

Fraud in fluid resuscitation research

John A Myburgh

Research fraud is an unacceptable breach of trust

Few issues in medicine provoke the wrath of the profession more than research fraud. In an era when evidence-based medicine has become the cornerstone of information about the safest and most effective way to practise medicine, fraudulent or unethical medical research represents an unacceptable breach of trust for clinicians, health policymakers and the general public.

Research fraud takes many forms, including plagiarism, duplicate publication and fabrication by falsifying or omitting data to create “positive” results. When the latter occurs, the damage to the reputation of investigators, institutions, specialties and the broader profession is often permanent.

An article published in *Anesthesia and Analgesia* in December 2009 by Joachim Boldt compared the effects of two colloid cardiopulmonary bypass pump-priming solutions — albumin

and hydroxyethyl starch (HES) — on physiological variables in 50 patients undergoing cardiac surgery.¹ It was retracted in October 2010.² Following concerns about the validity of some of the results, raised in letters from readers, an enquiry to the institution where the study was conducted confirmed that no institutional review board approval had been obtained. A formal inquiry by the state medical authority of Rheinland-Pfalz, Germany, confirmed that the study had been entirely fabricated on the basis that there were no original patient or laboratory data to support the findings. Furthermore, Boldt had confessed to forging the signatures of the coauthors, who denied participating in the fabrication.³

Boldt had been a prolific author and the retraction of this report immediately cast doubt on the scientific and ethical validity of his previous and subsequent publications. This suspi-

cion was confirmed in two open letters published by the editors-in-chief of 18 journals that retracted a further 87 reports.

While these publications concern a range of topics in anaesthesia and perioperative care, 11 were reports on the safety and efficacy of a relatively new HES preparation used for fluid resuscitation, 6% HES 130/0.4. These reports constitute a substantive body of literature that has been used in manufacturers' product information sheets and submissions to regulatory authorities, including the Therapeutic Goods Administration (TGA). Although HES preparations have been used as resuscitation fluid for over 40 years, particularly in Europe, 6% HES 130/0.4 was the first HES approved by the TGA (in November 2006). Since 2008, the use of 6% HES 130/0.4 in Australia has increased, which is consistent with reports that show that it is the most commonly used resuscitation fluid on a global basis, although there is marked variability in selection and use of resuscitation fluids from country to country.⁴

Before confirmation of the first retraction, two updated Cochrane systematic reviews on resuscitation fluids — comparing colloids with crystalloids⁵ and comparing different colloid solutions⁶ — included a sensitivity analysis excluding studies published by Boldt. Both reviews concluded that excluding these reports did not change the conclusions that there was no evidence from randomised controlled trials that (a) resuscitation with colloids reduced the risk of death compared with crystalloids or (b) any one colloid was more effective or safer than any other. The reviews highlighted the urgent need to conduct large-scale high-quality trials of fluid therapy.

The Crystalloid Versus Hydroxyethyl Starch Trials, being conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group and the George Institute for Global Health, are underway. These trials will compare the effects of 6% HES 130/0.4 and saline for resuscitation in intensive care units, using patient-centred outcomes — specifically, mortality and the incidence of acute renal injury.

The magnitude of the Boldt case is unprecedented in intensive care medicine. It ranks with the fraudulent research conducted by Wakefield (measles–mumps–rubella vaccine),⁷ Sudbo (non-steroidal anti-inflammatory drugs and the risk of oral cancer)⁸ and Hwang (embryonic stem cell cloning).⁹ That these cases of major research fraud have occurred within the past decade, despite increases in ethics governance and regulatory processes within the jurisdictions involved, highlights the determination of fraudulent researchers to publish their reports. The reasons driving this are complex and include career pressure, financial incentives, the ease of fabricating data, and the proliferation of electronic media.¹⁰

Researchers and institutional human research ethics committees are expected to act in accordance with the Australian Code for the Responsible Conduct of Research. This code is issued by the Australian Research Integrity Committee, which was established by the National Health and Medical Research Council and the Australian Research Council to bolster responsibilities of research organisations.¹¹ Equally, journals have a key role in verifying that appropriate ethics review processes have been completed and ensuring that only studies of the highest levels of internal and external scientific validity are published.

While the protection of patients who participate in clinical trials is the ultimate consideration of ethics governance proc-

esses, it is imperative that high-quality research conducted with the highest levels of ethical integrity and scientific validity continues to provide the best information for clinicians.

Competing interests

I have received logistic support and an unrestricted grant, paid to the University of Sydney and the George Institute for Global Health, from Fresenius Kabi to conduct the Crystalloid Versus Hydroxyethyl Starch Trials. I have received reimbursement, paid to the George Institute for Global Health, from Fresenius Kabi for international travel to attend trial planning meetings and for a presentation at a sponsored meeting.

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