Reviewer's report

Title: Network meta-analysis incorporating non-randomized studies for assessing medical product safety: pitfalls and opportunities

Version: 2
Date: 6 June 2015

Reviewer: Gert van Valkenhoef

Reviewer's report:

Major compulsory revisions
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1. The authors address an interesting and timely topic, the inclusion of non-randomized studies in network meta-analysis. A few of these studies have already appeared, and a treatment of the assumptions underlying such analyses, as well as the various options available for conducting them, is very welcome. I appreciate the balanced account of assumptions underlying network meta-analysis as well as the impact of confounding. However, as a "Methodology" paper the current account seems rather thin. I would suggest that the authors add much more detail on the methods they describe, as well as worked examples and/or simulation studies to contrast them if they wish to present this as a "Methodology" article. Otherwise, I think the work would be more suited as a "Commentary" paper. I think it could be an excellent commentary on the current state of the art, if my other comments below are addressed.

2. The manuscript contains many confusing and/or grammatically incorrect sentences. The authors need to carefully proofread their work and correct it to avoid confusion. Examples:

   - "Conduct of network meta-analysis of non-randomized studies", paragraph 1 - "although the methods have been largely applied to RCTs" does not fit the sentence.
   - "Conduct of network meta-analysis of non-randomized studies", paragraph 2 - "but with additional risk of bias given these studies have may stil also be limited" does not make sense.
   - "Conduct of network meta-analysis of non-randomized studies", paragraph 3 - "Some non-randomized study designs and some may be better suited for network meta-analysis than others." does not make sense.
   - "Comparing and combining findings from non-randomized studies with RCTs", paragraph 1 - "to evaluate the comparative performance nonrandomized studies and" does not make sense.
   - "Future directions", paragraph 1 - "the likelihood that patients are more similar among compared with inclusion of" does not make sense.
3. "What is network meta-analysis?", paragraph 1 - "The key assumption underlying any meta-analysis is transitivity of the studies." - it would be more accurate to say the key assumption is "exchangeability of the studies", and the following two sentences do indeed characterize exchangeability, not transitivity. This assumption is also present for pair-wise meta-analysis. The difference is that in pair-wise meta-analysis, the violation of that assumption can only lead to heterogeneity, whereas in network meta-analysis it can lead to non-transitivity of the relative treatment effects (which is loosely the same thing as inconsistency). I think the observations made at the end of the paragraph regarding pair-wise meta-analysis would also be more clear if framed in this way. The work by Jansen & Naci (2013) that the authors cite provides a similar framework (as do several more technical papers by Lu & Ades).

4. "Conduct of network meta-analysis of non-randomized studies", paragraph 3 - "The network meta-analytic methods chosen will depend on the study designs of non-randomized studies." - This statement is entirely vacuous. The authors do not specify which methods of network meta-analysis are to be considered, nor which characteristics of the design of non-randomized studies should impact the choice, or how. The remainder of the paragraph seems to deal with methods to adjust for confounding in observational studies, which is a different issue.

5. "Comparing and combining findings from non-randomized studies with RCTs", paragraph 2 - "Alternatively, non-randomized studies could be incorporated as prior information if a Bayesian approach is used." - Please explain how that is different from naive pooling?

6. "Comparing and combining findings from non-randomized studies with RCTs", paragraph 2 - none of the alternative approaches to incorporating non-randomized evidence are discussed in any detail. This section needs to be expanded greatly to enable the reader to understand the issues at hand. Especially the bias adjustment models need further description.

7. "Future directions", paragraph 1 - "albeit at a potential cost of reduced precision." - It is unclear to me whether this would result in an undesirable loss of precision, or the (desirable) elimination of double counting.

8. "Future directions", paragraph 2 - "has used pair-wise meta-analysis to combine data within CNODES" - please explain what this means exactly? Are results from CNODES themselves the result of meta-analysis? Would that not jeopardize the ability to correct for confounding in a consistent manner? What about the possibility of double counting of participants (as mentioned in the previous comment) if pair-wise meta-analysis is used?

Minor Essential Revisions
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9. "What is network meta-analysis?" paragraph 1 - "all treatments included in the network meta-analysis could have been included in a trial" - would be clearer to
say "a single trial" or "the same trial" (especially given that observational studies are also considered). Perhaps it would be useful to explicitly use "jointly randomizable".

10. "Conduct of network meta-analysis of non-randomized studies", paragraph 1 - "The validity ... comparisons." - this characterization seems better suited to the section introducing network meta-analysis assumptions. I don't have a problem with the reminding the reader of this assumption and that it is especially problematic for non-randomized studies, but this is not the place to introduce the concept.

11. "Box 1" - "The application of network meta-analysis in non-randomized studies is more complex and less understood than traditional approaches for stakeholders." - the phrase "for stakeholders" doesn't connect well with the remainder of the sentence. Please rephrase. It is also unclear if "traditional approaches" refers to pair-wise meta-analysis incorporating non-randomized studies, or to network meta-analysis with only randomized studies.

12. "Box 1" - point 4 under disadvantages seems redundant / overlapping with point 1. Please distinguish them more clearly.

Discretionary Revisions

13. "What is network meta-analysis?" - I would prefer a section heading that is not a question.

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

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

Declaration of competing interests:

I declare that I have no competing interests