Reviewer's report

Title: Network meta-analysis incorporating randomized controlled trials and non-randomized comparative cohort studies for assessing the safety and effectiveness of medical treatments: Challenges and opportunities

Version: 3 Date: 17 August 2015

Reviewer: Gert van Valkenhoef

Reviewer's report:

I thank the authors for the thorough revision they have made. I think the reduced word count will help get the points across to more readers, and the quality of the writing has improved as well. I am now quite happy with the manuscript in general, but I do have a few specific comments.

Major compulsory revisions

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1. Figure 3 needs to be revised. The caption should mention whether the "Combined" effect is a pair-wise combined effect or the estimate from NMA. Based on the "B vs. A" comparison I have assumed that it is a pooled estimate from NMA. In this case, the effects should be transitive, yet this does not appear to be the case. For example A and B are equally effective according to the "B vs A" comparison, yet the effects of "C vs A" and "C vs B" are quite different. In subfigure (B) the pooled effects are the same as in subfigure (A) even though the randomized evidence has drastically shifted - this is not realistic.

Minor Essential Revisions

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2. The abstract could be made more concise and cohesive. It is now quite verbose and not always easy to follow (see below for an example).

3. "Network meta-analysis of RCTs and non-randomized comparative cohort studies", paragraph 4: The Bayesian hierarchical model could use some expansion. The current text says some about what it can do, but nothing about what it is.

Discretionary Revisions

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4. Abstract: "inclusion of non-randomized studies is increasingly common and desirable" - reads as if the inclusion of non-randomized studies is increasingly desirable. It would also be helpful to more closely connect this sentence to "Non-randomized studies can complement RCTs ...", which provides a rationale for why this would be desirable.
5. "Background", paragraph 2: please break up the final sentence into several.

6. "Introduction to network meta-analysis", paragraph 1: "because the studies themselves were not randomized" is ambiguous. Although the alternative meaning contradicts the definition of RCT, it could still be confusing.

7. "Rationale and caveats for including non-randomized comparative cohort studies in NMA", paragraph 3: It would be useful to discuss at least one alternative to the ITT approach and why it may result in a different estimate.

8. "Network meta-analysis of RCTs and non-randomized comparative cohort studies", paragraph 3: "There is limited research in this area, especially the latter two approaches." Actually there currently seems to be significant interest in this area. It would be fair to say that little has been published so far, though.

9. "Network meta-analysis of RCTs and non-randomized comparative cohort studies", paragraph 5: "requires considerable time, effort, and costs than including only RCTs." needs to be reformulated.

10. "Network meta-analysis of non-randomized comparative cohort studies in large distributed data networks", paragraph 3: "more assessable for analysis by others", should that be "more accessible"?

11. Figure 1/2: The caption could be expanded to explain the content of the subfigures.

12. Figure 2A, left panel: "True treatment effect small of negligible" - small OR negligible.

13. Figure 2A, middle/right panel: "less exaggerated" is strange here, because it precedes "exaggerated". Either reverse the order of the panels, or change the wording (e.g. "somewhat exaggerated" vs "greatly exaggerated").

Level of interest: An article of importance in its field

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

Declaration of competing interests:

I declare that I have no competing interests