wanted to transform Art.57.4 LPTh, which only grants permission to the Federal Council, into a mandatory provision. The proposal would have obliged the Federal Council to pass the necessary regulation. It was opposed by the pharmaceutical industry, which prefers to keep a strict tab on information related to its clinical trials.[3671] The proposal was thus defeated before Parliament. Yet the minority's hunch was good: As of July 2005, the Federal Council had not yet passed any regulation to broaden the range of publicly available data.[3672] This inaction is due to a fear that publication of clinical trials could hurt the interests of the Swiss pharmaceutical industry if no similar requirement is in force in neighboring countries.[3673] Swissmedic apparently waits to see whether the European Community will make such publication mandatory (the "please, after you" syndrome). In the meantime, Swissmedic provides practically no information on ongoing or completed clinical trials.

Interestingly, a breach in this wall of secrecy was contemplated for clinical trials viewed as entailing a higher level of risk. Under the June 2003 proposed revision of the OClin, gene therapy trials and those involving GMMOs would have been subject to increased exposure: Swissmedic would have disclosed general background information, including the medical condition being studied.[3674] However, this proposed change was finally not retained.

[3670] The information made available could include trials' normal or premature termination. *See also* Articles 62 and 67 LPTh.

[3671] Parliamentary Debate, BO 2000 N 164.

[3672] See also, with respect to Article 62.2 LPTh, the answer of the Federal Council of March 26, 2003, to the motion submitted by Parliamentary member Franziska Teuscher, at http://www.parlament.ch/afs/data/f/gesch/2002/f_gesch_20023748.htm.

[3673] This concern was raised before Parliament by Marc Suter. BO 2000 N 165.

[3674] See the June 2003 proposal for a revised Article 18a OClin.

10.4.2.2. In the United States

10.4.2.2.1. Information while the trial is underway

In the United States, the Clinical Trials Data Bank provides extensive information about clinical studies. This on-line system lists all trials testing the effectiveness of pharmaceuticals against serious or life-threatening diseases.[3675] Treatment INDs (see subsection 3.4.6.2. above) are deemed clinical trials for the purpose of this program.[3676] Other trials can be reported on a voluntary basis.[3677]

The database indicates the purpose of the trial, a brief description of its study design and its proposed interventions, the eligibility criteria, and the location of the research facilities (inside or outside the United States[3678]). Additionally, patients wanting to enroll are offered a phone number to obtain more information. The website also indicates if recruitment is still underway. The information remains available even after the trial is over or the drug approved.

The language used to present the information must be readily understood by lay people. Sponsors must enter the information into the system within 21 days starting with the opening of the trial for enrollment. They must keep the information up-to-date by communicating any change within 30 days. In addition, the FDA recommends that clinical holds (i.e., interruption) be announced sooner, that is within 10 days.

Unfortunately, the system does not compel sponsors to submit their trial *findings*. Providing this information is still purely optional.[3679] Hence, former subjects cannot use it to learn more about trials in which they took part. For the time being, subjects enrolled in a clinical trial are given the right to access only their own safety reports.[3680]

Besides this Clinical Trials Data Bank, the FDA publishes a detailed list of all clinical investigators, CROs and IRBs involved in clinical trials conducted under an IND.[3681] The U.S. National Cancer Institute (part of the NIH) also hosts a web page on international cancer clinical trials.[3682] Additionally, the FDA posts on the Internet its Warning

---

3675 See webpage at http://clinicaltrials.gov. *See also* FDA, Guidance for Industry, Information Program on Clinical Trials for Serious and Life-Threatening Diseases and Conditions, (Mar. 2002), at http://www.fda.gov/cder/guidance/4856FNL.PDF [hereinafter FDA (Information Program)].

3676 *See id.* at 5-6. On the contrary, expanded access protocols are not submitted to this reporting obligation.

3677 This concerns, for example, trials intended to test the safety of a compound or trials that are not intended to treat a serious diseases. See also 21 C.F.R. § 312.130(a) ("The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.").

3678 If a trial is conducted outside the United States, but under an IND filed before the FDA, it must be reported to the Clinical Trials Data Bank, provided it meets the other conditions (e.g., a drug trial with an efficacy endpoint against a serious or life-threatening disease).

3679 If a sponsor decides to publish such findings, it must follow the format dictated by the FDA. "This information, which, according to the structure of the Clinical Trials Data Bank, must come from the published literature, should be linked by including the unique MEDLINE identifier for citations of publications. You can use the link section provided to allow pointers to webpages directly relevant to the protocol." FDA (Information Program), *supra* note 3675, at 8.

3680 *See* 21 C.F.R. 312.130(c).

3681 The list is available at http://www.fda.gov/cder/foi/special/bmis/index.htm.

3682 National Cancer Institute (NCI), User's Guide for PDQ® Clinical Trials Search, at http://www.nci.nih.gov/search/clinicaltrials/usersguides. For example, for prostate cancer, the NCI database lists 139 clinical trials (as of June 27, 2005). For each clinical trial, the website provides summary information intended for either patients or health professionals. See also the NIH website for genetic modification trials at http://www.gemcris.od.nih.gov/Contents/GC_CT_RPT_MAKER.asp.

Letters to sponsors, investigators and IRBs (see subsection 9.3. above); these letters describe with significant details the charges made against these parties.

10.4.2.2.2. Information when the drug is under review

To obtain a marketing authorization, the sponsor has to submit to the drug agency detailed reports of its clinical trials. These reports incorporate the sponsor's assessment of the drug's safety and efficacy. They are circulated for review within the agency. They may be communicated to advisory committees, often composed of experts not employed by the agency.[3683] While agency employees perform their reviewing work outside the public eye and are bound to respect confidentiality,[3684] advisory committee meetings are often public. In the United States, under FOIA, public access to such meetings is the rule.[3685] Hence, information submitted to committee members becomes available to interested third parties, whether patient groups or competitors of the sponsor. The sponsor may only shield information from disclosure if it is deemed a trade secret or confidential commercial information. The FDA has adopted guidelines to clarify what information sponsors must make available and what they can withhold.[3686] Typically, "summaries of safety and effectiveness data," including summary information about drug reactions, are deemed non-confidential. The sponsor's protocols and its proposal for drug label are also made publicly available. On the other hand, the sponsor does not have to provide raw clinical or preclinical data,[3687] and can also retain information about the drug's formulation, including chemistry, manufacturing and control ("CMC") information.

10.4.2.2.3. Information once development effort is abandoned

FDA regulations also entitle the public to access clinical trial information when the sponsor has entirely stopped to pursue marketing approval for its drug. In that case, safety and effectiveness data contained in its former application to the agency should be made available. One of the aims of this disclosure is to warn other sponsors that this avenue of research proved fruitless.[3688] The information may also be helpful to other countries that are considering approving the same drug, whether on the basis of the same or different data.[3689] Patients, research subjects and the public in general may use the information to evaluate for themselves how safe the research was.

3683 In the United States, see OIG (FDA Review), *supra* note 20, at 10-11. "[T]he percentage of approved new drugs that had an advisory committee decreased from 19 percent in 1998 to 12 percent in 2001 …." *Id.* at 11.

3684 Article 62.1 LPTh.

3685 *See* OIG (FDA Review), *supra* note 20, at 10.

3686 *See* FDA, CDER, Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings, Draft Guidance, (Dec. 1999), at http://www.fda.gov/cder/guidance/3479dft.pdf [hereinafter CDER (Disclosing)].

3687 According to FDA's CBER, raw data mean "a complete data set of case report forms, case report tabulations, or line listings. Data that summarize individual or multiple subject outcomes/results are considered summaries. Summaries may include examples of specific findings." *Id.* at 6.

3688 *See, e.g.,* Motion of Public Citizen Health Research Group in Court of Appeal case versus FDA, Schering and Hoechst Marion Roussel, at section A (July 20, 1998), at http://www.citizen.org/print_article.cfm?ID=978.

3689 *See, e.g.*, Public Citizen Health's reply in support of its cross-motion for summary judgment in its case against the FDA, Hoechst Marion Roussel and Schering Corp. (Aug. 29, 1997) at

The industry complains that such information can be exploited by competitors to design their own clinical trials. It is therefore pushing for a narrow interpretation of the disclosure regulation. It cites the regulatory exception made for extraordinary circumstances.[3690] Pharmaceutical firms have argued that extraordinary circumstances should be understood broadly and include any damaging disclosure of valuable confidential information.[3691]

There is very little, if any, information about drug applications that the FDA rejected.[3692] Despite several calls that the FDA supply basic facts about these denied NDAs, the FDA considers that it lacks the authority to do so.[3693] Hence, the public may not know which drugs have failed to receive approval and for which reasons. The best source for such information is probably investment firms because they consistently keep track of important clinical trials sponsored by major pharmaceutical companies (see subsection 9.2.6. above).

10.4.2.3. In the European Union

The European Union has reached a midway point,[3694] still valuing transparency less than the United States, but more than Switzerland.[3695]

Since 1995, the EMEA has undertaken an overhaul of its policies on access to information access.[3696] The goal is to make the EMEA more transparent and more user-

---

http://www.citizen.org/litigation/briefs/FOIAGovtSec/articles.cfm?ID=977 [hereinafter Public Citizen (Hoechst)].

3690 *See* 21 C.F.R. § 312.430(f).

3691 "According to the defendants [Hoechst Marion Roussel and Schering Corp.], an IND is not abandoned as long as a manufacturer claims that it is not. No matter how generalized the claim might be, according to defendants, the manufacturer's statement is entitled to blind deference by both the FDA and a reviewing court. If defendants are right, the public cannot successfully force disclosure of information about drug testing that has gone awry...." Public Citizen (Hoechst), *supra* note 3689. *See further* Public Citizen Health Research Group v. FDA, 185 F.3d 898, p.905 (D.C.Cir. 1999).

3692 The available information often originates from the company itself because of financial reporting requirements aimed at the investor community. If a company has advertised the fact that it has a drug in late stage clinical development (which it generally does), then the company must provide similar information when development is stopped because of a FDA decision not to approve the candidate product. However, this"financial" information may not necessarily reach the general public. *See, e.g.*, Junod, *supra* note 3547.

3693 *See* OIG (FDA Review), *supra* note 20, at 20, 24 and 28.

3694 *See* Article 255 of the E.U. Treaty; Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, O.J. L 145 p.43-48, (31.05.2001), in particular its Article 4 on exceptions to access; text available at http://europa.eu.int/cgi-bin/eur-lex/udl.pl?REQUEST=Seek-Deliver&COLLECTION=oj&SERVICE=all&LANGUAGE=en&DOCID=2001l145p0043. *See also* Pierre-Alexis Feral, *L'accès du Public aux Documents des Institutions Communautaires: La Consécration d'un Droit Fondamental de l'Union Européenne*, EUROPE, JURISCLASSEUR 5-7 (Jul.2001); McKenna & Andersen, *supra* note 1405, at 267. *See more generally* Richard Smith, *Transparency: a modern essential*, 328 BMJ 1136 (May 8, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7448/0-f.

3695 In Switzerland, preparation work for a Federal Law on transparency in the administration ("LTrans") began in 1998. The Federal Council's Message was released in February 2003 (http://www.ofj.admin.ch.themen/oeffprinzip/bot-f.pdf). The Law was finally adopted by the Swiss Parliament on December 17, 2004 (text at http://www.admin.ch/ch/f/ff/2004/6807.pdf). The LTrans has not yet entered into force because its ordinance needs to be drafted and accepted. See the summary webpage kept by the Federal Office of Justice, (last updated Mar. 22, 2004), at http://www.ofj.admin.ch/themen/oeffprinzip/intro-f.htm.

friendly. How this will affect clinical trials is still unclear. Possibly, GCP inspections may be subject to increased transparency. Moreover, the revised version of Directive 2001/83/EC adopted in 2004 will be fully implemented by November 2005; the Directive shall broaden access to several types of documents. However, in the European Union as in other countries, the pharmaceutical industry consistently resists all attempts to place business and scientific records under greater public scrutiny.[3697]

Presently, the public has access to the following information:

i) for each newly approved drug, the European Public Assessment ("EPAR") is made public. It includes the following sections: a background, an abstract, a patient's package leaflet, a summary of product characteristics ("SPC") for physicians, the outer and inner package labeling, the scientific discussion, the steps taken before and after issuance of the authorization.[3698] The scientific discussion is the most useful document to understand how the Committee for Medicinal Products for Human Use ("CHMP," formerly "CPMP") assessed preclinical and clinical data in support of the marketing application.[3699] This assessment ends with a conclusion on the overall risk/benefit ratio.[3700] EPARs are updated whenever necessary to take into consideration new information (e.g., results of phase IV clinical studies).[3701] Commercially confidential information is redacted from the EPAR.[3702]

ii) for authorized drugs:
   - statements of withdrawal or suspension; these statements expose, in some details, the underlying reason.[3703] Sponsors that voluntarily withdraw drugs have to indicate whether they are doing so for commercial or for safety reasons.[3704] Drug withdrawal results in the removal of the corresponding EPARs from the EMEA's website.[3705]

3696 The most recent phase of this overhaul took place from August to October 2003. Starting in August 2003, the public and groups of interested parties were asked to comment on the EMEA's proposals to increase transparency. EMEA, Public consultation on EMEA transparency initiatives, (Aug. 13, 2003) (EMEA/D/21621/03/Consultation), at http://www.emea.eu.int/pdfs/general/manage/mbar/2162103en.pdf [hereinafter EMEA (2003 Consultation)]. On the result of the consultation procedure, see EMEA, New EMEA transparency policy measures (Oct. 31, 2003) (EMEA/MB/52/03/Rev 1/Final), at http://www.emea.eu.int/pdfs/general/manage/mbar/Transparancy%20pol/005203en.pdf.

3697 *See, e.g.,* European Federation of Pharmaceutical Industries and Associations ("EFPIA"), EFPIA Proposals for Improving Regulatory Communication and Transparency, Position Paper, (Nov. 22, 2000), at http://www.efpia.org/4_pos/sci_regu/Transpfinal.PDF.

3698 *See* also the paragraphs 3 and 4 of Article 21 of amended Directive 2001/83/EC.

3699 The Scientific Discussion summarizes all that is known about the new drug (its manufacture, its preclinical development and a description of its clinical trials).

3700 The EMEA plans to include, in the EPAR, a reference to both the majority and the minority opinions within the CPMP. *See* EMEA (2003 Consultation), *supra* note 3696, at 2 (point 2).

3701 *See, e.g.,* CPMP, Scientific Discussion regarding Rebif (CPMP/0022/98) (2002), at 17-18, at http://www.emea.eu.int/humandocs/PDFs/EPAR/Rebif/002298en6.pdf.

3702 *See* Article 13.3 of Regulation 726/2004.

3703 See for example the EMEA public statement on the recommendation to suspend the marketing authorization for Orlaam (levaetylmethadol) in the European Union, (Apr. 19, 2001), at http://www.emea.eu.int/pdfs/human/press/pus/877601en.pdf. In contrast, withdrawals operated in agreement with the marketing authorization holder are not commented in as much details. Compare with EMEA, Public statement on Trovan / Trovan IV / Turvel/ Turvel IV, (Mar. 21, 2001), at http://www.emea.eu.int/pdfs/human/press/pus/233501en.pdf.

3704 *See, e.g.*, EMEA, Public Statement on Vitravene, (Aug. 6, 2002), at http://www.emea.eu.int/pdfs/human/press/pus/1238202en.pdf.

3705 *Id.*

- the changes brought to the marketing authorization (mostly type I and type II variations).[3706]
- important new medical information.[3707]

iii) for drugs which were turned down for marketing authorization, only limited information is presently available.[3708] The EMEA indicates which drug authorizations were refused and briefly states why.[3709] A summary of the negative CPMP opinion is provided.

iv) little information is available on investigational drugs in clinical trials, since access to the EUDRACT database is restricted. Neither physicians nor the public at large can consult it.[3710]

The 2001 Directive on good clinical practice also sets up a database.[3711] Yet, use of the database is restricted to the authorities of Member States, to the European Agency for the Evaluation of Medicinal Products ("EMEA") and the European Commission.[3712] The public has no access. On the contrary, "confidentiality of the data is strictly observed."[3713]

10.5. Record keeping

Under Swiss law, both the sponsor and the investigator must keep records for at least 10 years following (normal or premature) termination of the trial.[3714] In the case of the sponsor, this obligation is extended until the expiry date of the last batch.[3715] It is not quite clear whether this rule refers to batches of the *still investigational* drug or also to

---

3706 The EMEA plans to make available the CHMP's summary of opinions supporting the requested changes. *See* EMEA (2003 Consultation), *supra* note 3696, at 4 (point 8).

3707 *See, e.g.*, EMEA Public Statement, High rate of virologic failure in patients with HIV infection treated with a once-daily triple nucleosides/nucleotide reverse transcriptase inhibitors combination containing didanosine, lamivudine and tenofovir, (Oct. 22, 2003), at http://www.emea.eu.int/pdfs/human/press/pus/509403en.pdf.

3708 See Articles 11 and 64.3 of Regulation 726/2004.

3709 *See, e.g.,* CPMP, EMEA, Final opinion of the Committee for Proprietary Medicinal Products on the refusal of a marketing authorization for Kronos, (Mar. 24, 1999) (CPMP/677-8/1999), at http://www.emea.eu.int/pdfs/human/opinion/014699EN.pdf; CPMP (Serostim), *supra* note 1678.

3710 *See further* Jane Burgermeister, *New EU trials database is criticized for lack of openness*, 328 BMJ 1094 (May 8, 2004), at http://bmj.bmjjournals.com/cgi/content/full/328/7448/1094.

3711 Article 11.1 of Directive 2001/20/EC. This database contains "(a) extracts from the request for authorization …; (b) any amendments made to the request …; (c) any amendments made to the protocol …; (d) the favourable opinion of the Ethics Committee; (e) the declaration of the end of the clinical trial; and (f) any reference to the inspections carried out on conformity with good clinical practice." In addition, in accordance to Article 17, the database records all "suspected unexpected serious adverse reactions to an investigational medicinal product." *See also* E.U. Guidance (Database), *supra* note 270. This database is distinct but linked to the SUSARs database under Article 17.3 of the Directive. *See* E.U. Guidance (SUSARs), *supra* note 270, at 3.

3712 *See* E.U. Guidance (Database), *supra* note 270, at 12. The sponsor has also access to its own information.

3713 Article 11.3 of the 2001/20/EC Directive.

3714 Article 25 OClin.

3715 Article 25.1 OClin. *See also* sections 5.5.6, 5.5.7, 5.5.11 (p.22) of ICH E6 (setting a minimum two-year conservation period).

batches after marketing approval.[3716] Under U.S. law, the obligation expires much sooner, after only two years.[3717]

Sponsors and investigators must keep different kinds of records, although the OClin describes them only in general terms. The sponsor must keep all information regarding the clinical trial,[3718] while the investigator must keep all raw data as well as all information necessary to identify the subjects and to provide them with a follow-up treatment should the need arise.[3719] In practice however, both sponsors and investigators should hold on to every documents relating to the trial.

[3716] The French version of Article 25.1 OClin refers to "*préparation testée*," the German version to "*Versuchspräparats*," the Italian to "*prodotto in sperimentazione*." Yves Chautems at Swissmedic indicated that the provision is to be revised, *supra* note 170.

[3717] 21 C.F.R. § 312.57 and § 312.62(c).

[3718] Article 25.1 OClin. The ICH E6 Guideline prescribes a shorter conservation period. *See* section 4.9.5 (p.18-19) cum section 1.23 (p.4) of ICH E6.

[3719] Article 25.2 OClin. *See also* SAMS (Integrity), *supra* note 1075, at 2.3. *See also* EFGCP (CRF), *supra* note 1421, at section 3, page 3; EFGCP (Records), *supra* note 3137. See in the United States: 21 C.F.R. § 312.62(c) (setting a 2-year retention period).

11. Conclusion

Sixty years ago, doctors had total control over patients. Their knowledge was unchallenged, their orders religiously obeyed. Little did patients know that the drugs they blindingly ingested were as much likely to save them as to hurt them. In fact, the more serious the disease, the higher the risks. Patients were mostly unaware of the hazards they were exposed to. Who would have told them? Certainly not the doctor. He might not even have been conscious of his own ignorance regarding the drug (in-) effectiveness and side effects.

For pharmaceutical companies, this was the golden age: They were making money by advertising loudly any compound for just about any medical condition. The public's misplaced trust alongside with doctors' arrogance and newspapers' financial interests guaranteed that governments would let these companies do what was in their best interest … and that of the national economy.

Today, doctors' paternalistic and overconfident attitude is well on its way out. The backlash came from patients questioning everything and everyone, from allopathic medicine to social sickness insurance, from doctors to governments. Doctors were forced to adapt, not only to their patients' demands, but also from those of governments and insurance companies. They were pushed to integrate a system of socialized medicine where all their medical decisions have become subject to private and public insurance control. Their revenues and way of life hang on the whim of constant tariff (re)negotiations.

Likewise, the pharmaceutical industry had to adapt tremendously. While previously free to market any product, it is now subject to regulations tighter than those of the banking or the nuclear industry. Drugs have to be proven safe and effective to a degree far exceeding that imposed to any other manufacturing industry (e.g., automobiles or cosmetics). Moreover, research must be conducted in a way that shows respect for both animals and human research subjects.[3720] While in the past a company's main expenses were manufacturing costs, now *billions* need to be invested in research to discover new drugs. What these companies disburse for research far surpasses what governments would be disposed to pay themselves. The result is that these companies have assumed a highly valuable mission for patients and society at large. A patient diagnosed with a serious disease could be saved *thanks only* to the research efforts of private firms.

Yet, R&D is an activity fraught with constant risks. The compound may fail at the research stage; drug agencies may refuse to issue a marketing authorization; governments may offer only inadequate social insurance reimbursement; the drug may have

[3720] In Switzerland, see Articles 7, 119.2 and 119a.1 of the Constitution (regarding human dignity) and Article 120.2 (regarding the dignity of creation). On this notion of dignity, see the interesting but controversial BMJ editorial: Ruth Macklin, *Dignity is a useless concept*, 327 BMJ 1419-20 (Dec. 20, 2003), at http://bmj.bmjjournals.com/cgi/reprint/327/7429/1419.pdf (pointing out that "[a] close inspection of leading examples shows that appeals to dignity are either vague restatements of other, more precise, notions or mere slogans that add nothing to an understanding of the topic." *Id.* at 1419). See also the many differing replies to this article, (at http://bmj.bmjjournals.com/cgi/eletters/327/7429/1419), in particular the good synthesis by Alexander M. Capron (from the World Health Organization), at http://bmj.bmjjournals.com/cgi/eletters/327/7429/1419#45072.

to be pulled out of the market due to unforeseen toxicity. And even once all these obstacles are overcome, the product is rapidly at the mercy of generic competitors.

The industry expected that all its efforts would earn the public's gratitude. The opposite occurred. Despite its successful transition from an unregulated and intrinsically dangerous industry into a highly regulated and extremely beneficial sector, the industry is the target of unabated criticism. Most complaints target drug prices, rightly lambasted for being excessively high and thus unfair to elderly patients or people from developing countries. Pharmaceutical firms are also reviled each time one of their products is withdrawn, even if the risk of serious adverse reactions was undetectable in clinical trials. Medical journals and patient advocacy groups demand to review clinical data and do not hesitate to challenge a drug's effectiveness.[3721]

The industry's trade associations appear to be at pains to account for this paradox: How can so many benefits be so poorly badly rewarded? For an explanation, the pharmaceutical industry should remember what happened to their "colleagues," the doctors. Indeed, government intervention is aimed, almost by necessity, at those groups whose actions affect the public interest the most. For example, an increasing number of people feel that life-saving drugs ought to be provided nearly free of charge to poor patients; they view any profits made "off the patients' back" as immoral. Others want powerful companies to demonstrate their social responsibility by adopting entirely transparent practices. Eventually, their views find resonance among parliament members and government officials. The consequence is that the greater public importance the pharmaceutical industry acquires, the higher the standards it will be held to.

Clinical trials illustrate this paradox. Fifty years ago, they simply did not exist as such[3722]. From a near total absence of rules, the pharmaceutical industry is now bound by ever more stringent and detailed regulations. Though not without resisting at first, the industry has managed to rise above each new challenge. The result is that drugs are increasingly effective, clinical trials yield ever more reliable data, patients have new therapeutic options, and populations enjoy unprecedented life expectancy.

Nonetheless, these benefits are not fairly distributed. Billions live in countries where access to drinking water, let alone medicines, is a rare privilege. Yet unfair wealth distribution should not be invoked to hide the very real achievements of scientists, researchers and regulators. The pharmaceutical industry should acknowledge that the strict scrutiny it is under is but a consequence of its vital contribution.

3721 *See, e.g.,* Editorial, *The statin wars: why AstraZeneca must retreat*, 362 LANCET 1341 (Oct. 25, 2003), at http://www.cardiology.nl/cardiology/pdf/editorial_the_statin_wars.pdf. See also the reply by AstraZeneca's CEO, 362 LANCET 1498 (Nov. 1, 2003), at http://www.essentialdrugs.org/edrug/archive/200310/msg00108.php.

3722 See the remarkable book by Philip J. Hilts: PROTECTING AMERICA'S HEALTH, THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION (Alfred A. Knopf 2003).

Glossary[3723]

Active comparator:	a drug (typically approved) used as a point of comparison to assess the safety and the efficacy of the investigational drug in a clinical trial.
Adverse Event:	any untoward medical occurrence in a subject, even if not necessarily caused by the drug.
Adverse Reaction:	any noxious and unintended response to a drug. A causal relationship between the drug and the reaction must be at least reasonable.
Abridged new drug application:	(ANDA) an application requested by the sponsor and granted by the FDA for generic drugs.
Assent:	a minor's affirmative agreement to participate in a trial.
Autologous:	in transfusion situations, a case where the donor and the recipient are the same person.
Bias:	factors related to the design, conduct, analysis of a trial that lead to erroneous results.
Bioavailability:	rate and extent to which a drug's active substance is absorbed and becomes available at the site of action.
Bioequivalence:	the basis for comparing generic and brand-name drugs, which requires that their bioavailability be equivalent.
Blinding:	keeping subjects unaware of whether they are receiving the investigational compound or the comparator product.
Blockbuster drug:	a drug whose annual sales exceed $1 billion.
Biologics:	"A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product" used in a medical treatment. In general, the word "drug" encompasses biologics.
Bolar exemption:	a rule that allows generic manufacturers to prepare their generic applications and hence perform the required comparative tests (between their drugs and the innovator reference product) before the expiry of the patent protecting the reference product.
Comparator:	the product (whether an active drug or a placebo) used in the clinical trial to compare its effects with those of the investigational compound.
Consent form (CF):	the form that provides necessary information to subjects so that they may decide whether to give their informed consent, by signing the form.
Case report form (CRF):	a form used to record the information requested by the protocol and communicate it to the sponsor.
Double-blinding:	keeping both subjects and the medical team ignorant of whether a given subject is receiving the investigational compound or the comparator product.

[3723] For more detailed glossaries, see from http://www.med.umich.edu/cacr/dictionary/A-B.htm; Applied Clinical Trials, Glossary, Clinical Research Terminology, from http://www.actmagazine.com/appliedclinicaltrials/data/articlestandard/appliedclinicaltrials/012002/42076/article.pdf.

Dosage form:	the physical form in which a drug is produced (e.g., solid oral or patch).
Dropout:	a subject who – voluntarily or not – does not participate in the trial until its completion.
DSMB:	a group that regularly reviews the unblinded data that arises from an ongoing clinical trial and that can decide, based on this information, whether to prematurely end the trial.
Effectiveness:	the desired measure of a drug's influence on a disease in the controlled circumstances of a RCT.
Efficacy:	the ability of a drug to produce a beneficial therapeutic effect.
Endpoint:	the precise criteria selected to judge the safety and efficacy of the drug based on the data gathered in a study.
Equipoise:	a state of true uncertainty as to which of two treatments proposed to research subjects is best.
Excipient:	the inactive ingredient added to the active ingredient to prepare a drug.
Formulation:	the ingredients that come into the preparation of a final drug product (e.g., different quality or quantity of excipients).
IND:	in U.S. terminology, an investigational new drug, that is the application that sponsor must submit to the FDA before being allowed to begin any drug clinical trial.
Investigator:	the individual taking responsibility for carrying out a clinical trial.
Marketing approval:	the authorization granted by a drug agency to place a given drug (for a given therapeutic indication) on the market.
Me-too drug:	a drug very similar to an existing drug, but with slightly different active ingredients.
Minimal risk:	according to the U.S. definition, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[3724]
New chemical entity (NCE):	a drug whose active substance has never been approved before.
New drug application (NDA):	the application that the sponsor files to obtain FDA approval for a new drug (as opposed to a generic drug).
New molecular entity (NME):	same as new chemical entity.
Off-label (prescription):	the practice of prescribing a drug in a way which is not covered by the drug's marketing authorization (for example, prescribing a drug for a different therapeutic indication than the one approved).
Orphan drug:	a drug intended for a small patient population (e.g., 200,000 or fewer patients in the United States).
Pharmacodynamics:	the study of the effects of a drug substance on the body's functions, focusing in particular on dose-response relationships.
Pharmacogenomics:	the study of how a patient's genetic profile influence the safety or efficacy of a drug.

[3724] *See* 45 CFR 46.102(i); 21 C.F.R. §56.102(i) and § 50.3(k).

Pharmacokinetics:	the study of drug absorption, distribution, metabolism and excretion (ADME) in humans or animals.
Pharmacovigilance:	the system for reporting adverse drug events once drugs are approved.
Phase I:	a trial aimed at obtaining preliminary information about a drug's safety on a small number of subjects (before the grant of marketing authorization).
Phase II:	a trial aimed at verifying the drug's safety and obtaining preliminary information about the drug's effectiveness (before the grant of marketing authorization).
Phase III:	a trial aimed at verifying the effectiveness of a drug on a large number of human research subjects (before the grant of marketing authorization).
Phase IV:	after the drug has received its marketing authorization, a clinical study to gather further information about the safety and the effectiveness of the drug, either in a larger group of patients or a more specifically defined group of patients.
Placebo:	a dummy product (e.g., pill) or procedure administered to the subject to trigger the placebo effect.
Placebo effect:	the common biological and psychological response to what is (erroneously) believed to be a true drug.
Prospective trial:	a trial where the test hypothesis is answered by actually collecting new data.
Protocol:	the written plan describing the clinical trial in details.
Randomization:	the assignment by chance (random) of subjects to the different arms of a clinical trial.
Raw data:	the observations and measurements as directly recorded by the researcher.
Retrospective study:	a study that investigates already available data or samples.
Route of administration:	the way the drug is administered to patients (e.g., intravenous or intrathecal route).
Standard operating procedures:	(SOPs) written instructions as to how a specific task must be performed.
Sponsor:	the party taking responsibility for launching or financing a clinical trial.
Strength:	the quantity of active ingredient in a drug (e.g., 10 mg).
Surrogate(endpoint):	a variable that *indirectly* measures the effect of the treatment.
Teratogenicity:	toxicity affecting the fetus.
Therapeutic indication:	the specific medical use(s) of a drug.
Therapeutic window:	the lapse of time available to perform a given medical intervention.
Type I error:	the erroneous rejection of the null hypothesis.
Type II error:	the erroneous failure to reject the null hypothesis.

List of court cases cited

U.S. court cases:

Abdullahi v. Pfizer, 2002 U.S. Dist. LEXIS 17436 (S.D.N.Y. 2002).

Aden v. Younger, 57 Cal. App. 3d 662 (Cal. Ct. App. 1976).

Ancheff v. Hartford Hospital et al., 799 A.2d 1067 (Conn. 2002).

Ass. American, Physicians and Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002).

Bailey v. Lally, 481 F. Supp. 203 (D.Md. 1979).

Baird v. American Medical Optics, 713 A.2d 1019 (N.J. 1998).

Barnson v. United States, 816 F.2d 549 (10th Cir. 1987).

Barrett v. United States, 660 F. Supp. 1291 (S.D.N.Y. 1987).

Begay v. United States, 591 F. Supp. 991 (D.Ariz. 1984), *aff'd* 768 F.2d 1059 (9th Cir. 1985).

Bonner v. Moran, 126 F.2d 121 (D.C.Cir. 1941).

Bouvia v. the Superior Court of Los Angeles County, 179 Cal. App. 3d 1127 (Cal. Ct.App. 1986).

Brown v. the Superior Court of the City and County of San Francisco, 44 Cal. 3d 1049 (Cal. 1988).

Bulloch v. United States, 721 F.2d 713 (10th Cir. 1983).

Bulman v. Myers, 467 A.2d 1353 (Pa. Super. 1983).

Burton v. Brooklyn Doctors Hospital, 452 N.Y.S.2d 875 (N.Y. App. 1982).

Busalacchi v. Vogel, 429 So. 2d 217 (C.A.Louis. 1983).

Cain v. United States, 643 F. Supp. 175 (S.D.N.Y. 1986).

Campaign for Responsible Transplantation v. Food and Drug Administration, 219 F. Supp. 2d 106 (D.C.C. 2002).

Canterbury v. Spence, 464 F.2d 772 (D.C.Cir. 1972).

Central Intelligence Agency et al. v. Sims et al., 471 U.S. 159 (1985).

City of Akron v. Akron Center for Reproductive Health, 462 U.S. 416 (1983).

Dahl v. HEM Research, Inc., 7 F.3d 1399 (9th Cir. 1993).

Daum v. SpineCare Medical Group, 52 Cal. App. 4th 1285 (Cal. Ct. App., 1997).

Davis v. Davis, 842 S.W.2d 588 (Tenn. 1992).

Doe v. Sullivan, 938 F.2d 1370 (D.C.Cir. 1991).

Edison Pharmaceutical Co. v. Food and Drug Administration, 600 F.2d 831 (D.C. Cir. 1979).

Farnsworth v. Procter & Gamble, 758 F.2d 1545 (11th Cir. 1985).

Federal Trade Commission v. Pantron I Corp, 33 F.3d 1088 (9th Cir. 1994).

Foflygen v. Allegheny General Hospital, 723 A.2d 705 (Pa. Super. 1999).

Glutzer v. Prudential Insurance Co., 183 F.R.D. 632 (N.D. Ill. 1999).

Grimes v. Kennedy Krieger Institute, 782 A.2d 807 (Md. 2001).

Harris v. Mutual of Omaha Co., 992 F.2d 706 (7th Cir. 1993).

Hecht v. Superior Court of Los Angeles County, 16 Cal. App. 4th 836 (Cal. Ct. App. 1993).

Heinrich v. Sweet, 49 F. Supp. 2d 27 (D. Mass. 1999).

Hendricks v. Central Reserve Life Insurance Co., 39 F.3d 507 (4th Cir. 1994).

Hoffmann-La Roche Inc. v. Yoder, 950 F. Supp. 1348 (S.D. Ohio 1997).

Holland-Rantos Co. v. U.S. Department of Health, Education and Welfare, 587 F.2d 1173 (D.C. Cir. 1978).

In re Baycol, 218 F. R. D. 197 (D. Minn. 2003).

In Re Cincinnati Radiation Litigation, 874 F. Supp. 796 (D. Ohio 1995).
In re Georges Jolles, 628 F.2d 1322 (C.C.P.A. 1980).
In re Wesley Gale Irons, 340 F.2d 974 (C.C.P.A. 1965).
Integra Lifesciences I, v. Merck, 331 F.3d 860 (Fed. Cir. 2003).
Jaffee v. United States, 663 F.2d 1226 (3d Cir. 1981).
Johnson v. Meltzler, 134 F.3d 1393 (9th Cir. 1998).
Karemer-Katz v. U.S. Public Health Service, 872 F. Supp. 1235 (S.D.N.Y. 1994).
Karp v. Cooley, 349 F. Supp.827 (S.D. Tex. 1972) *aff'd* 493 F.2d 408 (5th Cir. 1974).
Kernke v. The Menninger Clinic Inc., 173 F. Supp. 2d 1117 (D. Kan. 2001).
Knecht v. Gillman, 488 F.2d 1136 (8th Cir. 1973).
Kronisch v. United States, 150 F.3d 112 (2d Cir. 1998).
Largey v. Rothman, 540 A.2d 504 (N.J. 1988).
Madey v. Duke University, 307 F.3d 1351 (Fed.Cir. 2002).
Mink v. University of Chicago, 460 F. Supp.713 (N.D. Ill. 1978).
Moore v. Regents of the University of California, 51 Cal. 3d 120 (Cal. 1990).
Nevin v. United States, 696 F.2d 1229 (9th Cir. 1983).
Orlikow v. United States, 682 F. Supp. 77 (D.C.C. 1988).
Perkins v. Desipio, 736 A.2d 608 (Pa. Super Ct. 1999).
Retwka v. Orentreich, 584 N.Y.S.2d 710 (S.Ct.N.Y. 1992).
Robertson v. McGee, 2002 U.S. Dist. LEXIS 4072 (N.D. Okl. 2002).
Roche Products v. Bolar Pharmaceutical, 733 F. 2d 858 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 856 (1984).
Salgo v. Leland Stanford Junior University Board of Trustees, 154 Cal. App. 2d 560 (1957).
Santucci v. Hyatt Corp., 955 F. Supp. 927 (N.D. Ill. 1997).
Schloendorff v. The Society of the N.Y. Hospital, 211 N.Y. 125 (N.Y. Ct.App. 1914).
Scott v. Bradford, 606 P.2d 554 (Okl. 1979).
Stanton v. Astra Pharmaceutical Products, Inc., 718 F. 2d 553 (3d Cir. 1983).
Steward v. Cleveland Clinic Foundation, 736 N.E.2d 491 (Ohio Ct. App. 1999).
T.D. et al. v. New York State Office of Mental Health, 228 A.D.2d 95 (N.Y. 1996).
Tansy v. Dacomed Corp., 890 P.2d 881 (Okl. 1994).
The Church of Scientology of California v. Richardson, 437 F.2d 214 (9th Cir. 1971).
The Founding Church of Scientology of Washington v. United States, 409 F.2d 1146 (D.C. 1969).
Thornwell v. United States, 471 F. Supp. 344 (D.C.C. 1979).
Tobin v. Astra Pharmaceutical Products, Inc., 993 F.2d 528 (6th Cir. 1993).
Transkaryotic Therapies, Inc. v. Bain & Co., 14 Mass. L. Rep. 397 (Mass. Super. Ct. 2002).
T-Up Inc. v. Consumer Protection Division, 801 A.2d 173 (C.App.Mar. 2002).
United States v. An Article … Acu-Dot, 483 F. Supp. 1311 (D.Ohio. 1980).
United States v. An Article or Device …, 333 F. Supp.357 (D.D.C. 1971).
United States v. Snyder, 291 F.3d 1291 (11th Cir. 2002).
United States v. Stanley, 483 U.S. 669 (1987).
Vick v. Coventry Health Care, 2001 U.S. Dist. LEXIS 12198 (D. Kan. 2001).
Warner-Lambert v. Heckler, 787 F.2d 147 (3d Cir. 1986).
Washington Legal Found. v. Henney, 56 F. Supp. 2d 81 (D.D.C. 1999).
Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609 (1973).

Whitlock v. Duke University, 637 F. Supp. 1463 (M.D.N.C. 1986).
Zeleznik v. Jewish Chronic Disease Hospital, 366 N.Y.S.2d 163 (N.Y. App. Div. 1975).
Zervos v. Verizon, 277 F.3d 635 (2d Cir. 2002).

Swiss court cases:

ATF 66 II 34
ATF 98 Ia 508 = JdT 1973 I 490
ATF 99 IV 208 = JdT 1974 IV 132
ATF 101 II 177 = JdT 1976 I 362
ATF 104 Ia 480
ATF 105 II 284
ATF 108 II 59
ATF 111 Ia 231
ATF 113 Ib 420 = JdT 1989 I 26
ATF 113 II 429 = JdT 1988 I 180
ATF 113 V 42
ATF 114 Ia 350
ATF 115 Ia 234 = JdT 1991 I 194
ATF 116 II 519 = JdT 1991 I 634
ATF 117 Ib 197 = JdT 1992 I 214
ATF 119 Ia 460 = JdT 1995 I 586
ATF 119 II 456
ATF 119 V 26
ATF 120 V 472
SJ 2000 p.358
ATF 127 I 145

Short Bibliography[3725]

PAUL S. APPELBAUM, CHARLES W. LIDZ & ALAN MEISEL, INFORMED CONSENT, LEGAL THEORY AND CLINICAL PRACTICE (Oxford Univ. Press 1987).

PETER S. ARNO & KARYN L. FEIDEN, AGAINST THE ODDS (HarperCollins 1992).

TOM L. BEAUCHAMP & JAMES F. CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS (Oxford Univ. Press, 5th ed. 2001).

ROBERT BAZELL, HER-2, THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER (Random House 1998).

BARUCH A. BRODY, ETHICAL ISSUES IN DRUG TESTING, APPROVAL, AND PRICING (Oxford Univ. Press 1995).

OLIVIER GUILLOD, LE CONSENTEMENT ÉCLAIRÉ DU PATIENT, AUTODÉTERMINATION OU PATERNALISME? (Editions Ides et Calendes 1986).

ALLEN M. HORNBLUM, ACRES OF SKIN (Routledge 1998).

JAMES H. JONES, BAD BLOOD, THE TUSKEGEE SYPHILIS EXPERIMENT (The Free Press 1981).

PAUL DE KRUIF, MICROBE HUNTERS (Harvest Book 1926).

SUSAN E. LEDERER, SUBJECTED TO SCIENCE (John Hopkins Univ. Press 1995).

PATRICK LEMOINE, LE MYSTÈRE DU PLACEBO (Editions Odile Jacob 1996).

ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH (2d ed. Urban & Schwarzenberg 1986).

PATRICIA LUTHY, ENREGISTREMENT ET CONTRÔLE DES MÉDICAMENTS SUR LES MARCHÉS DES PRODUITS PHARMACEUTIQUES SUISSE ET EUROPÉEN (Thèse Lausanne Payot 1993).

DOMINIQUE MANAÏ, LES DROITS DU PATIENT FACE À LA MÉDECINE CONTEMPORAINE (Helbing & Lichtenhahn 1999).

HARRY M. MARKS, THE PROGRESS OF EXPERIMENT, SCIENCE AND THERAPEUTIC REFORM IN THE UNITED STATES, 1900-1990, (Cambridge History of Medicine 1997).

PAUL M. MCNEIL, THE ETHICS AND POLITICS OF HUMAN EXPERIMENTATION (Cambridge Univ. Press 1993).

RICK MURDOCK & DAVID FISHER, PATIENT NUMBER ONE (Crown Publishers 2000).

ODILE PELET, ORGANES, TISSUS, CELLULES: LOIN DU CORPS, LOIN DE LA PERSONNE? (Staempfli 2002).

ARTHUR AND ELAINE SHAPIRO, THE POWERFUL PLACEBO, FROM ANCIENT PRIEST TO MODERN PHYSICIAN (John Hopkins Univ. Press 1997).

DOMINIQUE SPRUMONT, LA PROTECTION DES SUJETS DE RECHERCHE NOTAMMENT DANS LE DOMAINE BIOMÉDICAL (Ed. Staempfli Berne, 1993).

VARIOUS AUTHORS, THE NAZI DOCTORS AND THE NUREMBERG CODE (Oxford Univ. Press 1992).

VARIOUS AUTHORS, ASPECTS DU DROIT MÉDICAL (Editions Universitaires Fribourg 1987).

VARIOUS AUTHORS, 75 ANS DE CONTRÔLE INTERCANTONAL DES MÉDICAMENTS (1975).

[3725] Only the books and the articles which have *often been cited* throughout this thesis are listed here.

Index

A

adverse reaction 78, 183, 190, 193, 262, 428, 473, 474
advertisements 74, 88, 279, 291, 327
assent 371, 391
auditors 164
autonomy 16, 17, 231, 392, 414

B

beneficence 16, 231
benefits of a trial 286, 346, 397
bias 7, 84, 197, 203
bioequivalence 85
biological material 70, 350, 352, 460, 463
brochure 201, 279, 283, 471, 484

C

canton 20, 22, 74, 259, 305, 497
CIOMS 3, 15, 124, 339, 358, 396, 423, 432, 442
compassionate 63, 65, 66, 199, 322, 348
compassionate
  treatment IND 64
confidentiality 268, 275, 432
conflicts of interest 139, 273, 349
Consort guidelines 513
contract 333, 334, 453, 479, 507
costs of clinical trials 99
CRF 201, 494
CRO 25, 165, 318, 328, 351, 493, 494, 495, 515

D

data protection 438
developing countries 119, 233, 237, 423
DSMB 169, 229, 369, 404, 504

E

efficacy 79
embryos 39, 42, 43, 44, 415
emergency 375, 381, 388, 389, 403, 404
empowerment 17, 330, 364
endpoints 238
equipoise 226
ethics committees 258, 331, 349, 364

F

footnote 6, 7

G

gene therapy 47, 316, 398, 495, 514

H

Helsinki 13, 145, 198, 227, 233, 235, 338, 367, 417, 423, 430, 431, 509, 512

I

ICH 3, 6, 24, 107, 433
  ICH E5 Guideline 108
  ICH E6 Guideline 108
incompetent 372, 384
informed consent 14, 21, 31, 33, 124, 273, 335, 406
intellectual property 90, 467
investigator 132

J

justice 17, 331

L

liability 89, 448
living human subject 52

M

monitors 160, 435, 469, 495, 500

N

narcotics 46
Nuremberg 10

P

payments to subjects 441
pharmacoeconomic 94
Phase I 175
Phase II 180
Phase III 182
Phase IV 184
placebo 93, 177, 182, 184, 187, 211, 214, 230, 233
preemption 74

prisoners 408
protocol 60, 196, 468
proxy consent 384, 388
publication 31, 89, 90, 133, 142, 145, 146, 157, 158, 198, 246, 259, 292, 337, 427, 506, 507

R

randomization 55, 224, 225, 247, 343, 439
recruitment 73, 180, 290, 299, 318
risks of clinical trials 102

S

safety 51, 77, 180, 192, 285
SAMS 20, 157, 259, 412, 510
seniors 373, 418
SMO 168
sponsor 128, 308, 334, 451, 456, 507
statistics 246
stem cell 43

T

transparency 5, 146, 263, 268, 296, 307, 507, 513, 514, 517
transplants 41
Tuskegee 27
type I and type II errors 105

V

VanTx 25, 304

W

women 179, 266, 410, 412, 413, 416

Table of contents

Acknowledgments IX

Summary of contents XI

Acronyms XIII

List of Principal Laws and Regulations cited XVII

1. Introduction 1
- 1.1. Scope of the thesis 1
- 1.2. Focus of the thesis 2
  - 1.2.1. A broad regulatory outlook 2
  - 1.2.2. Medical literature 3
  - 1.2.3. Economic literature 4
  - 1.2.4. Ethics 4
- 1.3. Laws under analysis 4
- 1.4. Plan of the thesis 7

Part I 9

2. Historical overview of clinical trial regulations 9
- 2.1. International principles 10
  - 2.1.1. The Nuremberg Code 10
  - 2.1.2. The Helsinki Declaration and other texts 13
  - 2.1.3. Three central ethical principles 16
  - 2.1.4. Patient empowerment 17
  - 2.1.5. A fundamental shift from a burden to a benefit 19
- 2.2. Historical overview of Swiss regulations on clinical trials 20
  - 2.2.1. Successive Swiss regulations of clinical trials 20
    - 2.2.1.1. Cantonal regulations 20
    - 2.2.1.2. Prescriptions of the Swiss Academy of Medical Sciences 20
    - 2.2.1.3. General federal provisions on informed consent 21
    - 2.2.1.4. Former intercantonal regulations 22
    - 2.2.1.5. Comprehensive federal regulations: the LPTh and the OClin 23
  - 2.2.2. Scandals in Switzerland: the VanTx affair 25
- 2.3. Historical overview of U.S. clinical trials regulations 26
  - 2.3.1. Scandals in the United States 26
    - 2.3.1.1. The Tuskegee study 27
    - 2.3.1.2. Radiation studies 28
    - 2.3.1.3. Mind control experiments 30
    - 2.3.1.4. Recent scandals 31
  - 2.3.2. Successive U.S. regulations of clinical trials 32
- 2.4. Historical overview of E.U. regulations 35

3. Definition of clinical trials 36
- 3.1. The three regional definitions 37
- 3.2. Clinical trials of therapeutic products 38
  - 3.2.1. Is there a rationale for the OClin's product-related limitations 38
  - 3.2.2. Definition of "therapeutic products" 40
    - 3.2.2.1. Pharmaceuticals 40

3.2.2.2. Transplants 41
3.2.2.3. Stem cell therapy 43
3.2.2.4. Narcotics 46
3.2.3. Gene therapy 47
3.2.3.1. Definition of somatic gene therapy 47
3.2.3.2. Opposition to gene therapy 48
3.2.3.3. Gene therapy and the OClin 49
3.2.3.4. Ex vivo gene therapy 50
3.2.4. The administration of a therapeutic product 50
3.2.5. Safety, efficacy and other properties 51
3.3. A living human subject 52
3.4. Research as compared to individualized health care 53
3.4.1. Systematic methods 54
3.4.2. Generalizable information 56
3.4.3. The criterion of intent 57
3.4.4. Status of the drug 59
3.4.5. Other elements to be taken into account 60
3.4.6. Specific borderline situations 61
3.4.6.1. Non-interventional studies 61
3.4.6.2. Expanded access programs 62
3.4.6.2.1. The international context 62
3.4.6.2.2. The various forms of compassionate use in the United States 63
3.4.6.2.3. The various forms of compassionate use in Switzerland 65
3.4.6.2.4. Do compassionate access programs come under the OClin? 66
3.4.6.3. Retrospective studies 68
3.4.6.4. Research on biological material 70
3.4.6.5. Clinical trials versus non-medical activities 71
3.5. The scope of the OClin 72
3.5.1. Temporal scope of the OClin 72
3.5.2. Geographical scope of the OClin 73
3.5.3. Preemption of cantonal regulations 74

4. The economic dimension of clinical trials 76
4.1. The objectives of clinical trials 76
4.1.1. Obtaining marketing approval 76
4.1.1.1. Proving the drug's safety 77
4.1.1.1.1. Historical background 77
4.1.1.1.2. Safety tests 78
4.1.1.2. Proving efficacy 79
4.1.1.2.1. Historical background of the efficacy requirement 79
4.1.1.2.2. The role of therapeutic indications 82
4.1.1.2.3. Required standard of substantiation 83
4.1.1.3. Proving bioequivalence 85
4.1.1.4. The marketing authorization process and its alternatives 86
4.1.2. Contributing to basic knowledge 86
4.1.3. Assisting physicians 87
4.1.4. Advertising the drug 88
4.1.4.1. Before marketing approval 88
4.1.4.2. After marketing approval 89
4.1.5. Minimizing liability 89
4.1.6. Intellectual property ("IP") 90

4.1.6.1. Getting IP rights ("IPR") 90
4.1.6.2. Defending patent infringement claims 91
4.1.7. Obtaining reimbursement status 93
4.1.8. Getting investors interested 95
4.1.9. Getting a pharmaceutical firm interested in a biotech company 96
4.1.10. Factors in deciding to launch a clinical trial 97
4.2. Economic issues in clinical trials 99
4.2.1. Costs of clinical trials 99
4.2.1.1. Number and length of trials 99
4.2.1.2. Estimates of total costs 101
4.2.2. Risks of clinical trials 102
4.2.3. Implications of clinical trial costs 103
4.2.3.1. Consequences on the industry 103
4.2.3.2. Consequences for patients 104
4.2.3.3. Consequences on price levels 105
4.3. Regional harmonization of clinical trial requirements 106
4.3.1. International Harmonization Conference 107
4.3.1.1. The ICH E6 Guideline 108
4.3.1.2. The ICH E5 Guideline 108
4.3.1.2.1. What role do ethnicity and race play? 109
4.3.1.2.2. Bridging studies 110
4.3.2 Recognition by Swissmedic of foreign clinical trials 112
4.3.3. Recognition of foreign clinical trials in the United States 114
4.4. Strategic weight of clinical trials, in particular in Switzerland 115
4.4.1. Strategic importance of clinical trials 115
4.4.2. Assets and drawbacks of Swiss clinical trials 116
4.5. Clinical trials in developing countries 119
4.5.1. Advantages and disadvantages of clinical trials in developing countries 120
4.5.2. Scandals in developing countries 122
4.5.3. Reactions to scandals 124

Part II 127

5. The professional participants in a clinical trial 127
5.1. The sponsor 128
5.1.1. Legal requirement pertaining to the sponsor 128
5.1.2. Who becomes sponsor? 129
5.1.3. Number of sponsors 130
5.1.4. The sponsor's duties 131
5.2. The investigator 132
5.2.1. Investigators' motivations 133
5.2.2. Sponsor's selection of investigators 134
5.2.3. Academic and commercial investigators 135
5.2.4. Number of investigators 136
5.2.5. Qualifications of the investigator 137
5.2.6. Responsibilities of the investigator 138
5.2.7. Investigators' institutions 139
5.3. Conflicts of interest involving sponsors and investigators 139
5.3.1. Impartiality of the investigator 141
5.3.1.1. Tension between research and therapy 141
5.3.1.2. Independence toward the sponsor 141
5.3.2. Financial issues 142
5.3.2.1. Types of financial involvements 143

5.3.2.2. Possible consequences 144
5.3.2.3. Disclosure of conflicts 145
5.3.2.4. Conflicts of interest in the United States 147
5.3.2.4.1. Historical background 147
5.3.2.4.2. FDA regulation on conflicts of interest 148
5.3.2.4.3. Changes in academic research institutions 151
5.3.2.5. Conflicts of interest in Switzerland 154
5.3.2.5.1. Provisions of the LPTh and the OClin 154
5.3.2.5.2. Policies of the Geneva University 156
5.3.2.5.3. SAMS policies 157
5.3.3. Conflicts of interest pertaining to confidentiality requests 158
5.3.3.1. The Olivieri case 158
5.3.3.2. Confidentiality clauses 159
5.4. Monitors 160
5.4.1. Obligation to monitor the trial 160
5.4.2. Role of the monitor 162
5.4.3. Appointment of monitors 163
5.5. Auditors 164
5.6. Contract research organizations 165
5.6.1. A growing presence 165
5.6.2. Permissible delegation 166
5.6.3. Activities commonly delegated 167
5.7. Site Management Organizations 168
5.8. Data Safety Monitoring Boards 169
5.8.1. Necessity of a DSMB 169
5.8.2. Appointment of a DSMB 170
5.8.3. Role of a DSMB 171

6. The types and characteristics of drug clinical trials 174
6.1. The different kinds of clinical trials 174
6.1.1. Phase I 175
6.1.1.1. Conditions of phase I trials 175
6.1.1.2. Objectives of a phase I trial 176
6.1.1.3. Therapeutic and nontherapeutic trials 177
6.1.1.4. Subjects recruited for a phase I trial 179
6.1.2. Phase II clinical trials 180
6.1.3. Phase III clinical trials 182
6.1.3.1. Objectives 182
6.1.3.2. Importance of phase III trials 182
6.1.3.3. Organization of phase III trials 183
6.1.4. Phase IV clinical trials 184
6.1.4.1. Phase IV trials requested by the drug agency 185
6.1.4.1.1. Reasons for phase IV studies 185
6.1.4.1.2. Characteristics of phase IV studies 186
6.1.4.1.3. Compliance with phase IV commitments 187
6.1.4.2. Phase IV trials decided by pharmaceutical companies 188
6.1.4.2.1. Objectives 188
6.1.4.2.2. Characteristics 189
6.1.4.3. Pharmacovigilance 190
6.1.4.3.1. Purpose of pharmacovigilance 190
6.1.4.3.2. Periodic safety update reports 191
6.1.4.3.3. Adverse reactions reports 193
6.1.5. Flexibilities in the phase division 193
6.2. The key documents of a clinical trial 196
6.2.1. The protocol 196

6.2.1.1. Contents of a protocol 197
6.2.1.2. Preparation of the protocol 198
6.2.1.3. Drug agencies' role in the design of clinical trials 199
6.2.1.4. Changes to the protocol 200
6.2.2. The brochure 201
6.2.3. Case report forms ("CRFs") 201
6.2.3.1. Role of CRFs 202
6.2.3.2. Completing and changing CRFs 203
6.3. The gold standard: chasing bias 203
6.3.1. Importance of randomized controlled trials 205
6.3.2. Historical aspects 207
6.3.3. Controls 208
6.3.3.1. Purpose of controls 209
6.3.3.2. The placebo effect 211
6.3.3.3. Active controls 213
6.3.3.3.1. Scientific difficulties in connection with active controls 213
6.3.3.3.2. Sponsors' preferences for placebos 214
6.3.3.3.3. Obligation to conduct comparative trials 216
6.3.3.3.4. Advantages of comparative trials 216
6.3.3.4. Washout periods 217
6.3.3.5. Hiding the control 218
6.3.3.5.1. Blinding 218
6.3.3.5.1.1. Single-blinding 218
6.3.3.5.1.2. Double-blinding 219
6.3.3.5.1.3. Other types of blinding 220
6.3.3.5.2. Two almost identical products 221
6.3.3.5.3. Inadvertent unblinding 222
6.3.3.5.4. Permissible unblinding 223
6.3.4. Randomization 224
6.3.5. Ethical problems related to controls and randomization 225
6.3.5.1. The notion of equipoise 226
6.3.5.1.1 Theoretical and clinical equipoise 226
6.3.5.1.2. Personal equipoise 228
6.3.5.1.3. Duration of equipoise 229
6.3.5.1.4. Consequences 230
6.3.5.2. The placebo controversy 230
6.3.5.2.1. The controversy in developed countries 231
6.3.5.2.2. The placebo controversy in developing countries 233
6.3.5.2.3. The revised Helsinki Declaration 233
6.3.5.2.4. Consequences in developed countries 235
6.3.5.2.5. Consequences in developing countries 237
6.3.6. The study's endpoints 238
6.3.6.1. Primary and secondary endpoints 239
6.3.6.2. Tracking endpoints 240
6.3.6.3. Surrogate endpoints 240
6.3.6.4. Post hoc analysis 242
6.3.7. Control of eligibility criteria 243
6.3.8. Dropouts 245
6.3.9. Duration of the trial 246
6.3.10. Statistics 246
6.3.10.1. Sample size 247
6.3.10.2. Underpowered studies 248

6.3.10.3. The p-value and confidence interval 249
6.3.10.4. Causation 250
6.3.10.5. Presentation of results 250
6.3.11. Quality assurance 252
6.4. Manufacturing controls and labeling 253

Part III 257

7. Approval of clinical trials 257
7.1. Approval of clinical trials by ethics committees 258
7.1.1. Organization of Swiss RECs 258
7.1.1.1. Historical perspective 259
7.1.1.2. Role of the canton under the LPTh 259
7.1.1.2.1. Cantonal appointment of RECs 259
7.1.1.2.2. Further cantonal responsibilities 261
7.1.1.2.3. Difficulties with the cantonal organization 262
7.1.1.3. Composition of RECs 263
7.1.1.3.1. Qualifications of REC members 263
7.1.1.3.2. Female REC members 266
7.1.1.3.3. Non-represented groups 267
7.1.1.3.4. Accountability 268
7.1.1.3.5. Knowledge of local conditions 268
7.1.1.4. Independence of RECs 270
7.1.1.4.1. The legal requirements 270
7.1.1.4.2. What independence for institutional RECs? 271
7.1.1.4.3. Conflicts of interest within RECs 273
7.1.1.5. External assistance 275
7.1.2. RECs' decision-taking process 276
7.1.2.1. Choice of REC 276
7.1.2.2. Multicentric review 277
7.1.2.3. The investigator's application 279
7.1.2.4. Information gathering process by the REC 282
7.1.2.5. Assessment criteria 283
7.1.2.5.1. Scientific validity 284
7.1.2.5.2. Relevance 284
7.1.2.5.3. Assessment of risks 285
7.1.2.5.4. Assessment of benefits 286
7.1.2.5.5. The balancing of risks and benefits 287
7.1.2.5.6. Appropriate information given to subjects 288
7.1.2.5.7. Financial relationship between the sponsor and the investigator 289
7.1.2.5.8. Review of recruitment procedures 290
7.1.2.5.9. Review of publication policies 292
7.1.2.6. The vote 293
7.1.2.7. The form of the decision 295
7.1.3. Information about the operation of RECs 296
7.1.3.1. In Switzerland 296
7.1.3.2. In other countries 297
7.1.3.3. Limits of the REC's assessment 299
7.1.4. Proposals for improving RECs 300
7.1.4.1. Continuing education 300
7.1.4.2. Longer deadlines 300
7.1.4.3. Funding RECs properly 301
7.1.4.4. "Private" RECs? 301

7.1.4.5. Public RECs 303
7.1.5. Supervision of ethics committees 305
7.1.5.1. Cantonal oversight in Switzerland 305
7.1.5.1.1 Sovereignty of each canton 305
7.1.5.1.2. Problems with cantonal oversight 306
7.1.5.2. A new role for Swissmedic 307
7.1.5.3. Oversight by the sponsor 308
7.2. Drug agency's approval of clinical trials 309
7.2.1. The clearance process 309
7.2.1.1. In Switzerland 309
7.2.1.2. In the United States 310
7.2.2. Contents of the application 311
7.2.3. Assessment of the application 313
7.2.3.1. In Switzerland 313
7.2.3.2. In the United States 314
7.2.4. The authorization process 315
7.2.4.1. Products involved 315
7.2.4.2. The application and the authorization process 316
7.2.5. The opportunities for appeal 317

8. Research subjects 318
8.1. Recruitment of subjects 318
8.1.1. Practical and economic issues 318
8.1.2. Factors affecting recruitment 320
8.1.2.1. Patient pool 320
8.1.2.2. Existence of alternative treatments 321
8.1.2.3. Eligibility criteria 322
8.1.2.4. Lack of information about the trial 324
8.1.2.5. Design of the trial 325
8.1.2.6. Cost issues 326
8.1.3. Recruitment strategies 326
8.1.4. Recruitment incentives for investigators 328
8.1.5. "Self-recruitment" 329
8.1.6. Fairness in recruitment 330
8.1.7. Research subjects registers 332
8.2. Legal qualification of the relationship 333
8.2.1. Contract between the investigator and the research subject 333
8.2.2. Contract between the sponsor and the research subject? 334
8.3. The informed consent process 335
8.3.1. Brief historical overview 336
8.3.2. Information provided 338
8.3.2.1. Research versus treatment 342
8.3.2.2. Risk disclosure 344
8.3.2.3. Benefit disclosure 346
8.3.2.4. Information about available alternatives 348
8.3.2.5. Information about conflicts of interest 349
8.3.2.6. Information about costs 351
8.3.2.7. Information about future research 352
8.3.2.8. Information about subjects' rights 353
8.3.3. Consent as a process 353
8.3.3.1. The main steps of the process 353
8.3.3.2. Right to think it over 355
8.3.3.3. Written consent forms 356
8.3.3.3.1. Purpose 356
8.3.3.3.2. Legal status 358

8.3.3.3.3. Frequent problems with consent forms 359
8.3.3.4. Testing comprehension 360
8.3.3.5. Patient advocates and witnesses 361
8.3.3.6. The role of the primary care physician 362
8.3.3.7. Right to ask questions 363
8.3.3.8. "Group consent" 364
8.3.3.9. Rights to refuse enrollment 366
8.3.3.10. Right to withdraw from the trial 367
8.3.3.11. Renewal of consent 369
8.4. Enrollment of incapable subjects 370
8.4.1. Two main categories 371
8.4.1.1. Article 55 LPTh: research on incompetent subjects 372
8.4.1.2. Article 56: emergency research 375
8.4.1.3. Classification difficulties 375
8.4.2. Special medical and ethical considerations 377
8.4.2.1. Special considerations in pediatric trials 377
8.4.2.2. Special considerations in emergency trials 381
8.4.3. Subsidiarity 383
8.4.4. Substitute to consent 384
8.4.4.1. Proxy consent for incompetent subjects 384
8.4.4.2. Proxy consent in emergency research 388
8.4.4.3. Consultation in emergency research 389
8.4.4.4. Assent 391
8.4.4.5. Signs of refusal 393
8.4.4.6. Recovered or newly acquired capacity 395
8.4.4.7. Advance consent 395
8.4.5. Level of benefits and risks 397
8.4.5.1. Defining direct and indirect benefits 397
8.4.5.2. The rule and the exception 398
8.4.5.3. How must benefits be assessed? 399
8.4.5.4. Level of risks 400
8.4.6. Additional requirements 402
8.4.6.1. Additional requirements under Article 55 LPTh? 402
8.4.6.2. Additional requirements for emergency trials 403
8.4.6.3. Public feedback in the United States 404
8.4.6.4. Community information in U.S. emergency research 404
8.4.7. Other exceptions to informed consent under U.S. law 406
8.5. Enrollment of "vulnerable" subjects 407
8.5.1. Prisoners 408
8.5.2. Women 410
8.5.2.1. Pregnant women 412
8.5.2.2. Research on ex utero embryos 415
8.5.2.3. Pregnancy registries 416
8.5.3. Terminally-ill patients 417
8.5.4. Seniors 418
8.5.5. Indigent people 420
8.5.6. Foreigners 421
8.5.7. Minorities 422
8.5.8. Subjects in developing countries 423
8.6. Other rights of research subjects 425
8.6.1. Right to receive proper health care 425
8.6.2. Follow-up 426
8.6.2.1. Debriefing 426
8.6.2.2. Right to follow-up information and care 428

8.6.2.3. Right to continued supply of the experimental product? 429
8.6.3. Confidentiality and privacy 432
8.6.3.1. Under the LPTh and the OClin 433
8.6.3.1.1. The LPTh and the OClin 433
8.6.3.1.2. ICH Guideline 433
8.6.3.1.3. Information to be provided 434
8.6.3.2. Article 321 and 321bis CP 436
8.6.3.2.1. Applicability 436
8.6.3.2.2. Exception to Article 321bis 437
8.6.3.3. Under the law on data protection 438
8.6.3.3.1. Right to access the file 439
8.6.3.3.2. Right to restrict access 440
8.6.3.3.3. Right to correct mistakes 440
8.6.4. Payments to and by subjects 441
8.6.4.1. Payments to subjects 441
8.6.4.1.1. Admissibility 441
8.6.4.1.2. Review by ethics committees 442
8.6.4.1.3. Amounts offered 443
8.6.4.2. Payments by subjects 444
8.6.4.2.1. Payment for the experimental product 444
8.6.4.2.2. Payments for other health care costs 445
8.6.4.2.3. Insurance coverage 446
8.6.5. Liability and compensation for damages 448
8.6.5.1. General principles of liability under Swiss law 449
8.6.5.1.1. The investigator's liability 450
8.6.5.1.2. The sponsor's liability under general legal principles 451
8.6.5.1.3. Other liable parties 452
8.6.5.2. The OClin system of liability and insurance coverage 452
8.6.5.2.1. Scope of liability under the OClin 454
8.6.5.2.2. Sponsor's insurance coverage 456
8.6.5.3. Review by ethics committees 458
8.6.5.4. Situation in the United States 459
8.6.6. Waivers 460
8.6.6.1. Waivers of rights 460
8.6.6.2. Biological material 460
8.6.6.2.1. The *Moore* case 461
8.6.6.2.2. Biological material ownership under Swiss law 463
8.6.6.2.3. Gratuity in research 465
8.7. Obligations of research subjects? 466
8.7.1. Obligation to follow directions 466
8.7.2. Subjects' confidentiality obligations? 467

9. Supervision of clinical trials 468
9.1. Reporting obligations 468
9.1.1. Changes to the clinical trial 468
9.1.1.1. Objectives of notification 469
9.1.1.2. Essential changes 470
9.1.1.2.1. Scope of the changes 470
9.1.1.2.2. REC review 471
9.1.1.3. Minor changes 472
9.1.2. Reporting obligations for adverse events 473
9.1.2.1. Adverse events and adverse reactions 474
9.1.2.1.1. Causality 474

9.1.2.1.2. Foreseeability 476
9.1.2.1.3. Severity 477
9.1.2.1.4. Form of the report 477
9.1.2.2. New facts threatening subjects' safety 478
9.1.2.3. Death of a subject 479
9.1.2.4. Deadly harm 480
9.1.2.5. Serious and unexpected adverse reactions 480
9.1.2.6. The complete file of adverse events 482
9.1.2.7. Reporting obligations of the sponsor to the investigator 483
9.1.2.8. Database of adverse reactions 484
9.1.2.9 Events that do not require reporting 484
9.2. Oversight by the authorities 485
9.2.1. Oversight by RECs 485
9.2.1.1. Extent of the post-approval role of RECs under Swiss law 485
9.2.1.2. IRBs' continuing review in the United States 486
9.2.1.3. Specific powers of RECs 487
9.2.2. Supervision by the drug agency 489
9.2.2.1. Trial suspensions 489
9.2.2.1.1. New information 489
9.2.2.1.2. Objective reasons 489
9.2.2.2. Remedial plans 492
9.2.2.3. Inspections in Switzerland 493
9.2.2.4. Disqualification of data 494
9.2.2.5. Inspections in the United States 495
9.2.2.6. Criminal inquiries 496
9.2.2.7. Appeals 496
9.2.3. Supervision of a clinical trial by the investigator's institution 497
9.2.4. Supervision of a clinical trial by the canton 497
9.2.5. Supervision by foreign agencies 498
9.2.6. Supervision by other entities 498
9.3. Frequent shortcomings of clinical trials 499

10. End of clinical trials 502
10.1. Common reasons for ending a clinical trial 502
10.1.1. Normal termination 502
10.1.2. Early termination 502
10.2. Notifying authorities 505
10.3. Preparing the study report 505
10.4. Publication and publicity 507
10.4.1. Publication by the investigator or the sponsor 507
10.4.1.1. Publishing both good and bad 507
10.4.1.2. Publishing without delays 511
10.4.1.3. Providing supporting documents 511
10.4.1.4. Not publishing unethical studies 512
10.4.1.5. The Consort Guidelines 513
10.4.2. Information available from drug agencies 514
10.4.2.1. In Switzerland 514
10.4.2.2. In the United States 515
10.4.2.2.1. Information while the trial is underway 515
10.4.2.2.2. Information when the drug is under review 516
10.4.2.2.3. Information once development effort is abandoned 516
10.4.2.3. In the European Union 517
10.5. Record keeping 519

11. Conclusion 521

Glossary 523

List of court cases cited 527

Short Bibliography 531

Index 533

Table of contents 535

Liste des ouvrages

Collection Genevoise

Baddeley, Margareta *1994*
L'association sportive face au droit
Les limites de son autonomie

Baddeley, Margareta (éd.) *1999*
La forme sociale de l'organisation sportive
Questions de responsabilité
Actes de la Journée de Droit du sport de la Faculté de droit de l'Université de Genève 25 mars 1999

Bellanger, François (éd.) *2000*
L'Etat face aux dérives sectaires
Actes du colloque du 25 novembre 1999

Cattaneo, Daniele *1992*
Les mesures préventives et de réadaptation de l'assurance-chômage
Prévention du chômage et aide à la formation en droit suisse, droit international et droit européen

Chaix, François *1995*
Le contrat de sous-traitance en droit suisse
Limites du principe de la relativité des conventions

Chappuis, Christine *1991*
La restitution des profits illégitimes
Le rôle privilégié de la gestion d'affaires sans mandat en droit privé suisse

Chatton, Gregor T. *2005*
Die Verknüpfung von Handel und Arbeitsmenschenrechten innerhalb der WTO
Politisches Scheitern und rechtliche Perspektiven

Chavanne, Sylvie *1993*
Le retard dans l'exécution des travaux de construction
Selon le Code des obligations et la norme SIA 118

Ducrot, Michel *2005*
La procédure d'expulsion du locataire ou du fermier non agricole: quelques législations cantonales au regard du droit fédéral

Dunand, Jean-Philippe *2000*
Le transfert fiduciaire: «Donner pour reprendre»
Mancipio dare ut remancipetur
Analyse historique et comparatiste de la fiducie-gestion

Dupont, Anne-Sylvie *2005*
Le dommage écologique
Le rôle de la responsabilité civile en cas d'atteinte au milieu naturel

Favre-Bulle, Xavier *1998*
Les paiements transfrontières dans un espace financier européen

Foëx, Bénédict *1997*
Le contrat de gage mobilier

Gafner d'Aumeries, Sonja *1992*
Le principe de la double incrimination
En particulier dans les rapports d'entraide judiciaire internationale en matière pénale entre la Suisse et les Etats-Unis

Garrone, Pierre *1991*
L'élection populaire en Suisse
Etude des systèmes électoraux et de leur mise en œuvre sur le plan fédéral et dans les cantons

Gerber, Philippe *1997*
La nature cassatoire du recours de droit public
Mythe et réalité

de Gottrau, Nicolas *1999*
Le crédit documentaire et la fraude
La fraude du bénéficiaire, ses conséquences et les moyens de protection du donneur d'ordre

Grant, Philip *2000*
La protection de la vie familiale et de la vie privée en droit des étrangers

Guibentif, Pierre *1997*
La pratique du droit international et communautaire de la sécurité sociale
Etude de sociologie du droit de la coordination, à l'exemple du Portugal

Hack, Pierre *2003*
La philosophie de Kelsen
Epistémologie de la *Théorie pure du droit*

Henzelin, Marc *2000*
Le principe de l'universalité en droit pénal international
Droit et obligation pour les Etats de poursuivre et juger selon le principe de l'universalité

Hottelier, Michel *1990*
L'article 26 CEDH et l'épuisement des voies de recours en droit fédéral suisse

Hottelier, Michel *1995*
Le Bill of Rights et son application aux Etats américains
Etude de droit constitutionnel des Etats-Unis avec des éléments comparatifs de droit suisse

Jeanneret, Yvan *2002*
La violation des devoirs en cas d'accident
Analyse critique de l'article 92 LCR

Jeandin, Nicolas *1994*
Le chèque de voyage

Junod Moser, Dominique *2001*
Les conditions générales à la croisée du droit de la concurrence et du droit de la consommation
Etude de droit suisse et de droit européen

Junod, Valérie *2005*
Clinical drug trials
Studying the safety and efficacy of new pharmaceuticals

Kastanas, Elias *1993*
Les origines et le fondement du contrôle de la constitutionnalité des lois en Suisse et en Grèce

Lampert, Frank *2000*
Die Verlustverrechnung von juristischen Personen im Schweizer Steuerrecht unter besonderer Berücksichtigung des DBG und StHG

Languin, Noëlle/ Liniger, Miranda/Monti, Brigitte/ Roth, Robert/Sardi, Massimo/ Strasser, François Roger *1994*
La libération conditionnelle: risque ou chance?
La pratique en 1990 dans les cantons romands

Manaï, Dominique *1999*
Les droits du patient face à la médecine contemporaine

Mandofia Berney, Marina *1993*
Vérités de la filiation et procréation assistée
Etude des droits suisse et français

Marchand, Sylvain *1994*
Les limites de l'uniformisation matérielle du droit de la vente internationale
Mise en œuvre de la Convention des Nations Unies du 11 avril 1980 sur la vente internationale de marchandises dans le contexte juridique suisse

Martenet, Vincent *1999*
L'autonomie constitutionnelle des cantons

Morand, Charles-Albert (éd.) *1991*
Les instruments d'action de l'Etat

Morand, Charles-Albert (éd.) *1992*
Droit de l'environnement: mise en œuvre et coordination

Morand, Charles-Albert (éd.) *1992*
La légalité: un principe à géométrie variable

Morand, Charles-Albert (éd.) *1995*
Aménagement du territoire et protection de l'environnement: la simplification des procédures

Morand, Charles-Albert (éd.) *1996*
La pesée globale des intérêts
Droit de l'environnement et de l'aménagement du territoire

Moreno, Carlos *2002*
Legal Nature and Functions of the Multimodal Transport Document

Morin, Ariane *2002*
La responsabilité fondée sur la confiance
Etude critique des fondements d'une innovation controversée

Oberson, Xavier *1991*
Les taxes d'orientation
Nature juridique et constitutionnalité

Papaux van Delden, Marie-Laure *2002*
L'influence des droits de l'homme sur l'osmose des modèles familiaux

Peter, Henry *1990*
L'action révocatoire dans les groupes de sociétés

Pont Veuthey, Marie-Claire *1992*
Le pouvoir législatif dans le canton du Valais

Scartazzini, Gustavo *1991*
Les rapports de causalité dans le droit suisse de la sécurité sociale
Avec un aperçu des différentes théories de la causalité

Schneider, Jacques-André *1994*
Les régimes complémentaires de retraite en Europe: Libre circulation et participation
Etude de droit suisse et comparé

Stieger-Chopard, Arlette *1997*
L'exclusion du droit préférentiel de souscription dans le cadre du capital autorisé de la société anonyme
Etude de droit allemand et de droit suisse

Tanquerel, Thierry *1996*
Les voies de droit des organisations écologistes en Suisse et aux Etats-Unis

Tevini Du Pasquier, Silvia *1990*
Le crédit documentaire en droit suisse
Droits et obligations de la banque mandataire et assignée

Trigo Trindade, Rita *1996*
Le conseil d'administration de la société anonyme
Composition, organisation et responsabilité en cas de pluralité d'administrateurs

Voïnov Kohler, Juliette *2006*
Le mécanisme de contrôle du respect du Protocole de Kyoto sur les changements climatiques: entre diplomatie et droit

Vulliéty, Jean-Paul *1998*
Le transfert des risques dans la vente internationale
Comparaison entre le Code suisse des Obligations et la Convention de Vienne des Nations Unies du 11 avril 1980

Werly, Stéphane *2005*
La protection du secret rédactionnel

Wisard, Nicolas *1997*
Les renvois et leur exécution en droit des étrangers et en droit d'asile

Recueils de textes

(anciennement «Série rouge»)

Auer, Andreas/ *2001*
Delley, Jean-Daniel/Hottelier, Michel/Malinverni, Giorgio (éd.)
Aux confins du droit
Essais en l'honneur du Professeur Charles-Albert Morand

Dufour, Alfred/Rens, Ivo/ *1998*
Meyer-Pritzl, Rudolf/ Winiger, Bénédict (éd.)
Pacte, convention, contrat
Mélanges en l'honneur du Professeur Bruno Schmidlin

Foëx, Bénédict/Thévenoz, Luc (éd.) *2000*
Insolvence, désendettement et redressement
Etudes réunies en l'honneur de Louis Dallèves, Professeur à l'Université de Genève

Kellerhals, Jean/ *2002*
Manaï, Dominique/Roth, Robert (éd.)
Pour un droit pluriel
Etudes offertes au Professeur Jean-François Perrin

Knapp, Blaise/Oberson, Xavier (éd.) *1997*
Problèmes actuels de droit économique
Mélanges en l'honneur du Professeur Charles-André Junod

Reymond, Jacques-André *1998*
De l'autre côté du miroir
Etudes récentes

Schönle, Herbert *1995*
Droit des obligations et droit bancaire
Etudes

Ouvrages collectifs
Présence et actualité de la constitution dans l'ordre juridique
Mélanges offerts à la Société suisse des juristes pour son congrès 1991 à Genève. *1991*

Problèmes actuels de droit fiscal
Mélanges en l'honneur du Professeur Raoul Oberson *1995*

Démocratie directe

Arx, Nicolas von *2002*
Ähnlich, aber anders
Die Volksinitiative in Kalifornien und in der Schweiz

Auer, Andreas (éd.) *1996*
Les origines de la démocratie directe en Suisse / Die Ursprünge der schweizerischen direkten Demokratie

Auer, Andreas (éd.) *2001*
Sans délais et sans limites?
L'initiative populaire à la croisée des chemins
Ohne Fristen und Grenzen?
Die Volksinitiative am Scheideweg

Auer, Andreas/ Trechsel, Alexander H. *2001*
Voter par Internet
Le projet e-voting dans le canton de Genève dans une perspective socio-politique et juridique

Delley, Jean-Daniel (éd.) *1999*
Démocratie directe et politique étrangère en Suisse/ Direkte Demokratie und schweizerische Aussenpolitik

Schuler, Frank *2001*
Das Referendum in Graubünden
Entwicklung, Ausgestaltung, Perspektiven

*Trechsel, Alexander/*Serdült, Uwe *1999*
Kaleidoskop Volksrechte
Die Institutionen der direkten Demokratie in den schweizerischen Kantonen 1970–1996

Trechsel, Alexander *2000*
Feuerwerk Volksrechte
Die Volksabstimmungen in den schweizerischen Kantonen 1970–1996

Droit et Histoire

(anciennement «Droit et Histoire», «Les grands jurisconsultes» et «Grands textes»)

Dufour, Alfred/Roth, Robert/ Walter, François (éd.) *1994*
Le libéralisme genevois, du Code civil aux constitutions (1804–1842)

Dufour, Alfred *1998*
Hommage à Pellegrino Rossi (1787–1848)
Genevois et Suisse à vocation européenne

Dufour, Alfred (éd.) *2001*
Rossi, Pellegrino
Cours d'histoire suisse

Dufour, Alfred *2003*
L'histoire du droit entre philosophie et histoire des idées

Dunand, Jean-Philippe *2004*
Keller, Alexis (éd.)
Stein, Peter
Le droit romain et l'Europe
Essai d'interprétation historique, 2ème éd.

Manaï, Dominique *1990*
Eugen Huber
Jurisconsulte charismatique

Monnier, Victor (éd.) *2002*
Bonaparte et la Suisse
Travaux préparatoires de l'Acte de Médiation (1803)
(Préfacé par Alfred Kölz)

Monnier, Victor *2003*
Bonaparte, la Suisse et l'Europe
Colloque européen d'histoire constitutionnelle pour le bicentenaire de l'Acte de médiation (1803–2003)

Reiser, Christian M. *1998*
Autonomie et démocratie dans les communes genevoises

Schmidlin, Bruno/ *1991*
Dufour, Alfred (éd.)
Jacques Godefroy (1587–1652) et l'Humanisme juridique à Genève
Actes du colloque Jacques Godefroy

Winiger, Bénédict *1997*
La responsabilité aquilienne romaine
Damnum Iniuria Datum

Winiger, Bénédict *2002*
La responsabilité aquilienne en droit commun
Damnum Culpa Datum

Droit de la propriété

Hottelier, Michel/ *1999*
Foëx, Bénédict (éd.)
Les gages immobiliers
Constitution volontaire et réalisation forcée

Hottelier, Michel/ *2001*
Foëx, Bénédict (éd.)
L'aménagement du territoire
Planification et enjeux

Hottelier, Michel/ *2003*
Foëx, Bénédict (éd.)
La propriété par étages
Fondements théoriques et questions pratiques

Hottelier, Michel/ *2005*
Foëx, Bénédict (éd.)
Protection de l'environnement et immobilier
Principes normatifs et pratique jurisprudentielle

Droit administratif

Bellanger, François/ *2002*
Tanquerel, Thierry (éd.)
Les contrats de prestations

Tanquerel, Thierry /
Bellanger, François (éd.) *2002*
L'administration transparente

Droit de la responsabilité

Chappuis, Christine/ Winiger, Bénédict (éd.) *2005*
Le préjudice
Une notion en devenir
(Journée de la responsabilité civile 2004)

This book describes how clinical trials of pharmaceuticals are conducted and regulated.

Clinical trials on human volunteers are necessary to test the safety and efficacy of pharmaceuticals (drugs) before the latter can be authorized and released on the market. The entire clinical development of a pharmaceutical lasts several years and involves thousands of volunteers. From a financial perspective, this development is both expensive and risky.

Clinical trials are situated at the intersection of science, law and economics. This book weaves together these various aspects. It is divided in three main sections, the first focuses on historical and economic issues, the second on scientific concepts, the third on the key legal provisions. Laws taken into consideration include those of Switzerland, the United States and the European Union. Although the emphasis is on Switzerland and its recently (2002) enacted legislation, comparisons are systematically made with E.U. and U.S. regulations and case law. Whenever reasonable, these texts are examined critically.

This book is not exclusively aimed at the legal profession. Although it makes extensive reference to laws, regulations, guidelines, and case law, it is accessible to all persons curious to know more about clinical trials. Physicians participating as investigators in clinical trials and regulatory departments of pharmaceutical companies should find it particularly helpful.