Reviewer’s report

Title: Emergent approaches to the meta-analysis of multiple heterogeneous complex interventions

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Reviewer: Nicky Welton

Reviewer’s report:

This is an interesting brief discussion of methods to deal with meta-analysis of complex interventions, that are by nature heterogeneous. I wasn’t clear if the paper was intended to be a comprehensive review of methods to date, or just to pick a few examples to illustrate some points. There is little substantial new material, except to distinguish between theory-lead approaches, and components-lead approaches, but the paper does give a critical appraisal of the pros and cons of the different approaches. Perhaps what is needed is a clearer motivation of why this discussion is needed (and lacking from the literature?) and what the paper adds. I think there are other problems that arise in trials of complex interventions (eg outcomes, and populations/settings), and perhaps the paper would benefit from mentioning some of these issues in discussion.

Major Compulsory Revisions

1. “Multiple Interventions Meta-Analysis” … there are many terms out there now, Mixed Treatment Comparisons, Network Meta-Analysis, Multiple Treatments Meta-Analysis. Give all as keywords, and introduce all at the beginning of the introduction (then can just pick the term you are most comfortable with subsequently). Note that Indirect Comparisons are not exactly the same, as these are only for star-networks where no direct evidence is available on the focal comparison.

2. In general referencing of the NMA literature is to very recent work, when in fact the methods have been around for a long time (dating back to Higgins and Whitehead in the 1990’s, Ades and Lu Stats in Med 2004, Caldwell et al BMJ 2005, and most comprehensively the series of papers in the MDM special issue 2013, vol 33 pp 597-691.

3. The structure might work better if you first introduce the two different approaches, and then provide a discussion of the pros and cons of each?

4. I think the two approaches are trying to answer different kinds of questions, so which to use will depend on what your objective is … In practise the definition of the components is the key thing, and should certainly be informed by theory and subject experts. So in practise there is a blurring of the two approaches.

5. p.7 top para I found this argument confusing to follow. Could you clarify?

6. In discussion; the problems here also hold with other kinds of heterogeneous interventions (eg doses) – there is probably a large body of literature to include (eg Naci et al BMJ 2014;349:g5741, Soares et al. Health Technology
Assessment 2012 16(7))

7. p.9 “Benefits and Drawbacks” The issue of heterogeneity is important and should be explained more clearly. By using theory approach you may be combining interventions that are in practice quite different (but motivated by the same theory). This means heterogeneity in outcomes from these interventions is more likely than where interventions are classified using components which more closely describe what is done when delivering the intervention. But this may not be the case, it is only an assumption. As said before the two approaches answer different questions.

8. p.9 lines 11-15 I found this confusing (& I wrote ref [26]!) I think you mean the additivity assumption?

9. p.9 lines 20-22. The answer to this question is that that combination represents the interventions with those combinations in the trials included in the systematic review. However, may have implications for design of new interventions (together with theory of course)

10. Consistency assumption. This isn’t really dealt with very clearly, in particular how this may due to heterogeneity in interventions, and better taxonomies may help explain inconsistency.

Minor Essential Revisions

11. p.8 line 11 “[26] observe” reword to “[26] propose”? In fact the meta-regression approach is pretty much equivalent to NMA with components, but provides a structured way to explore lumping together of component combinations (if sufficient data to allow this). Another reference I think it would be appropriate to include is: Madan et al JRSSA 2014 177:295-314 (and the HTA report it cites with full details: Chen et al)

12. p.10 lines 20-21. Convergence shouldn’t be a problem as long as evidence network connects. Cannot do the analysis if this is not the case. With complex interventions it may not be straightforward to assess if the network connects for a given outcome.

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

Quality of written English: Acceptable

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

Declaration of competing interests: 

I declare that I have no competing interests