

CHEST and the impact of fraud in fluid resuscitation research

John Myburgh

On 28 October 2010, Dr Steven Shafer, the editor of *Anesthesia and Analgesia*, published an editorial retracting an article published in December 2009 by Joachim Boldt and colleagues describing the effects of two cardiopulmonary bypass pump priming solutions — albumin and 6% hydroxyethyl starch (HES) (130/0.4) in a balanced salt solution.¹ Concern about the validity of some of the results had been raised in a series of letters from readers. After several months of enquiries, Boldt's institution, Klinikum Ludwigshafen, confirmed that that no institutional review board (IRB) approval for this study had been granted, no informed consent had been obtained, and no randomisation process or follow-up questionnaire described in the study had been conducted. A formal inquiry from Landesärztekammer Rheinland-Pfalz (the State Medical Authority of Rhineland-Pfalz), published in a second letter by Dr Shafer,² confirmed that the study had been entirely fabricated on the basis that there were no original patient or laboratory data to support the findings of the study, and that albumin had not been used as a priming solution in the institution since 1999. Furthermore, Boldt had confessed to forging the signatures of the coauthors on the copyright transfer form to *Anesthesia and Analgesia*, and the coauthors denied participation in the fabrication.

The retraction of this report immediately cast doubt on the scientific and ethical validity of all of Boldt's previous and subsequent publications. Two letters published by the editors-in-chief of 18 journals³ confirmed the retraction of 87 of Boldt's articles on a range of subjects, including 11 reports of fluid resuscitation with 6% HES (130/0.4), predominantly among patients undergoing anaesthesia and in perioperative settings. These reports constitute a substantive body of published literature on the safety and efficacy of 6% HES (130/0.4), and some have been cited in manufacturers' product information sheets, submissions to regulatory authorities, and clinical trial protocols.

Of the latter, the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) is a prime example.⁴ CHEST is an investigator-initiated, multicentre, 7000-patient randomised controlled trial comparing the effects of fluid resuscitation with 6% HES (130/0.4) with the effects of saline among intensive care patients on 90-day mortality. It is being conducted in 33 intensive care units in Australia and New Zealand and is endorsed by the Australian and New

Zealand Intensive Care Society Clinical Trials Group. It is funded by the National Health and Medical Research Council, the New South Wales government and Fresenius Kabi Australia and New Zealand, who have provided logistic support and unrestricted grant funding. Recruitment commenced in November 2009.

The CHEST Management Committee acted promptly after the publication of the letter from the editors-in-chief on 4 February 2011 by notifying all Principal Investigators and the Data Monitoring Committee (DMC) of the retracted paper on 9 February 2011. In addition, an urgent systematic review of all randomised controlled trials of 6% HES (130/0.4) versus other resuscitation fluids on outcomes aligned with CHEST was conducted by the CHEST Management Committee.

After the publication of the second letter from the editors-in-chief on 4 March 2011, the CHEST Management Committee formally notified the Principal Investigators, the DMC and all lead Human Research Ethics Committees and IRBs in writing on 8 March 2011 about the retracted trials, specifically stating that four trials had been included in the CHEST protocol, which would be subsequently amended. A copy of the completed systematic review was forwarded to the above; the review confirmed that there was no difference in absolute mortality between 6% HES (130/0.4) and other resuscitation fluids and that this result was not altered with the inclusion of retracted studies. It also concluded that the overall quality of randomised controlled trials was low and the results of CHEST were urgently required.

On 9 March 2011, the first preplanned interim analysis of the first 2000 patients was conducted by the DMC, which recommended that the trial continue. A second interim analysis is scheduled after the recruitment of 4000 patients. Recruitment has continued and is due to be completed in November 2011, with the results expected by March 2012.

CHEST will therefore provide substantive evidence about the safety and efficacy of one of the most commonly prescribed resuscitation fluids on a global basis. The results may change practice, but perhaps are made more important in the context of an unprecedented case of research fraud in critical care medicine.

It is hoped that the proactive processes that the CHEST investigators developed in response to this rapidly evol-

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ing scandal highlight the importance of effective communication with all stakeholders in collaborative trials.

The full extent and consequences of this fraud are yet to be realised. It is likely that increased scrutiny of ethical and research governance processes by journals, including *Critical Care and Resuscitation*, will be required. Researchers must be aware of the obligations and responsibilities of conducting research and that the most impeccable and transparent standards cannot be compromised.

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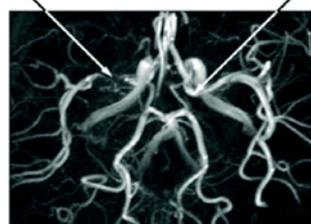
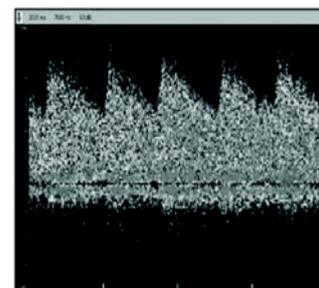
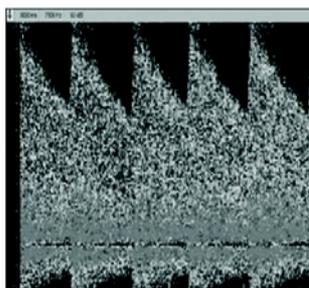
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