Ethical requirements and authorship: not much room for interpretation

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EDITORIAL

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In this issue, we are retracting an article that was recently published by Ochmann et al., in which randomised patients underwent colon surgery anaesthetised with desflurane either in 30% oxygen or in 80% oxygen. This interesting, albeit relatively small, study was intended to advance our knowledge on the potential benefit of intraoperative hyperoxegenation on the incidence of postoperative nausea and vomiting. The authors measured intramuscular tissue oxygenation using a polarographic micro-oxygen sensor that was inserted into the deltoid muscle. They also reported on high-performance liquid chromatographic measurements of serotonin levels in plasma and platelets. The authors concluded that hyperoxegenation leads to a significantly higher tissue oxygenation, to a significant decrease in serotonin levels and to a lower incidence of postoperative nausea and vomiting. The affiliation of four of the six authors was Klinikum Ludwigshafen, Ludwigshafen, Germany. Readers may recall the recent case of scientific misconduct of Boldt, who had failed to receive ethical approval for a large number of his studies, and who worked at the very same Klinikum Ludwigshafen. In an attempt to clarify whether reports from authors from the same hospital, other than Boldt, may have been published in our journal, and if these same reports had received valid ethical approval, we searched for relevant publications in Medline, using the search strategy (Klinikum Ludwigshafen[Affiliation]) AND ‘European journal of anaesthesiology’[Journal]. That search retrieved eight publications. Seven were co-authored by Boldt, and, due to the aforementioned ethical problems, they all had to be retracted last year.

The eighth report was the publication by Ochmann et al., which is retracted in the current issue. When reading the article by Ochmann et al., two observations were remarkable. First, although Klinikum Ludwigshafen was named as one of the authors’ affiliations, Boldt’s name was not listed on the byline as a co-author. This was unexpected, as some of the authors of the article by Ochmann et al. had co-authored several of the 88 Boldt articles that had to be retracted due to lack of ethical approval; Beschmann was a co-author of three retracted Boldt publications, Röhm of 36 and Piper of 50. Second, and in contrast to most of the retracted Boldt articles, detailed evidence of ethical approval is provided in the publication by Ochmann et al.; in the Methods section, it reads ‘after approval from the ethics committee of the medical association of Rheinland-Pfalz [837.074.03 (3736)] and obtaining written informed consent...’. The unsolicited, voluntary specification of a protocol number suggests that the study protocol had indeed been reviewed by a competent ethics committee and had received approval. Why otherwise would the authors specify a protocol number? To verify that assumption, as with all the articles that Boldt had published in the European Journal of Anaesthesiology, we contacted the ethics committee of the medical association of Rheinland-Pfalz and asked them to confirm that the Ochmann et al. study had indeed received ethical approval.

In their reply, the medical association of Rheinland-Pfalz confirmed that a study protocol with that number and dealing with perioperative hyperoxegenation had been submitted by Boldt and Piper, and had received ethical approval in 2003. However, according to the study protocol, the authors planned to include patients undergoing cardiac, not colon surgery, to randomise them to 40 and 100%, rather than 30 and 80% oxygen, and to measure immunological markers (for instance, interleukin) and not serotonin. There were other obvious discrepancies between the protocol and the published study. The hypothesis that an inspired oxygen fraction of 80% attenuated serotonin release in patients scheduled for colorectal surgery was not mentioned in the protocol. Perhaps most alarmingly, it also failed to describe an invasive tissue oxygen measurement using a catheter that was to be inserted into the patient’s deltoid muscle. Accordingly, the medical association of Rheinland-Pfalz concluded that the study protocol No. 837.074.03 (3736) did not correspond to the publication by Ochmann et al., in the European Journal of Anaesthesiology and that ethical approval for this study was never granted.

Subsequently, the editors of the journal contacted the senior author of the paper by Ochmann et al., Dr Piper, and asked for an explanation and clarification. None was forthcoming. Piper argued that patients were properly informed about the aims of the study and the procedures and, in evidence, he submitted to the editorial office a copy of a signed patient declaration form that could indeed have been the form that was used for the study.
However, the form was neither dated, nor did it even contain a protocol number. When forwarded to the medical association of Rheinland-Pfalz, they were unable to confirm that the form was part of the original study protocol No. 837.074.03 (3736).

As a consequence, the editors have decided to retract the article by Ochmann et al.

This case of obvious scientific misconduct raises yet again, important questions about authorship and ethical requirements for clinical research.

According to our Guide to Authors, we ask that all authors sign a standard covering letter. We ask them to confirm that they have read and approved the submitted article. They are then asked to confirm that they have met the criteria for authorship as established by the International Committee of Medical Journal Editors (ICMJE), and that they believe that the article represents honest scientific endeavour. We expect them to be able to verify the validity of the reported results. The ICMJE criteria demand that all persons designated as authors should meet the qualifications for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. To be credited, authors must meet three criteria: first, to have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; second, to have drafted or revised the article critically for important intellectual content; third, to have approved the final version to be published.

It appears that Boldt, together with Piper, had submitted study protocol No. 837.074.03 (3736) to the ethics committee of the medical association of Rheinland-Pfalz. That protocol eventually led to the Ochmann et al. publication. However, when the article was published, Boldt was not listed as a co-author. Review of the editorial process revealed that Boldt was an original co-author of the Ochmann et al. manuscript when it was first submitted to the journal in November 2009. Boldt’s name was still on the byline of the second revision submitted in April 2010 that was eventually accepted for publication. It was only during proof reading that the authors chose to omit Boldt’s name. It was about this time that the Boldt debacle was unearthed, and it is likely that the authors did not want to jeopardise their reputation by co-publishing with an individual who was accused of scientific misconduct. It remains unclear, though, how an author who adheres to the ICMJE criteria, as required in our Guide to Authors, and who signs our standard covering letter, may co-author dozens of faulty articles without being aware of any misconduct.

This case tells us that when details of ethical approval, for instance, a protocol number, are given in a journal submission, we cannot guarantee that the protocol approved initially, matches that of the study eventually published. These authors were changing experimental and control interventions, primary endpoint, and measurements without ever submitting an amendment to the competent ethics committee. In the European Directives relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use it reads (Article 10, Conduct of a clinical trial, paragraph a):

after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the competent authorities (…) of the reasons for, and content of, these amendments and shall inform the Ethics Committee (…)

and also

(…) the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form. If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

Thus, the message is clear; seeking to change the aim of a study or add yet another measurement is not what matters, but what is essential is that before implementation, any change in the study protocol is put to the Ethics Committee as an amendment, for their opinion, and the subsequent permission rests with them. The question then is what makes a change substantial or significant and what is likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial. It may be argued that posthoc changing of the primary endpoint of a study may not necessarily harm enrolled patients. However, we cannot dismiss the possibility that the invention of a new primary study endpoint might lead to bias in the interpretation of the data, and as a consequence, misleading conclusions. Also, most of us would probably agree that insertion of a catheter into a patient’s deltoid muscle is substantial and significant. The question is not whether the investigators believe that the measurement of tissue oxygenation is important and worthwhile, or whether patients were adequately informed about the aim of the study and the procedures. It is whether an independent ethical committee, whose members do not have any conflict of interest concerning the study and who are involved in neither design, nor the performance of the study, nor analysis of data, has considered and approved the study protocol that describes the invasive measurement. In the case of the article by Ochmann et al., it appears that the authors have themselves made the decision to implement changes in
the study protocol, without any advice from an ethics committee. This is unacceptable.

Acknowledgements
The author declares that he has not received support from any organisation for the submitted work, has no financial ties with any organisations that might have an interest in the submitted work and has no other relationships or activities that could have influenced the submitted work. This article was checked and accepted by the Editors, but was not sent for external peer-review.

References