Reviewer's report

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

Version: 2
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Reviewer: Shannon Cope

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Overall:
The authors have developed a commentary based on their expertise that addresses an important topic. This is a timely question that requires careful consideration and this paper can help provide the background to educate readers on the relevant issues. However, a more in-depth exploration of the issues surrounding this topic would improve this commentary.

Major revisions:

1. Throughout the paper, the term ‘non-randomized studies’ is used; this is a very broad term that includes many different types of study designs. Although the authors seem to restrict their discussion to comparative (cohort?) studies, this is not clear. Given the target audience of this commentary, it is important to differentiate the types of non-randomized studies that are explicitly considered for inclusion in NMAs by the authors as well as those that are not. For example, the authors have not addressed single-arm studies, which may provide the link for an otherwise disconnected network. Therefore it is critical that the authors provide clear overview of study types and how each is considered (or not considered) in context of NMA.

2. The third paragraph of introduction suggests few NMAs have incorporated non-randomized studies and identified four references. Although this statement is fairly subjective, it should be clarified that the identification of these references was not systematic and that only examples are provided. A review by Verde et al. 2015 has identified three additional clinical applications which should be referenced at a minimum (Combining randomized and nonrandomized evidence in clinical research: a review of methods and applications. Research Synthesis Methods 6(1):45-62). Highlighting the need for a more systematic approach to answer these questions, while acknowledging the challenges of doing so (given differences in terminology of non-randomized studies etc.), would strengthen this paper.

3. The first paragraph focuses on adverse events and refers to Box 1. However, the logic provided in Box 1 is not limited to adverse (or rare) events. The paper should either be broadened to all outcomes or be updated to include a clear rationale for a focus on adverse events. There is already much more acceptance in looking beyond RCTs for adverse events, given the often huge amount of
uncertainty in NMA of AEs (especially in more complicated or sparse networks). Therefore, the broader question regarding use of non-randomized trials for all outcomes may provide a more useful commentary, in additional to providing a more relevant exploration of the costs and benefits of this additional evidence.

4. In the second paragraph of ‘Comparing and combining findings from non-randomized studies with RCTs’ the authors identify the methods of one example where non-randomized studies were included (i.e. Hutton et al.). However, there is no mention of the methods that were used by the other clinical applications. This seems highly pertinent to understand what is currently being done in the identified examples. Since high impact journals such as BMJ are open to analyses incorporating non-randomized evidence, the quality of the existing applications has clear implications regarding importance of alternative methods for including non-randomized evidence.

5. The methods by Schmidz et al. are summarized briefly (as was done by Verde et al.); however, these references are not complete (i.e. missing Soares et al. 2014; McCarron et al. 2010/2012). Due consideration for these papers is required at minimum.

6. The first paragraph regarding ‘What is NMA’ provides useful introduction for readers not familiar with this type of analysis. However, there are several papers dedicated to assessing the transitivity assumption and Figure 1 does not seem to do justice to the existing literature in this area. Similarly, several key references are missing from the methods regarding identification of inconsistencies. Since this background regarding NMAs is well established in the literature, authors should reference the work more completely, or assume a more informed reader and provide a more in-depth discussion regarding the differences when considering non-randomized evidence.

7. In the paragraph addressing ‘Confounding in randomized trials and non-randomized studies’ it is unclear what is meant by ‘unadjusted confounding’. Prior to this sentence authors identify the risk of differences in unmeasured treatment effect modifiers. If the differences are unmeasured, adjustments will not reduce bias unless adjusting for a specific kind type of bias that is expected – therefore this is confusing and needs to be clarified. References on adjusting for bias in NMAs would strengthen this section (if that is the intent).

8. The third paragraph in ‘Conduct of network meta-analysis of non-randomized studies’ begins to address the assessment of transitivity in non-randomized trials. However, the background regarding NMAs does not properly emphasize the importance of identifying potential treatment effect modifiers a priori, which has been recommended in several guidelines and has very important implications for how non-randomized evidence is considered. Since NMAs have already started to consider non-randomized studies, ensuring the process to do so is robust may be the most important message, and therefore should be addressed more specifically. Along these lines, emphasizing the process to assess quality of non-randomized studies and the challenges in doing (tools to do so etc.) improve the manuscript.
9. It would be interesting for authors to assess the conditions under which exploring non-randomized trials would be expected to provide additional benefits beyond the expected costs. Given the absence of clear guidelines or agreement from HTA agencies, it seems that there is an opportunity to highlight the lack of consensus on how best to handle non-randomized trials in the context of NMAs and to provide suggestions.

Minor revisions:

1. The introduction states that RCTs are preferred for methodological reasons. However, it seems these reasons should be outlined more clearly as the subsequent sections assume a fairly naïve reader. The research question really hinges on whether it is worthwhile to explore other evidence despite the ‘well-established methodological reasons’, and therefore this should be clear in the beginning (rather than specifying this later on).

2. The first paragraph regarding ‘Conduct of network meta-analysis of non-randomized studies’ does not seem to provide any information that is specific to including non-randomized trials and could be eliminated.

3. The second paragraph in ‘Conduct of network meta-analysis of non-randomized studies’ addresses the advantages of considering non-randomized evidence. This would be more helpful in the introduction to justify the research question.

4. The paragraph addressing ‘Confounding in randomized trials and non-randomized studies’ is important for readers to understand the risk of including non-randomized studies. Figure 2 is useful in this sense, although does not seem to acknowledge possibility that confounding could lead to smaller (biased) treatment effect in non-randomized trials. Literature regarding bias (and direction of bias) would improve this section.

5. The practical implications of considering non-randomized studies for a systematic review (or HTA) process in terms of additional time, costs, and overall impact on decision-making have not been discussed, which would seem important given the audience.

**Level of interest:** An article whose findings are important to those with closely related research interests

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

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interest.