Clinical fairness - Improving bedside rationing

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This publication URL: https://archive-ouverte.unige.ch//unige:5411
Publication DOI: 10.13097/archive-ouverte/unige:5411

Bioethics ISSN 0269-9702 (print); 1467-8519 (online)
Volume 22 Number 4 2008 pp 191–202
doi:10.1111/j.1467-8519.2008.00631.x

ARTICLES

VULNERABILITY IN RESEARCH AND HEALTH CARE; DESCRIBING THE ELEPHANT IN THE ROOM?

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Keywords
vulnerable populations, clinical ethics, research ethics, patient selection

ABSTRACT
Despite broad agreement that the vulnerable have a claim to special protection, defining vulnerable persons or populations has proved more difficult than we would like. This is a theoretical as well as a practical problem, as it hinders both convincing justifications for this claim and the practical application of required protections. In this paper, I review consent-based, harm-based, and comprehensive definitions of vulnerability in healthcare and research with human subjects. Although current definitions are subject to critique, their underlying assumptions may be complementary. I propose that we should define vulnerability in research and healthcare as an identifiably increased likelihood of incurring additional or greater wrong. In order to identify the vulnerable, as well as the type of protection that they need, this definition requires that we start from the sorts of wrongs likely to occur and from identifiable increments in the likelihood, or to the likely degree, that these wrongs will occur. It is limited but appropriately so, as it only applies to special protection, not to any protection to which we have a valid claim. Using this definition would clarify that the normative force of claims for special protection does not rest with vulnerability itself, but with pre-existing claims when these are more likely to be denied. Such a clarification could help those who carry responsibility for the protection of vulnerable populations, such as Institutional Review Boards, to define the sort of protection required in a more targeted and effective manner.

INTRODUCTION

Broadly, we agree that the vulnerable should be afforded some kind of special attention, or protection. Defining vulnerable persons or populations, however, has proved more difficult than we would like. This is both a theoretical and a practical problem. On a theoretical level, uncertainty as to what we mean by vulnerability is unsatisfactory because although we agree that this notion has a strong pull, we cannot account for this pull, justify it, or define its limits. On a practical level, we cannot know who should be afforded the protection due to vulnerable persons, or what form this protection should take. Contradictory definitions can lead to confusion for those who are supposed to protect the vulnerable, and wrong definitions may be acted upon.

Attempts to define vulnerability have differed in their scope.[1] At the broad end, we find a European 'principle of vulnerability', which should be considered as a universal

[1] M.C. Ruof. Vulnerability, vulnerable populations, and policy. *Kennedy Inst Ethics J* 2004; 14: 411–425.

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expression of the human condition[2] and requires us to respect 'the right balance between this logic of the struggle for immortality and the finitude of the earthly presence of human suffering'[3] This and other such broad definitions[4] encompass humanity in its entirety. At the restrictive end of the spectrum, 'vulnerability' in research on human subjects is often applied to individuals who are unable to give informed consent or who are more likely to be exploited.[5] These restrictive definitions have been critiqued, even in this context, as both 'too broad and too narrow' by authors who proposed to replace special scrutiny for vulnerable populations with ongoing protection of individuals according to existing regulations, and focused attention on 'characteristics of the research protocol and environment that present ethical challenges'.[6]

The definition of vulnerability for the purposes of healthcare and research with human participants is thus an unanswered question. That such an important question is open should be regretted. Giving up the concept could represent abandonment of a needed moral safeguard.[7] A definition that includes humanity itself does not provide such an account, as it cannot provide reason for *special* protection. A restrictive definition will thus be required. It cannot, however, be restrictive to the point of forcing us either to exclude persons that should validly be considered vulnerable, or to pretend they fulfil some other criteria for vulnerability when in fact they do not. For example, if we consider that vulnerability in research ethics is centred on the inability to give voluntary informed consent, we may have a convincing case for excluding terminally ill patients from vulnerable groups. If we remained convinced that they are nevertheless vulnerable, our argument could only be that they are indeed incapable of giving valid informed consent. As it has been pointed out, this is unsatisfactory.[8]

Fortunately, existing definitions seem mistaken only in part and may be mutually complementary. Descriptions sometimes resemble those of the proverbial elephant described by people with only partial views. In this paper, I will show how existing definitions of vulnerability in medical research and clinical care are insufficient, and attempt a definition of vulnerability as a claim to special protection that is both comprehensive and usable. I will also address some possible concerns with this proposal.

WHAT IS VULNERABILITY IN RESEARCH AND HEALTH CARE?

Restrictive definitions of vulnerability in research and health care can be roughly described as consent-based, harm-based, or comprehensive.

Consent-based definitions include that proposed by the ICH tripartite guidelines,[9] or by CIOMS, which defines the vulnerable as 'Those who are relatively (or absolutely) incapable of protecting their own interests'.[10] The Belmont report defines the vulnerable explicitly on grounds of 'their dependent status and their frequently compromised capacity for free consent'.[11] Perhaps in an attempt to complement their definitions and give a more comprehensive picture, guidelines for ethical conduct of human subjects research have also provided lists of vulnerable groups (Table 1). Although they do provide useful examples, these lists can be long, and lack an organizing principle. It is not clear that they are based on the definitions offered by the same guidelines, or even on a solid family resemblance between the listed groups.

More basically, however, it is not clear that the sort of thing we mean by vulnerability should refer strictly to being at risk of giving faulty consent. This understanding of vulnerability is appealing in situations where we do, indeed, count on people's choices to protect them. If we believe that informed consent is the principal protection of human subjects of research, and crucial in clinical care

[2] E. Levinas. 1961. *Totalité et infini*. Den Haag: Phenomenologica.

[3] J.D. Rendtorff. Basic ethical principles in European bioethics and biolaw: autonomy, dignity, integrity and vulnerability – towards a foundation of bioethics and biolaw. *Med Health Care Philos* 2002; 5: 235–244.

[4] D. Callahan. 2000. The Vulnerability of the Human Condition. In *Bioethics and Biolaw, Volume II: Four Ethical Principles.* P. Kemp, et al., eds. Copenhagen: Rhodos International Science and Art Publishers; and Centre for Ethics and Law in Nature and Society. A. MacIntyre. 1999. *Dependent Rational Animals*. Chicago and La Salle, Illinois: Open Court. M.H. Kottow. Vulnerability: what kind of principle is it? *Med Health Care Philos* 2004; 7: 281–287.

[5] J.P. Lott. Module three: vulnerable/special participant populations. *Developing World Bioeth* 2005; 5: 30–54.

[6] C. Levine, et al. The limitations of 'vulnerability' as a protection for human research participants. *Am J Bioeth* 2004; 4: 44–49.

[7] J.P. DeMarco. Vulnerability: a needed moral safeguard. *Am J Bioeth* 2004; 4: 82–84; discussion W32.

[8] M. Agrawal. Voluntariness in clinical research at the end of life. *J Pain Symptom Manage* 2003; 25: S25–S32.

[9] ICH Steering Committee. 1996. ICH Harmonized Tripartite Guideline. In *Guideline for Good Clinical Practice E6.*

[10] CIOMS. 2002. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva, Switzerland: CIOMS.

[11] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington D.C.: Departement of Health, Education, and Welfare.

Table 1. Examples of vulnerability in international guidelines for research ethics

Source	*Cited examples of vulnerability in human subjects research*
Belmont report	• Racial minorities • The economically disadvantaged • The very sick • The institutionalized
45 CFR 46	• Children • Prisonners • Pregnant women and foetuses
Declaration of Helsinki	• Incompetent persons • Persons susceptible to coercion • Persons who will not derive direct benefits from participation • Persons for whom research is mixed with clinical care
CIOMS	• Those with limited capacity or freedom to consent or to decline to consent . . . [including] children, and persons who because of mental or behavioural disorders are incapable of giving informed consent, • Junior or subordinate members of a hierarchical group . . . [such as] medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police, • Elderly persons, • Residents of nursing homes, • People receiving welfare benefits or social assistance and other poor people, • The unemployed, • Patients in emergency rooms, • Some ethnic and racial minority groups, • Homeless persons, • Nomads, • Refugees or displaced persons • Prisoners • Patients with incurable disease • Individuals who are politically powerless • Members of communities unfamiliar with modern medical concepts
ICH tripartite guidelines	• Members of a group with a hierarchical structure such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees in the pharmaceutical industry, members of the armed forces, and persons kept in detention • Patients with incurable diseases • Persons in nursing homes • Unemployed or impoverished persons • Patients in emergency situations, • Ethnic minority groups, • Homeless persons • Nomads, • Refugees, • Minors, • Those incapable of giving consent

as well, then anchoring vulnerability to consent is tempting. We let people make their own choices and count on this to protect them. So we should only afford better protection to those less able to protect themselves in this way. Human subjects research, however, present us with examples of human activities where consent is a necessary but insufficient condition to ethical practice.[12] The same is true to a degree in health care as well. As a patient, I will often lack crucial information and will thus need health care providers to have my interest at heart more than in other types of choices. In some clinical situations, decisions have the structure of a 'prisoners' dilemma': what we consider to be our best option can only be chosen if we are sufficiently confident that others will choose the same option. If everyone chooses generic substitution for a benign ailment, the money available will benefit everyone including those in situations of greater need. If, however, I am the only one to sacrifice the small degree of comfort involved by, for example, taking a pill less comfortable to swallow, no significant benefit will accrue and I will lose out.[13] In both of these activities, we

[12] E.J. Emanuel, et al. What makes clinical research ethical? *Jama* 2000; 283: 2701–2711.

[13] S.A. Hurst, et al. Conserving scarce resources: willingness of health insurance enrollees to choose cheaper options. *J Law Med Ethics* 2004; 32: 496–499.

do not, in fact, expect consent to do all the protective work. Whether this is because we believe that consent is often flawed to the degree of requiring other safeguards,[14] or because we believe it to be intrinsically insufficient, does not change the impact this has on vulnerability. If additional safeguards other than consent are required for everyone, and if vulnerability can exist in relation to these other safeguards, then consent-based accounts of vulnerability are insufficient.

A variant of this view expands consent-based vulnerability to include limits on the ability to avoid exploitation.[15] But this sort of definition turns out to be either too broad or too narrow, depending on what we mean by exploitation. If we include harm, disrespect, and injustice[16] within the definition of exploitation, we are left with a poor understanding of the sort of wrong exploitation is. A stricter definition such as an 'unfair distribution of burdens and benefits from an interaction',[17] or treating someone 'in a way to which he could not possibly consent'.[18] is more useful but means that the consent-based concept of vulnerability is not expanded very much by the inclusion of an added risk of exploitation. Moreover, if exploitation is a consent-based kind of wrong, then the problems outlined above will also apply here. For example, if there is indeed a right to access to healthcare, then being denied such access would constitute a wrong. It would, however, certainly not amount to exploitation. In research, not giving research subjects the result of the project they participated in can signify a lack of respect but it would be a stretch to call it exploitation. Whether we count on Institutional Review Boards (IRB), researchers,[19] or clinicians to provide additional safeguards for non consent-based wrongs, we do recognize that such wrongs exist.

Alternatives to consent-based views of vulnerability include harm-based definitions. One such view accepts a broad definition of vulnerability as universal human fragility, and goes on to define the sort of concept useful to health care and research as *susceptibility* to compound additional harms.[20] This susceptibility is present when we become biologically weak or diseased, and this is what justifies additional protection. This, however, only recognizes added likelihood of *additional* harm. To give a counter-example, women and children may frequently be at greater risk of incurring harms but – according to this view – this may not count unless they have already incurred a first harm. Furthermore, it is not clear that people who are at higher risk of being disrespected or of giving invalid consent would be included under this definition. What these persons risk is being wronged, rather than being harmed. Thus, though it captures important aspects of the intuitions that drive our notion of who is vulnerable and resembles safeguards sometimes intended specifically to exclude persons at increased risk of harm in research,[21] this definition is too narrow. In a way it is the mirror image of consent-based views of vulnerability and shares the same fault: insufficient comprehensiveness.

Faced with the risk that a definition of vulnerability may be too narrow, some have proposed combined or otherwise more comprehensive definitions.[22] Vulnerability may, for example, be considered to include 'groups of people (i) whose capacity to safeguard their own interests as research participants, through the process of informed consent or refusal, is compromised; or (ii) who are more likely to take on the burdens of participation in research, in virtue of some feature they share, *and* this is not compensated for by other suitably related benefits (not money); or, (iii) who are less likely to gain the benefits of participation in research, in virtue of some feature they share, and this is not compensated for by other benefits to them (or to others similarly situated)'.[23] This bases vulnerability on both consent and fairness in subject selection. This view is appealing because it covers both equity and freedom. Inasmuch as there are wrongs other than transgressing the requirement for consent or fairness, it will however be insufficient as well. If we are more likely to have our confidential information disclosed, for example, this definition will not consider us to be vulnerable.

A promising broad definition is offered by Agrawal, who views vulnerability as 'increased potential that one's

[14] S.J. Edwards. Restricted treatments, inducements, and research participation. *Bioethics* 2006; 20: 77–91.

[15] K. Kipnis. 2001. Vulnerability in Research Subjects: A Bioethical Taxonomy. In *Ethical and policy issues in research involving human research participants.* National Bioethics Adivosiry Commission, ed. Bethesda, MD.

[16] D.B. Resnik. Exploitation in biomedical research. *Theor Med Bioeth* 2003; 24: 233–259.

[17] E.J. Emanuel, et al. Undue inducement in clinical research in developing countries: is it a worry? *Lancet* 2005; 366: 336–340.

[18] C. Korsgaard. The Reasons We Can Share. *Social philosophy and policy* 1993; 10: 24–51.

[19] G.B. Tangwa. Moral agency, moral worth and the question of double standards in medical research in developing countries. *Developing World Bioeth* 2001; 1: 156–162.

[20] Kottow 2004 *op. cit*. note 4, M.H. Kottow. The vulnerable and the susceptible. *Bioethics* 2003; 17: 460–471.

[21] D. Wendler. When should 'riskier' subjects be excluded from research participation? *Kennedy Inst Ethics J* 1998; 8: 307–327.

[22] P.J. Nickel. Vulnerable populations in research: the case of the seriously ill. *Theor Med Bioeth* 2006; 27: 245–264. R. Macklin. Bioethics, vulnerability, and protection. *Bioethics* 2003; 17: 472–486.

[23] Nickel *op. cit.* note 22.

interests cannot be protected'.[24] As he correctly notes, labelling the inclusion of vulnerable subjects as automatically unethical is incorrect. It can put these people at a disadvantage, for example if their systematic exclusion from research leads to missed opportunities to gain knowledge useful to them.[25] This definition recognizes that we have all sorts of interests that may require protection, and that we may be at risk as regards each of them. Ethical research with vulnerable populations requires more of investigators and IRBs. In some cases, this greater effort will be successful, and the interests of vulnerable persons will be protected in the end. Sometimes, however, this will not be feasible without, for example, excluding them from a protocol. In some instances, however, the reason why our interests cannot be protected is that some of them are limited by human finitude. In such cases, our interests will be truly impossible to protect in a way that places them clearly outside the responsibility of clinicians and researchers. Someone who is at a high risk of dying of a terminal disease is certainly at 'increased potential' that her 'interests cannot be protected'. But this could not ground any claim that IRBs give greater than usual protection in this case to the specific interest of living a longer life. Moreover, in some instances our vulnerability may lie in a greater likelihood of requiring protection in the first place. This will happen whenever our interests are discounted, however easy they may be to protect if the concern is present. Garcia proposes to base the requirement for special scrutiny on the concept of equal protection, which requires justifications for unequal treatment.[26] Affording equal ethical protection, however, is not limited to avoiding unequal treatment per se and can include using different treatments to compensate higher risks.

Mixed definitions have been offered for vulnerability in clinical care also, and tend to focus on the risk of neglect and lack of access to care.[27] The Agency for Healthcare Research and Quality defines vulnerable populations as those less able to safeguard their own needs and interests adequately, a view based on consent or self-determination, but also as populations who may incur different health outcomes traceable to unwarranted disparities in their care, or stemming from special needs for care or barriers to care (Table 2).[28]

The prominence of barriers to care, or the risk of neglect in this wording, reflects the visibility of lack of access as a potential wrong incurred in clinical care. Lack of access to health care, or even to health, is however not the only source of vulnerability in clinical care. Individuals can be wronged without incurring loss of their opportunity to achieve maximum possible health, if they are deprived of the means for self-determination. People at greater risk of having confidential information disclosed are also left out of these definitions.

The difficulties involved in navigating between insufficient comprehensiveness and excessive broadness, if all are to be considered vulnerable,[29] have fuelled a critique of using the concept of vulnerability in research at all.[30] The authors of this critique argue that the concept of vulnerability has lost force through the inclusion of too many groups identified as vulnerable. This may be true, but only insofar as individuals who belong to such groups are systematically and sometimes inaccurately labelled as vulnerable. This is an avoidable practice.[31] In addition, classifying groups as vulnerable can be stereotyping: for example classifying the poor or pregnant women, as vulnerable is insulting if we mean that they are not capable of decision-making. If we recognize that their vulnerability is due to greater likelihood of being offered a bad risk-benefit ratio or of being disrespected, then this classification constitutes a justified attack on the perpetrators rather than a slur on the victims. The authors also note that vulnerability is often understood in relation to enrolment in research, whereas certain individuals require ongoing protection. Although it does not tell us what vulnerability is, this is an important point.

VULNERABILITY AS A CLAIM TO SPECIAL PROTECTION

I propose that vulnerability as a claim to special protection should be understood as *an identifiably increased likelihood of incurring additional or greater wrong*.

[24] Agrawal *op. cit.* note 8.

[25] V. Merton. The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *Am J Law Med* 1993; 19: 369–451.

[26] S.A. Garcia. Equal protection clause enforcement as a model for protecting vulnerable human research subjects. *Am J Bioeth* 2004; 4: 81–82; discussion W32.

[27] Agency for Healthcare Research and Quality. 1999. Request for applications on measures of quality of care for vulnerable populations. L.A. Aday. 2001. *At Risk in Amedica; The Health and health Care Needs of Vulnerable Populations in the United States*. San Fransisco, California: Josey-Bass. M. Danis & D.L. Patrick. 2002. Health Policy, vulnerability, and vulnerable populations. In *Ethical Dimensions of Health Policy*. M. Danis, et al., eds. Oxford, New York: Oxford University Press.

[28] Agency for Healthcare Research and Quality *op. cit.* note 27.

[29] F.J. Leavitt. Is any medical research population not vulnerable? *Camb Q Healthc Ethics* 2006; 15: 81–88.

[30] Levine *op. cit.* note 6 p. 4.

[31] DeMarco *op. cit.* note 7.

Table 2. Examples of vulnerability in clinical care

Source	*Cited examples of vulnerability in health care*
Agency for Healthcare Research and Quality	• Populations less able than others to safeguard their own needs and interests adequately. • Populations who may incur different health outcomes traceable to unwarranted disparities in their care or stemming from special needs for care of barriers to care.
Aday	• Social status ○ Age: infants, children, adolescents, elderly ○ Gender: females ○ Race and ethnicity: African Americans, Hispanics, native Americans, Asian Americans • Social capital ○ Family structure: living alone, female head ○ Marital status: single, separated, divorced, widowed ○ Voluntary organizations: non-member ○ Social networks: weak • Human capital ○ School: less than high school ○ Jobs: unemployed, blue collar ○ Income: poor, low income ○ Housing: substandard
Danis and Patrick	• Those at risk at any particular point in time for unequal opportunity to achieve maximum possible health and quality of life because of differences in intrinsic and extrinsic resources that are associated with good health. ○ Financial circumstances ○ Place of residence ○ Cultural background and ethnicity ○ Age ○ Health conditions (such as terminal illness or mental illness, impairments, including psychological and cognitive ones, and functional status or disability, such as inability to communicate effectively)

Vulnerability in this sense is not restricted to the likelihood of faulty consent or even to the limited capacity to defend one's own interests. If we understood the worst, or perhaps the only, wrong to be lack of respect for self-determination, and that no harm is done to the willing, then this definition would be identical to previous ones. The examples of research and clinical care, however, show us situations where we do not expect even ordinary patients or subjects to protect all their interests themselves. When even ordinary, non-vulnerable people are not expected to protect their own interest, then additional elements become visible. Some interests are more likely than others to be placed at risk. They may be harder to achieve and thus to defend. This affects some individuals even when they would be completely capable of defending their own interests in other settings. Even for those able to consent, an increased likelihood of incurring additional or greater wrong means that we expect self-determination to do more work in their case. If a claim exists that we should afford the same protection to all regarding a claim we consider valid, then additional requirements other than complementing faulty consent will be required.

This definition is restricted to wrongs, including wrongful harms and the wrongs that we incur when something to which we have a valid claim is denied us. It cannot extend to any additional harm, or any interest more likely to be difficult to protect, because it is not the case that we have a duty to protect all interests from all harms. I could, for example, decide to enrol in research as a sales representative to be introduced to potential future customers. If this did not function as expected, one of my interests would certainly have been harmed, but we would hardly expect an IRB to protect me from this sort of frustration.

This definition requires vulnerability as a claim to special protection, to be defined starting from the sorts of wrongs likely to occur. We thus agree with Levine and colleagues,[32] who propose that attention must be focused on the characteristics of the research protocol and environment, rather than restricted to characteristics of potential subjects, and that it should regard the ongoing conduct of research as well as enrolment. In the definition proposed here, there is no single specific transgression linked with vulnerability. The substantial contents both of vulnerability itself and of the transgressions associated with it will change with the nature of the wrongs involved. In one sense or another, many individuals will be vulnerable, but this will not mean that they are vulnerable in identical ways. This could partly explain the

[32] Levine *op. cit.* note 6.

difficulties in defining vulnerability for the purposes of research with human subjects and clinical care. We seem to be caught between only two alternatives: defining everyone as vulnerable or sticking to notions based on a very limited number of wrongs. These in turn either fail to recognize some valid claims to special protection, or require conceptual contortions such as that which consists in describing someone as vulnerable on a consent-based view when their capacity to consent should really not be questioned. This problem is solved if we define vulnerability as proposed here.

This definition is limited in the sense that it does not identify all forms of vulnerability, such as those associated in general with being human, fallible, mortal, and capable of suffering. It is, however, relevant in an important way, as it is circumscribes the forms of vulnerability requiring additional attention as compared with the care we usually take to avoid perpetrating wrongs. It is also limited as a definition in that it does not provide a clear cut-off line between the vulnerable and the non-vulnerable. Inasmuch as some individuals and groups will indeed be identifiably more likely to suffer wrongs, however, it provides a framework both for recognizing these groups systematically and for designing ways to address their specific kinds of vulnerability.

If an identifiably increased likelihood of incurring additional or greater wrong exists, including any wrongful harm, then there is an increased risk of moral transgression. Vulnerability in this sense is thus a two-way street and affects those who practise health care and research as well. This will be the case any time that an identifiable agent acts in way that predictably affects vulnerable persons.

Applying this definition of vulnerability could take the form of a four step approach:

1) Is there an identifiable potential wrong?
2) If yes, are some people identifiably more likely than others to incur this wrong, or likely to incur it to a greater degree?
3) Who shares in the duty to minimize, or avoid, this wrong, and does it include us in any way?
4) What should we do to minimize this increased likelihood or degree, or to compensate for it in ethically justifiable ways?

The mere definition of vulnerability does not identify those with a share in the responsibility for protecting the vulnerable. Applying this definition thus requires the addition of step 3 (Figure 1). Depending on the sort of wrong identified, those responsible for preventing it will vary.

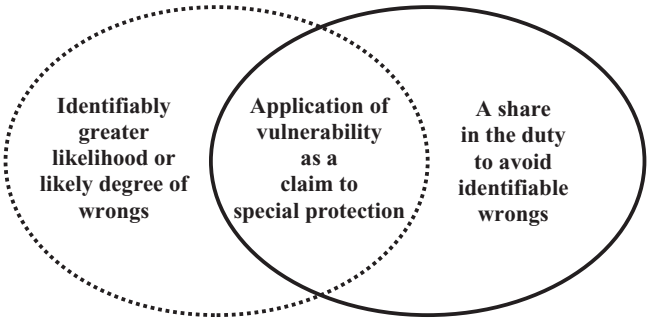

Figure 1. Two ingredients to apply vulnerability as a claim to special protection.

APPLICATION TO RESEARCH ETHICS

If we accept the proposed definition, it is not surprising that vulnerability proves hard to define: it is as multiple as potential wrongs and as sources of greater likelihood of suffering them. It also involves some judgment, because it is a matter of degree. This, however, does not void the concept of its usefulness. We may disagree in a grey zone; but differences in the likelihood of suffering wrong will often be sufficiently marked to be uncontroversial.

Using the concept of vulnerability in research ethics has proved difficult for the same sort of reason. General principles of research ethics exist to protect subjects from wrongs, including wrongful harms. Thus, the special scrutiny required by IRBs to deal with vulnerability is not a difference in kind but a difference in degree of care for ethical criteria that are, indeed, the same. Again, the concept of vulnerability is not rendered useless by this, as it serves to identify groups of individuals that do, in fact, need and merit this special care in the application of criteria for ethical research.

One application to research ethics, then, is to aid IRBs in applying special scrutiny to protect vulnerable subjects but in a targeted way. The first of our four questions would thus be what IRBs examine as part of their regular work:

1) Are any potential research subjects at risk of being wronged in any way by this research project?

For each potential wrong, the other three questions would then become:

2) Are some potential subjects identifiably more likely than other persons to incur this wrong, or likely to incur it to a greater degree?
3) Is our IRB among those who share in the duty to minimize, or avoid, this wrong?

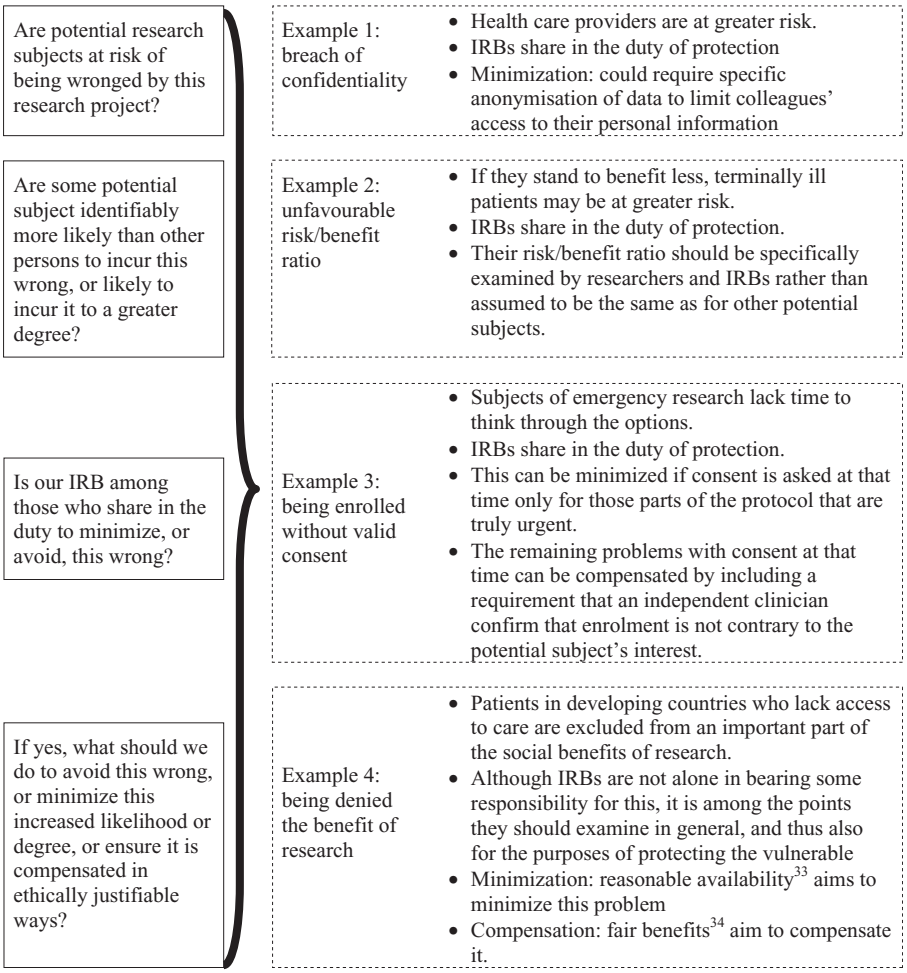

Figure 2. Examples of application of this approach by IRBs.

4) If yes, what should we do to avoid this wrong, or minimize this increased likelihood or degree, or ensure it is compensated in ethically justifiable ways?

Based on recognized requirements for ethical research with human subjects,[35] examples of vulnerability are shown in Table 3. Actions required for special protection would need to be tailored to the sort of wrong to be avoided, and to the source of the specific vulnerability (Figure 2).

As outlined above, the relevant question for an IRB at the third step will be 'does this include us?' rather than 'are we solely responsible for this?'. This is an important point, as understanding protection of the vulnerable in research in this way would expand the responsibilities of IRBs. Rather than checking a list of predefined vulnerable groups, they would have to identify who was vulnerable based on the wrongs likely to occur in the case of each protocol they reviewed. This is consistent with their role. Before being regulatory institutions, IRBs primarily have a moral function to protect human subjects of research. Moreover, this expansion of their role would remain limited to wrongs actually linked to research. They would not become responsible for protecting the vulnerable from any kind of wrong whatsoever. Rather than going through a list of pre-identified vulnerable populations, then, IRBs would go

[33] World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Edinburgh; 2000. http://www.wma.net/e/policy/b3.htm (accessed July 17th 2007).

[34] Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Ethics. Fair benefits for research in developing countries. Science 2002; 298(5601): 2133–2134.

[35] Emanuel *op. cit.* note 12.

Table 3. Using this definition in research with human subjects

Requirements	*Examples of vulnerability*
Social or scientific value	• Lack of access to either benefit or knowledge derived from research
Scientific validity	• Rare disease, leading to difficulties in reaching statistical power to demonstrate therapeutic effectiveness
Fair subjects selection	• All persons likely to be victims of discrimination
Favorable risk-benefit ratio	• Potentially higher risks: unstable patients, emergency research, foetuses, pregnant women • Potentially lower benefits: subjects in phase I studies, terminally ill patients • Subjects whose risk-benefit ratio might sometimes be the object of lesser concern to those responsible for protection: terminally ill patients, disenfranchised persons, poor subjects in developing countries, subjects without access to health care outside of research.
Independent review	• All persons likely to be victims of discrimination, if those responsible for review share discriminatory views.
Informed consent	• Difficulties in receiving or understanding the relevant information: not knowing the language used, or how to read • Lack of decision-making capacity: some children, some patients with mental disorders, comatose patients. • Lack of freedom to make a voluntary choice ○ Through limited freedom: prisoners ○ Through social weakness: minorities, refugees, sometimes women ○ Through hierarchical weakness: lab employees, students
Respect for potential and enrolled subjects	• Health care providers, researchers and students close to the study team who are at increased risk of faulty confidentiality • Groups and communities at risk of stigmatisation in the interpretation of study results

through a list of potential research-related wrongs (Table 3).

Another application to research ethics could be in thinking through double standards. Critiques have put forward that lower ethical standards are used in developing countries.[36] While this is often true, this accusation is sometimes leveled at protocols that actually use all the same standards used in rich countries. The Tenofovir trial was one such example.[37] A possible interpretation using the definition of vulnerability proposed here could run like this. If subjects in developing countries are, on the whole, less likely than subjects in Western countries to see their claims met, additional efforts may be required for them. Not just equivalent efforts, but actually greater ones. This also helps to distinguish problematic double standards based on research-related wrongs from those that may be problematic based on other sorts of wrongs. Not providing additional protection against the risk that dangers to the poor could be discounted is clearly problematic and within the remit of IRBs. Not providing adequate roads may very well be problematic, but lack of roads is clearly not a research-related risk and thus outside the remit of IRBs. Not providing access to treatment will be harder to attribute precisely because it is not quite clear to what extent it can be considered a research-related wrong. Once we know this, however, applying the definition of vulnerability presented here does distinguish double standards that IRBs should concern themselves with from those outside their scope.

APPLICATION TO THE ETHICS OF CLINICAL CARE

Basic requirements for the ethical conduct of research with human subjects are relatively uncontroversial. The nature of valid claims in clinical care is debated to a greater degree. Application of the concept of vulnerability proposed here to this field can be expected to reflect this. Importantly, however, this does not invalidate the use of this notion. We should expect greater controversy as to what constitutes a valid claim; but once we admit a claim as valid, we become able to identify vulnerable populations as those more likely to be denied fulfillment of this claim, and to identify measures likely to prevent this.

Examples of requirements proposed for ethical clinical care are shown in Table 4. They include having access to healthcare, adequate financial coverage, not being harmed, self-determination, confidentiality, getting fair consideration in resource allocation, and having a voice as a stakeholder in healthcare. Access can be further divided into the elements proposed by Penchansky and Thomas: *availability*, or the degree to which the provider has the necessary resources to meet the patient's needs,

[36] P. Farmer & N.G. Campos. New malaise: bioethics and human rights in the global era. *J Law Med Ethics* 2004; 32: 243–251, 190–241.
[37] K. Page-Shafer, et al. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *Lancet* 2005; 366: 1499–1503.

Table 4. Using this definition in clinical care

Examples of requirements		*Examples of vulnerability*
Having access to health care	1. Availability	• Patients with rare diseases, need for interventions requiring expensive technology
	2. Accessibility	• Distance from health service, responsibility for dependent relatives
	3. Accommodation	• Long or inflexible working hours
	4. Affordability	• Poverty, uninsurance, underinsurance, distance (high transportation costs)
	5. Acceptability	• Populations with reason to distrust the health care system
Adequate financial coverage		• Greater likelihood of being denied insurance, such as pre-existing conditions, or risk factors.
Not being harmed		• Patients more likely to be treated in unusual ways, such as health care providers and their families, or patients from whom litigation is feared.
Self-determination /Autonomy		• Difficulties in receiving or understanding the relevant information: not knowing the language used, or how to read • Difficulties in requesting a role in decision-making. • Lack of decision-making capacity: some children, some patients with mental disorders, comatose patients. • Lack of freedom to make a voluntary choice ○ Through limited freedom: prisoners ○ Through social weakness: minorities, refugees, sometimes women ○ Through hierarchical weakness: hospital employees, students
Confidentiality		• Public figures, health care providers, families of health care providers
Getting fair consideration in resource allocation.		• Patients at risk of seeing their interest discounted, such as: ○ terminally ill patients, ○ elderly patients, ○ cognitively impaired or handicapped persons, ○ disenfranchised or socially marginalized persons.
Having a voice as a stakeholder in health care.		• Disenfranchised or socially marginalized persons.
Avoiding illness?		• Persons with less access to health literacy • Persons at the lower end of the socio-economic spectrum.

accessibility, or the ease with which the patient can physically reach the location of health services, *accommodation*, or the degree to which the health service is organized in ways that meet the constraints and preferences of patients, *affordability*, or how the provider's charges fit with the patients' ability and willingness to pay, and *acceptability*, or the extent to which patients are comfortable with the characteristics of the health services and vice versa.[38] Examples of vulnerability linked to these requirements are shown in Table 4.

Whenever resources are allocated, vulnerability also applies to those more likely to see their claims transgressed or discounted in allocation processes. Importantly, this may not mean that anyone less likely to have resources allocated to them is vulnerable in this way: it would depend on their risk of having their claims discounted, rather than on the final result. For example, if decisions about admission to intensive care for people with short life-expectancies were likely to be based on an evaluation that their needs should count for less, then this would constitute vulnerability. If the same decisions were systematically made with the same sort of considerations afforded anyone, such as likelihood of benefit and quality of life, then they might still be allocated intensive care less frequently, but their claim would not have been discounted.

Clearly, some populations will only be considered vulnerable in the sense proposed here if they do, indeed, have a valid claim to whatever it is they are more likely to be denied. On some counts, this may be more controversial than in others. For example, some populations are more at risk of becoming ill in the first place.[39] If we have a right limited to access to health care, then this would constitute a part of normal human fragility, not vulnerability as a claim to special protection. If, however, the claim to provide health care is based on a requirement to equalize health itself as a precondition of fair equality of opportunity,[40] then a greater likelihood of becoming ill would constitute vulnerability, a claim to special protection as outlined here.

[38] R. Penchansky & J.W. Thomas. The concept of access: definition and relationship to consumer satisfaction. *Med Care* 1981; 19: 127–140. C.G. McLaughlin & L. Wyszewianski. Access to care: remembering old lessons. *Health Serv Res* 2002; 37: 1441–1443.

[39] M. Marmot. 2004. The Status Syndrome; How Social Standing Affects Our Health and Longevity. London: Bloomsbury Publishings.

[40] N. Daniels. 1985. *Just Health Care*: Cambridge University Press.

SOME POSSIBLE CONCERNS

Importantly, this definition accepts that the claim to protection is based not on vulnerability itself, but on some other valid source. Attempts to ground obligations directly in vulnerability have been made both in continental philosophy[41] and in bioethics.[42] Concern could exist that if we do not have a requirement to respect a principle of vulnerability, then the vulnerable could lack protection. This concern, however, presupposes an existing claim to protect the vulnerable. Clearly, then, such a claim cannot originate in the principle itself, as it seems to ground the very need for it. The present proposal accepts that the vulnerable have a claim to protection; but this claim is grounded in other claims that we recognize anyway. If a claim for anything exists, then the higher likelihood that this claim will be transgressed generates a requirement for greater attention *that this claim be fulfilled* whatever this, pre-existing, claim may be. The obligation to avoid wronging is not derived directly from a principle of vulnerability but from another source; specifically, from a valid claim that some wrong should be avoided, including the wrong we incur when a good to which we have a valid claim is denied us. If vulnerability increases the likelihood of being wronged, it also increases the attention required to avoid any wrong that we should avoid for other reasons. This both clarifies and strengthens the claim for protection: we do not need to recognize a specific requirement based on vulnerability but only a situation where fulfilling existing requirements requires additional care.

Some may say that defining vulnerability in this way makes the concept superfluous, since it means nothing further than a claim to fulfil duties that we have anyway. This does not, however, void the notion of its use. An increased risk is morally relevant. It can change the actions required to provide protection in degree (for example providing more security for confidentiality) or in nature (as when potential research subjects should be excluded from a protocol). Vulnerability thus truly means something different from the mere existence of a pre-existing claim.

We may also wonder whether the strength of the pre-existing claim might not be affected by the added difficulty. There are, after all, instances where duties exist in part because the burden to the agent is not too great, as in the rule of rescue.[43] As this suggests, however, this would depend on the sort of claim considered. In research with human subjects, for example, a claim that was too difficult to fulfil might have to lead to the exclusion of potential subjects from the protocol. This is because we do not actually have a claim to participate in research per se. In health care, this would play out very differently. If we have any claim to health care, then added difficulty would not affect it directly. How much added effort is required when more is needed is indeed an open question, but this is due to the need to balance claims against those of others,[44] rather than because the claim itself is diminished.

This definition of vulnerability is silent as to whose duty it is to fulfil existing claims. The simple answer might be that whoever had this duty in the first place still has it in the case of vulnerable persons. This, however, should mean anyone who *shares* in the duty to avoid the identifiable wrong (Figure 1). Asking who is *the* agent responsible, as if there had to be a single one, is simplistic, as we consider that different people may have different sorts of duties to fulfil the same claim. A child's parents may have a duty to make sure she does not fall into a pond but this does not relieve me of a duty to rescue her if I happen to be there when she does. The problem of requirements for ancillary care, which has proved particularly thorny in research ethics, is an example. If governments have a duty to provide health care to their citizens but fail to do so, how much of this duty falls to researchers? Although we will not attempt to answer this question here, it is noteworthy that there are four counts on which researchers may have such a duty to some degree. Entrustment of their health by research subjects was proposed as grounds for this.[45] That they are on the spot and able to help, as in the rule of rescue, could constitute another. If we should do our share of a collective duty to fulfil such claims,[46] then researchers and sponsoring institutions could do their share in by providing ancillary care. Finally, the advantages that researchers and sponsoring institutions sometimes reap, from the very fragilities that make their subjects vulnerable, could also ground such a duty. Increasing recognition that some claim to ancillary care

[41] Levinas *op. cit.* note 2.

[42] D.C. Thomasma. The Vulnerability of the Sick. *Bioethics Forum* 2000; 16: 5–12.

[43] A. McIntyre. Guilty Bystanders? On the Legitimacy of Duty to Rescue Statutes. *Philosophy and Public Affairs* 1994; 23: 157–191.

[44] N. Daniels. Four unsolved rationing problems. A challenge. *Hastings Cent Rep* 1994; 24: 27–29.

[45] L. Belsky & H.S. Richardson. Medical researchers' ancillary clinical care responsibilities. *Bmj* 2004; 328: 1494–1496.

[46] L.B. Murphy. 2000. *Moral Demands in Nonideal Theory*. Oxford, New York: Oxford University Press.

exists[47] could be understood as a growing realization of just this problem.

Finally, the definition of vulnerability proposed here does not address differences in the way that people may have become vulnerable. As has been proposed, differences between vulnerabilities that originate in injustice, or misfortune, or that are the fault of the vulnerable person herself, could well be relevant.[48] According to the view proposed here, however, this would affect the legitimacy of the claim being considered, rather than the definition of vulnerability itself.

[47] R. Macklin. Four forward-looking guidance points. *Developing World Bioeth* 2001; 1: 121–134.
[48] D.W. Brock. 2002. Health Resource Allocation for Vulnerable Populations. In *Ethical Dimensions of Health Policy.* M. Danis, et al., eds. Oxford: Oxford University Press: 283–309.

Acknowledgments

The author warmly thanks Bernard Baertschi PhD, Marion Danis MD, and Alex Mauron PhD, for very insightful and constructive comments, as well as her students. This work was funded by the Bioethics Institute at the University of Geneva, and by the Swiss National Science Foundation.

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