Reviewer’s report

Title: Can we rely on the best trial? A comparison of individual trials and systematic reviews

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Reviewer: Christian Gluud

Reviewer’s report:

Glasziou and co-workers have compared the estimated intervention effects and P-values of meta-analyses in Cochrane systematic reviews to the estimated intervention effects and P-values of the trial contributing most weight to the meta-analysis. There seems to be reasonably good agreement between the trials and the meta-analyses. The study is of interest. The data are clearly presented. I have the following suggestions for the authors.

* Major Compulsory Revisions

1. The comparison seems biased towards finding agreement as the authors seem to compare 167 evaluable meta-analyses, of which 35 only contained a single trial. Thereby they may skew the observed association towards agreement. A more proper analysis seems to be between the trial contributing most weight to the meta-analysis and the meta-analyses containing two or more trials. Sensitivity analyses could then be between the trial contributing most weight to the meta-analysis and the meta-analyses containing three or more trials; four or more trials; and five or more trials.

2. The authors use 'best' (e.g., title) and 'largest' interchangeably about their 'index' trial. This seems confusing. I suggest they use the same term every time, e.g., a more correct term, i.e., the trial carrying most weight.

3. The background can be shortened. If I remember correctly The Women’s Health Initiative trial provided evidence that hormone replacement carried health harm. That was projected by a meta-analysis published about 10 years earlier in the BMJ. So maybe this example is not the most well selected?

4. I have difficulties accepting that the authors have chosen the wrong 'gold standard'. Both randomized clinical trials and systematic reviews of randomized clinical trials may reach wrong conclusions due to systematic errors ('bias'); random errors ('play of chance'); and design errors (e.g., wrong comparator, etc.). Accordingly, a comparison of the trial carrying most weight with the result of a meta-analysis of the same trial plus additional trials has to consider all error mechanisms. I think the authors come 'too easy about this fact'. So, how many of the trials had adequate methodology and hence low risk of bias among the 'heavy' trials and among all trials in the meta-analysis? How well was the association between the findings of the 'heavy' trials and their meta-analysis when only those trials carrying less than 50% of the weight was included?
5. Which outcomes were assessed? This is especially relevant for the discussion on the influence of bias on the results (Wood, BMJ, 2008).

6. How does the authors define an adequately powered trial (p. 9)? Please see recent provocative discussion from Gordon Guyat's group that we do not need that much large trials any more after we have got systematic reviews.

7. I have problems with the proposed 'poor man's systematic review' approach: if you can't find a systematic review then try to find a 'large' trial and use this for guidance. The problem is that when we identify one large trial (however defined) we do not know what we have missed. I agree that it takes time to do systematic reviews - but compare this to the time it takes to do a trial, then systematic reviewing comes out as the most cost-effective winner.

8. I think the authors need to discuss information size considerations in meta-analyses, e.g., as estimated in trial sequential analyses of cumulative meta-analyses.

9. The authors should reconsider their statistical analyses. By using meta-analyses that have been carried out they are able to identify the trial having most weight. Would is not then be more relevant to assess that trials sensitivity and specificity, their predictive value for the result of the meta-analysis (PVpos and PVneg) as well as the likelihood ratio of positive and negative trials for the ultimate result of its meta-analysis?

* Minor Essential Revisions

1. P.2 One option could be in stead of is.

2. The authors should use trials and not studies, if it is trials that are meta-analyzed.

3. The authors should use 'outcome measure' in stead of 'endpoint'

4. P. 10. 'lower quality' should become 'lower methodological quality (and hence increased risk of systematic errors ('bias')).'

* Discretionary Revisions

None.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests