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The Boldt debacle

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Recently, the Editors-in-Chief of 18 specialist journals, drawn mainly from anaesthesia and intensive care, have made a joint statement regarding 88 published clinical trials conducted without Ethics Committee approval by the German anaesthetist Dr Joachim Boldt.¹ The trials were performed at the Klinikum Ludwigshafen, a non-university hospital in the State of Rheinland-Pfalz, Germany, where until recently Boldt was head of the Department of Anaesthesia.

In Germany, since April 1994, according to regulations based on the Code of Deontology, researchers are obliged to seek approval and/or advice for a planned research project from an Ethics Committee that is affiliated to either the German Federal Medical Association or a University. Until 2001, a researcher working in the State of Rheinland-Pfalz would submit a copy of approval from an Ethics Committee, together with the trial protocol and patients' informed consent forms, to the Landesärztekammer Rheinland-Pfalz (LÄK-RLP). The LÄK-RLP would generally follow the recommendation of the Ethics Committee, but in some cases asked for minor modifications. In 2001, the Ethics Committee of the LÄK-RLP became solely responsible for all the research performed in this State.

The aim of this Editorial is to identify the articles that Boldt has published in the *European Journal of Anaesthesiology*, those without Ethics Committee approval that need to be retracted, those that may still be regarded as valid and then to assess what the implications of this debacle will be for the Journal.

Boldt and co-workers have published 19 articles in the *European Journal of Anaesthesiology*.^{2–20} These were all published between 2001 and 2010, except for one that was published in 1987.²

According to the enquiry led by the LÄK-RLP, eight of these articles had no approval from any Ethics Committee.^{7,11,14,17,18} These are retracted in the present issue of the Journal. In three of these, the authors stated that the studies were performed after approval by the 'Institutional Review Board',^{7,11,12} and in the other five, it

was claimed that approval was obtained from the 'Ethics Committee'.^{13–15,17,18} This was not the case, as the Klinikum Ludwigshafen had neither an Institutional Review Board nor an Ethics Committee. Also, Boldt and co-workers were unable to provide any evidence that these studies had received ethical approval from any other competent institution. When enquiries were made by the LÄK-RLP, negative responses were received from the Ethics Committee of the Universities of Giessen and Mannheim (which are both close to Ludwigshafen) and LÄK Hessen (State Medical Association for Giessen) (personal communication, I. Wessler, Landesärztekammer Rheinland-Pfalz, Germany; 14 March 2011).

Four articles had approval from an Ethics Committee, according to the LÄK-RLP.^{5,9,16,20} One of these⁵ was initially classified by the LÄK-RLP as lacking ethical approval, as the headings of the study protocol differed from the article that was eventually published in the *European Journal of Anaesthesiology*, as were the number of analysed patients per group (protocol $n = 20$ and article $n = 15$). In this article, it was claimed that the Ethics Committee of the hospital had given approval, although such a committee has never existed (personal communication, I. Wessler; 4 March 2011). It was also acknowledged that B. Braun, Melsungen, Germany had supported the study with a grant and provided the study fluids.⁵ However, the company B. Braun specified that they were the legal sponsor of this study and that the study was monitored by an external contract research organisation which also performed the data analysis and compiled the final study report. They went on to state that eventually the publication was written by Boldt and that the company was not involved in its preparation (personal communication, U. Brauer, Chief Medical Officer, B. Braun, Melsungen, Germany; 4 April 2011).

Interestingly, among the four articles that had ethical approval according to the LÄK-RLP, one stated in the methods section in some detail that 'the study was approved by the Institutional Ethics Committee (Landesärztekammer Rheinland-Pfalz, Mainz, Germany, No. 837.284.04)'.⁹

Two Boldt articles did not require ethical approval according to the LÄK-RLP.^{10,19} One was a survey on nutritional support in German ICUs.¹⁹ The other, which was published in the *European Journal of Anaesthesiology* in 2008, did not mention any ethical approval¹⁰ and was very similar to one of the authors' previous publications in another journal from 2004.²¹ According to the LÄK-RLP, this last study²¹ did not need ethical approval, as it was an

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epidemiological study of levosimendan, a drug that was not uncommon in German ICUs (personal communication, I. Wessler; 14 March 2011). However, in that 2004 article it states that 'our study was approved by the ethics committee of the hospital'.²¹ This cannot be true, as Klinikum Ludwigshafen, where the study was performed, never had an Ethics Committee. Also, upon enquiry, the main author of both articles confirmed that eight of the 27 patients who received levosimendan in the 2008 article¹⁰ had already been included in the case series from 2004²¹ (personal communication, Lehmann; 4 March 2011).

There have been five further Boldt articles in the *European Journal of Anaesthesiology*. Two are conventional narrative review articles^{4,8} and two are letters.^{3,6} Finally, only one Boldt article, which, because it was published in 1987,² was not evaluated as it was outside the scope of the LÄK-RLP investigation. Their remit was limited to a systematic evaluation of the status of Ethics Committee approval for research conducted by Boldt dating back only to 1999.

Why do these eight articles need to be retracted?

Failure to get Ethics Committee approval means that the research must be considered unethical. Some types of data collection, such as routine audit, which may result in publication, do not necessarily require ethical review. Lack of review and approval does not necessarily indicate that the research was unethical, but simply that the appropriate safeguards and processes have not been applied.²² The question of whether there were real patients behind the studies and whether they gave informed consent, and whether the reported data, analyses and conclusions were scientifically valid, does not require an answer to justify retraction. Klinikum Ludwigshafen has commissioned an investigating committee to systematically assess the reliability of the findings presented in the articles by Boldt.¹

What are the implications of this debacle?

The modern meaning of debacle is the 'imagery of a sudden and chaotic disaster which completely and irreparably ruins something'.²³ Retraction of 88 articles for lack of Ethics Committee approval is definitely a debacle. The future will tell what the impact of the retraction of the articles by Boldt on patient care will be.²⁴ For the reputation and credibility of clinical science and anaesthesia, the damage is tremendous.^{25,26}

What can we learn from this debacle?

For the Journal, there are three lessons to be learned.

First, all articles by Boldt that need to be retracted due to lack of Ethics Committee approval stated clearly that such approval was granted, either by an 'Ethics Committee' or an 'Institutional Review Board' (which is the US

American term for Ethics Committee). These statements were false and this creates suspicion that standard declarations such as 'the study was performed after having obtained approval from the Institutional Review Board' or 'we enrolled patients after having received approval from the local Ethics Committee' are often empty phrases. Already in 2010, the *European Journal of Anaesthesiology* has adopted a new rule that all articles dealing with original human or animal data must include at the beginning of the Methods section a detailed statement on ethics approval. This paragraph must contain information on the name and address of the Ethics Committee responsible, the protocol number that was attributed by this committee, the name of the Chairperson (or the person who approved the protocol) and the date of approval by the Committee. At our weekly editorial board meeting, we regularly identify potentially interesting, newly submitted articles that lack this crucial information. These manuscripts are not further considered for publication until the authors have completed that paragraph. Usually, authors fill in these details on request and re-submit their article within days. Interestingly, since we introduced the new rule in July 2010, a dozen articles that lacked details on ethical approval and were returned to their authors never came back to us.

Second, we must realise that ethical requirements still differ between countries, even within Europe. In May 2004, the European Union Clinical Trials Directive (EUCTD) came into force.²⁷ The different European Union member states have endorsed that Directive, but have also included individual changes and have implemented it in a variety of ways. The Directive states that it does not apply to non-interventional trials in which patients are assigned to a particular therapeutic strategy that is not decided in advance by a trial protocol, but falls within current practice. This applies to situations in which the prescription of the medicine is clearly separated from the decision to include the patient in the study. For the levosimendan study,^{10,21} the authors chose not to submit their study protocol to the competent Ethics Committee. Ideally, it should not be the authors who decide whether their study needs ethical approval or not, but they should seek this advice from an Ethics Committee before starting to enrol patients. It would then be left to that Ethics Committee to waive informed consent if this was thought unnecessary.

And finally, conflicts of interest must be declared overtly; full transparency is needed. It is certainly unsatisfactory when, as in one of the articles by Boldt,⁵ the authors acknowledge laconically that a pharmaceutical company had provided the study drugs and a grant, when in fact that company was the legal sponsor of the study, supervised data analysis through an external contract research organisation and participated in editing the manuscript through that contract research organisation. In this Journal's guide to authors, it states that 'if there was

support from a pharmaceutical company or a manufacturer, it must be clearly stated what the role of the company was (for instance, editing of the protocol, financial support, drug supply, data analysis, writing of the paper). It is also clear that it is the authors' responsibility to honestly and comprehensively declare any conflict of interest and to specify the role of, for instance, a sponsor.

In conclusion, the Boldt debacle demonstrates how fragile and delicate scientific publication remains. Much of the process still relies on confidence, integrity and authority. Journal editors of all medical disciplines know all about the consequences of the 'publish or perish' philosophy that still prevails in many medical faculties. In anaesthesia, we have learned to accept guidelines to prevent clinical disasters and to improve patient safety.²⁸ We may need similar rules and safeguards to prevent future debacles in scientific publishing.

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