Reviewer’s report

Title: Vibration of effects from diverse inclusion/exclusion criteria and analytical choices: 9,216 different ways to perform an indirect comparison meta-analysis

Version: 0 Date: 21 Jun 2019

Reviewer: Evan Mayo-Wilson

Reviewer's report:

This is a very interesting study. It's been well conducted and written clearly, and it would be of interest to a general audience. My questions are mostly related to the interpretation of results.

The authors could clarify the research question this study answers. That is, the "vibrations" observed in this study are attributable to many sources, including different inclusion criteria and different statistical methods. Some of what the authors call "analytical choices" or "methodological choices" would fundamentally change the question that a systematic review or meta-analysis sought to answer; these aren't just minor changes to the methods of analysis. "Positive" and "negative" results from different meta-analyses aren't necessarily contradictory if the inclusion criteria are so different that the results would apply to different research questions.

Could the authors say more about the combinations of methods that produced the extreme results - Are these methods plausible? At the extremes, are the inclusion criteria and the statistical methods ones that we might expect to see in a real paper, or are they obviously strange (e.g., clinically heterogeneous studies combined using fixed effects)? The discussion explains that some combinations of methods wouldn't make sense in a normal systematic review and meta-analysis - do they only observe extreme results by using unlikely combinations of methods, or do realistic combinations also produce discordant results?

Could the authors clarify how they decided to select a source (e.g., journal article or conference abstract) and to extract results for inclusion in the meta-analysis when multiple results were available for the same study? The authors refer to a paper I wrote (Ref 97), in which we described the impact of using different data sources for the trials in a meta-analysis. We also found that some sources included numerous outcome definitions and methods of analysis, leading to multiple results in the same source for a single outcome domain (https://www.ncbi.nlm.nih.gov/pubmed/28529187). By cherry-picking results from each included study, we could change the results of our meta-analyses without changing either the trial inclusion criteria or the methods of meta-analysis. The authors partially address this issue by including three "outcomes" (which aren't defined completely using all 5 elements, e.g.,
If the authors haven't considered multiple outcome definitions and multiple results from each eligible study as a potential source of VoE, then the authors might have underestimated the extent to which meta-analysts could fiddle their results.

I think the discussion is very good, but I'd like to know more about how the authors suggest we apply VoE in practice. I assume VoE might help identify which methodological choices are most influential - could the authors say more about how a systematic reviewer / meta-analyst might look for the major sources of "vibration"? How would we use this method alongside GRADE or other frameworks for describing our confidence in evidence - would you use this as evidence to downgrade, for example?

If many results are possible, which result should we trust? The authors note that most meta-analyses are retrospective, so the meta-analytic result following pre-specified methods might be problematic if authors knew a lot about the eligible studies before starting a study. The average VoE result might not answer a clinically meaningful question. The extreme VoE results might answer clinically different questions. I expect we'll find many meta-analyses where we can change the results by fiddling the data - Is this necessarily a problem? The authors have artfully shown what a mess we're in. How do we make sense of this?

Having done this VoE analysis, what do the authors think about the true difference between these drugs? Did this VoE analysis change their previous interpretation of results?

Could the authors expand the legends and include some additional guidance about how to read / interpret the figures? I think I understand Figure 1, but the shapes of Figures 2 and 3 make them relatively more difficult to interpret. Figure 2 looks like it might be a map of an island? Please, could you walk readers through these figures?

Minor points:

Appendix 3 is unusual. A table (e.g., usual Cochrane format) might be easier to follow.

Are "congress abstracts" conference abstracts? The former term seemed unusual to me.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Not applicable
Are the conclusions drawn adequately supported by the data shown?
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