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NEWS

# "Independent" reanalysis of landmark starch solutions trial was published by original authors

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Academics who refused calls to share the data underlying their landmark trial that triggered the downfall of starches for fluid resuscitation have announced an "independent reanalysis," which confirms their original findings.[1]

However, they have not made their data available to the wider scientific community—a key element of transparent research practice and what other academics have been calling for.[2 3]

The 7000 patient trial, CHEST (Crystalloid versus Hydroxyethyl Starch Trial),[4] is one of the most important pieces of evidence concerning the effects of hydroxyethyl starch solutions for increasing intravascular volume in patients in intensive care.

Published in the *New England Journal of Medicine* in 2012, CHEST reported that the hydroxyethyl starch investigated, Voluven, was no different than saline in terms of mortality but led to greater use of renal replacement therapy. The trial helped persuade drug regulators in Europe and the US to issue safety warnings in 2013.

In February the US health watchdog Public Citizen sent a petition to the Food and Drug Administration calling for hydroxyethyl starch intravenous solutions to be removed from the market,[5] a move supported by CHEST's lead author, John Myburgh.[6]

But the global healthcare company Fresenius Kabi, which makes Voluven and was a major funder (€3.5m (£3.15m; $4m)) of the trial, has long contended that the study was improperly reported.[2] Before the trial the company took the unusual step of signing away all rights to the data, a decision it later came to regret. In 2014 it sought the assistance of *The BMJ* to intervene with the CHEST investigators. It then asked the Yale Open Data Access Project (YODA) to serve as an independent intermediary between the CHEST investigators and a reanalysis team to be determined, but the academic investigators rejected YODA's offer.[2]

The latest "independent analysis" is the first time the CHEST data have been re-examined. But the way the new analysis has been carried out raises questions about the reliability of the findings (box).

According to the new report, published as a short research letter,[1] the reanalysis was conducted by the Duke Clinical Research Institute and "confirms the integrity of the original analysis and provides support for the conclusion of the original article."

But only two of the eight authors of the reanalysis are from the Duke institute. The other listed authors all come from the George Institute for Global Health, which administered the original study. They include three authors of the original 2012 publication, including the study's principal investigator, Myburgh.

*The BMJ* contacted all eight authors for comment. It asked Myburgh and the two other researchers who authored both the original 2012 report and the reanalysis how they could describe the new report as "independent," given their involvement, but they didn't reply. Only the new report's lead author, Anushka Patel (not an author of the 2012 report), replied, but she did not answer this question.

She told *The BMJ* in an email that "the aim of the re-analysis was to determine whether the primary results of the study, as presented in Table 2 of the original manuscript, were accurate. I believe the Letter is self-explanatory in this regard and we do not plan to comment further."

Michael Murray, who testified at the FDA during its deliberations on hydroxyethyl starch in 2012 and has written an editorial on the need for sharing the CHEST data,[3] commented: "I am obviously pleased they re-analyzed their data, not surprised their conclusions didn't change, but disappointed that it doesn't appear that the investigators are inclined to share their data. They missed the point of my editorial."

Vinay Prasad, assistant professor of medicine at Oregon Health and Science University and an adviser to *The BMJ*, said, "Independent re-analysis means you make the data available for someone else to analyze. Re-analyzing your own data is like standing in front of the mirror and concluding you look good whether your face is turned left or to the right."

The *New England Journal of Medicine*, which published the reanalysis, defended the authors' decision to call the reanalysis "independent." Jennifer Zeis of the NEJM Group told *The BMJ*, "The Duke Clinical Research Institute (DCRI) team analyzed the data from the CHEST study independently and without input from the CHEST authors beyond their confirmation that the

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data had been correctly received and the data elements correctly identified. The analysis itself was solely the work of the DCRI team. That analysis was then returned to the CHEST investigators, who wrote a letter to the editor based on the DCRI findings. Reflecting that process, the letter was signed by investigators from the CHEST study as well as persons from the DCRI team."

Prasad, however, was unconvinced: "This is still problematic. It returns the decision to publish to the original investigators. Who may say 'scrap it' if the analysis was not similar. Independent means all stages, including manuscript preparation and decision to submit, are independent."

*The BMJ* asked the Duke authors whether they were contractually permitted to publish independently of the George Institute. Karen Pieper, who led the Duke team, was unsure. "I don't have the contract available to know. It was not part of my discussion with them when we were working on the contract, because I was not interested in that being part of our responsibilities. But that said, Duke legal does put language into contracts concerning our publication rights. So it may be in there. I just don't know."

The trial data also remain the property of the George Institute, a sharp contrast to drug companies' ongoing efforts to enable wider access to clinical trial data as part of good research governance.[7]

As at 2016, no systematic review nor meta-analysis independent of the trial authors had examined the raw data. Regulators, too, decided to restrict the use of hydroxyethyl starch products without having seen the raw data.[7]

Competing interests: I have read and understood BMJ policy on declaration of interests and declare that the Yale Open Data Access Project (YODA) paid all expenses for me to join a June 2012 planning meeting to discuss YODA's forthcoming data sharing policy. This payment was later reimbursed by *The BMJ*. I consider the YODA team to be colleagues. Also, I am an unpaid member of the IMEDS steering committee at the Reagan-Udall Foundation for the FDA, which focuses on drug safety research. Vinay Prasad, quoted in this article, and I are co-recipients of a grant from the Laura and John Arnold Foundation to establish a RIAT Support Center. Also see http://www.bmj.com/about-bmj/editorial-staff/peter-doshi.

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### Problems with the CHEST reanalysis

According to the new report in the *New England Journal of Medicine*,[1] the George Institute "commissioned an independent reanalysis" from Duke Clinical Research Institute, supplying it with the trial database and original case report forms.

Karen Pieper, one of the Duke authors of the report, told *The BMJ* that Duke provided "external validation of the primary results of the manuscript."

But before it received the data Duke did not stake out its own independently written protocol and statistical analysis plan. Instead it used the roadmap provided by the George Institute.

Pieper said, "I reviewed their statistical analysis plan (SAP) for validity, mapped out the derivation of the variables based on the SAP, and created a specification for the results table."

As *The BMJ* reported last year,[2] the CHEST protocol[8] and statistical analysis plan[9] were published after the trial began enrolling patients, and Myburgh refused *The BMJ*'s request to share documents pre-dating the start of the trial, meaning that the outcome definitions provided could not be compared with those at the start of the study.

Before the new reanalysis, one major area of contention had been the analysis of treatment related adverse events. The 2012 publication said that there were significantly more adverse events in the hydroxyethyl starch group than in the saline group: 180/3416 (5.3%) versus 95/3358 (2.8%) (P<0.001).[4] But the manufacturer, Fresenius Kabi, alleged that patients had been inappropriately moved from the saline group to the starch group. A correct analysis, it contended, would show no significant difference.[2]

In 2013 the *NEJM* defended its 2012 publication after Fresenius first raised concerns. Last year, however, a *BMJ* investigation released a 2013 document written by the George Institute that detailed 29 adverse events in patients who had been randomized to the saline group but counted in the starch group (see the supplementary data of *The BMJ*'s article).[2] Myburgh subsequently acknowledged "a typographical transcription error," and the *NEJM* published a correction.[10 11] A new P value was published for any treatment related adverse events, with new denominators for the calculation, still showing a statistically significant increase with starch when compared with saline (180/3871 (4.6%) versus 95/2870 (3.3%) (P<0.006)).

Myburgh and colleagues' revised calculation is identical to that reported in this week's reanalysis. And both the original 2012 paper and the reanalysis carry a footnote saying that adverse events in the starch group "includes those in patients who received HES [hydroxyethyl starch] both before and after randomization." However, the reverse did not occur: adverse events in patients randomized to hydroxyethyl starch but who received saline before randomization were not shifted to the saline tally. This procedure resulted in 1001 more patients in the starch group than the saline group.

Asked why patients were moved between groups in one direction only, Pieper replied, "This is better answered by those who developed the original protocol at George Institute. It is logical, though, since HES was the new treatment, that one would be interested in the use of any HES versus none with respect to safety concerns."

But neither the protocol[8] nor the statistical analysis plan[9] describes this approach.

Fresenius maintains[2] that a correct analysis would use the intention to treat population, consistent with the statistical analysis plan.[9]

The new reanalysis of adverse events names the population analyzed as the "safety set," further stating that "adverse events were reanalyzed as defined in the Supplementary Appendix, available with the full text of the 2012 article at NEJM.org." But the notion of the "safety set" population was first introduced among the edits made to the manuscript and supplemental appendix last year,[10] and it did not appear in either the 2012 supplementary appendix, published protocol, or statistical analysis plan.

It is also unclear how the CHEST investigators overcame their earlier concerns about informed consent when sharing the data.

Myburgh told *The BMJ* last year that his key objection to the role of the Yale Open Data Access Project was the requirement to make the data publicly available, which would mean that Fresenius could obtain access. He expressed concern about the company's "ulterior motives which contradict or do not adhere to the scientific principles we adhere to." But he also said that CHEST trial data could not be shared because of patient consent.

The trial's consent form, which he refused to share, contained provisions that "specifically preclude" data sharing, he said. *The BMJ* was unable to locate any such provisions in a copy of the consent form seen and published as part of its investigation last year (see supplementary data of *The BMJ*'s article).[2]

*The BMJ* asked Myburgh how sharing data with the Duke institute was possible, given these provisions, but he had not responded by the time of publication.