Reviewer's report

Title: The aprotinin saga and the risks of conducting meta-analyses on small randomised controlled trials - a re-analysis of a Cochrane report

Version: 2 Date: 25 November 2008

Reviewer: Roger Harbord

Reviewer's report:

This manuscript is a critique of part of a Cochrane review in light of the results for mortality of the recently published BART trial of aprotinin.

I agree with the editor's suggestion that this manuscript should be considered as Correspondence, or perhaps Debate. Although the manuscript contains some research, in the form of a review of the studies included in one of the Cochrane analyses, in the main it is an opinion piece and should be placed to make this clear to the reader from the outset. I have reviewed it on that basis - while I may disagree with some of the author's opinions, that is not a reason for not publishing them, and as long as it is clear to the reader that the article represents one person's point of view, the manuscript need not be balanced or impartial. On that basis, I have no major compulsory revisions.

I was unable to obtain the full text of the study (Dietrich 1992) that the author claims should not have been included in the Cochrane review as it was an observational study not an RCT, but it appears clear from its abstract that the author is correct.

Minor Essential Revisions

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1) Title: Cochrane reviews are referred to as such, rather than as a Cochrane report, so the title should be reworded, e.g. "... a critique of a Cochrane review" or "a critical appraisal of a Cochrane review" or "a re-appraisal of a Cochrane review".

2) Introduction: Confidence intervals should be included for the mortality rate ratio in the BART study and the odds ratios for the observational studies rather than simply stating they were "statistically significant".

3) Methods: "The questions raised were [1] ... [3] ... [4] ..." Elsewhere the author has used numbers in square brackets for citations to references, but I assume the numbers here are simply numbering the questions? In which case, why no [2]?

4) Discussion, para 3: The editorial [17] appeared before publication of the BART study, not after.
5) The last sentence of the Discussion implies that apoprotinin has been withdrawn from the market, but it is not made clear when or by whom. This should be stated in the Introduction.

Discretionary Revisions

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6) The author does not discuss whether the apparent discrepancy between the results of the various studies could be due to chance rather than bias. One means to help assess this would be to include a forest plot of the results of the various studies discussed, showing the summary point from the Cochrane meta-analysis rather than the 52 individual trials.

7) It would also be informative to re-compute the summary odds ratio and confidence interval omitting the observational study (Dietrich 1992) that was incorrectly included. This would clearly move the summary result closer to the null and increase the width of its confidence interval.

8) In reading the Cochrane review, it struck me that the Dietrich 1992 study reported lower mortality on apoprotinin than control, unlike the recent observational studies, and it may be worth making this explicit in the manuscript and discussing possible reasons (this was a very early observational study before apoprotinin was widely used and before the granting of FDA approval so it is possible that the selection bias differed in direction from that in the recent observational studies; it was included in the Cochrane review without any adjustment for confounders).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I am a co-convenor of the Cochrane Collaboration's Screening and Diagnostic Tests Methods Group and a member of the Cochrane Collaboration's Statistical Methods Group. I have been reimbursed expenses incurred in the former role but have not received fees, funding or salary from the Cochrane Collaboration or any of its entities.