Author's response to reviews

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

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Author's response to reviews: see over
Dear Systematic Review Editors:

Thank you very much for giving us the opportunity to resubmit our manuscript “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”. We appreciate your helpful comments and suggestions. Based on the reviewers’ suggestions, we have revised the manuscript. Below are our responses (in bold) to address the concerns raised by the reviewers. We hope you find them satisfactory. We have attached a revised version of our manuscript with the outlined changes.

Reviewer #1:
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.

We have revised the figure. The ‘Combined' clearly indicates this is an NMA combining randomized and non-randomized studies.

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).

We have made the suggested edits and made the abstract more concise.

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.

We have made the suggested edits and provided more description about Bayesian hierarchical model.

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.

**We have made the suggested edits.**

5. "Background", paragraph 2: please break up the final sentence into several.

**We have made the suggested edits.**

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.

**We have removed the sentence to avoid confusion.**

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.

**We now describe several additional analyses that can be done in RCTs or non-randomized studies, such as as-treated analysis and per-protocol analysis, and provide a nice reference by Hernan and Hernandez-Diaz that compares these different analytic approaches.**

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.

**We have added the term “published” to reflect this: “There is limited published research in this area, especially the latter two approaches.”**

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.

**We have made the suggested edits.**

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"?

**Corrected.**

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

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

Corrected.

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").

Corrected.

Reviewer #2
14. Lines 92-4: “…a NMA of RCTs…is not randomized evidence because the studies themselves were not randomized”. This sentence seems out of place here; the paragraph might be strengthened by removing the sentence or adding detail to put it into context.

We have removed this sentence to avoid confusion.

15. Lines 183: Should be “…considerably more time, effort, and costs…”

Corrected.

16. Box 1, 2nd advantage point: By definition, an NMA assesses multiple treatments simultaneously, regardless of whether observational data is included. Rather, it is worth clarifying that observational data might improve network density and could connect disconnected networks.

We have added a bullet reflecting this comment in Box 1.

Reviewer #3
17. There is no discussion here regarding meta-regression. If you have access to distributed data networks, the more powerful approach would be to perform meta-regression using the individual patient data from observational studies as well as RCTs. This is critical, because even if the estimate from cohort study is unbiased, the population may differ from RCTs.

We have added a paragraph addressing this comment (third paragraph of the “Network meta-analysis of non-randomized comparative cohort studies in large distributed data networks” section).

18. Lines 182-185. The differences in costs of performing NMA with observational evidence are mentioned, but it would be more useful to suggest possible restrictions
regarding quality of observational studies, especially with respect to types of analyses that minimize risk of confounding (i.e. propensity score matching etc.).

**We have added a paragraph highlighting this.**

Minor revisions:
19. Line 51: It's not clear if including non-randomized trials is desirable, although you could argue it should be 'considered'

**We have edited the sentence, it now reads “inclusion of non-randomized studies may sometimes be considered”.

20. Line 105: 'been' should be change to 'be'

**Corrected.**

21. Lines 128-140: The authors seem to assume that high quality observational studies will not have differences in treatment effect modifiers, which is not necessarily the case. While it is imperative to assess quality, especially for cohort studies, this paragraph should be revised to avoid confusing these two ideas.

**We have added a sentence at the end of this paragraph to address this issue**

22. Line 135: How is GRADE specific to NMA context? Please clarify.

**The paper referenced describes a four-step approach to rate the quality of evidence in each of the direct, indirect, and NMA estimates based on methods developed by the GRADE working group.**

23. Lines 137-138: check capitalization for STROBE when written in full

**Corrected.**

24. Line 183: replace 'than' with 'as compared to'

**Corrected.**

25. Line 220: grammar is incorrect - needs to be rephrased

**Corrected.**