Author's response to reviews

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

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Author's response to reviews: see over
To the Editor

Thank you for your comments, and for the comments of our reviewers. We have addressed them comprehensively below, and we feel they have made this paper much better.

On the whole, we have attended to drawing a clearer need for this specific analysis in the background to our discussion, and to linking this more carefully to the range of questions that could be asked about complex interventions through meta-analyses. We locate our discussion specifically in the need to understand how this particular statistical method can be transferred from pharmacological/clinical interventions to complex psychosocial interventions, especially in light of little specific treatment of this in prior publications.

We look forward to your reply.

With thanks and best wishes

G.J. Melendez-Torres, with Chris Bonell and James Thomas

Reviewer 1 (Dr Nicky Welton)

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.

- Thank you for these comments, and for your helpful advice below. We have offered a clearer steer as to what this paper adds and why it is important. We locate this in the context of our discussion of how previous treatments of this topic have not considered specifically the challenges of grafting this statistical method onto non-pharmacological interventions. Starting on page 4 line 6, we develop the critical disjunction between uses of this method in pharmacological interventions and in psychosocial interventions. We further discuss how the goal of this paper follows on from this key difference in lines 22-24 on page 5. We then draw out through the entire discussion how the specific questions each method asks are key to understanding complexity of interventions.

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 in available on the focal comparison.
• We now introduce these and highlight our term of choice. We also include these additional terms as keywords.

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

• We now acknowledge the ‘historic’ dimensions of these methods including these citations and others.

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?

• In response both to this point and your point below—we now provide first a brief overview of the different approaches and the questions they seek to answer, then discuss the pros and cons of these in the body of the discussion, and then summarise this in the conclusion. Thank you for offering this key additional viewpoint.

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.

• This is certainly an area that requires further methodological research. We now discuss this on page 15, lines 3-11.

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

• The core of our assertion here is that there may be cases when statistically it will be helpful to split nodes due to different distributions. Lines 3-20 on page 8 now better capture this key distinction.

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))

• We address this, and your point below, in our discussion (see the section Implications for Research). Specifically, we address the importance of careful selection of effect modifiers across trials. Thank you for flagging this opportunity for additional depth in our discussion.

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.
This has sparked for us an additional discussion of the ‘causal interpretations’ implied by these two approaches. Thank you for this critical insight. We discuss this in depth in ‘Implications for Research’.

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

- We have clarified this and we hope you agree that this discussion, with the additivity assumption included, is clearer.

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)

- We agree that the answer to this question may appear at face to be obvious, but we have flagged the subsequent considerations for intervention implementation and design.

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

- We now discuss this more closely at the end of the section on benefits and drawbacks of the clinically meaningful units approach.

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)

- Thank you for this suggestion. We have adjusted this wording and brought through more clearly that these approaches are ‘more equivalent than not’. We have also cited the Madan paper in the same section. We read Madan et al in preparation of this article and are pleased to have the opportunity to include it in this revision.

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.

- We have removed this confusing reference to convergence and replaced it with a discussion of inadequate data.

Reviewer 2 (Dr Howard White)

These are all discretionary revisions
I am not that keen on the use of the word complex, although I recognize it is now common. Patricia Rogers has distinguished between complex and complicated. Complicated are interventions with many components. Complex has complex causal pathways which are difficult to disentangle (I don’t agree, but that is how it’s presented). Anyway, the definition used by the authors seems to fall somewhere between the two: multiple components, but with some interest in interactive effects.

So my main comment is that there is something of a disconnect between the different parts of the paper. As presented, the method can generate comparisons of A vs B, A vs C and B vs C. But we also want A+B vs C (and if there is no untreated, treatment as usual or placebo control, vs that also), A+C vs B, B+C vs A, and A+B+C vs control. Can the method do that? (I assume so if there are some factorial designs in the set of studies available for meta-analysis, but the authors need make this explicit).

Once that issue is addressed, then there can be a discussion of ‘disentangling’. Studies may not be a factorial design, but just of say A+B. So if we have studies of A and B separately, we can presumably use these data to estimate the effect s of A and B, and synergy or redundancy from having the two components together in the A+B study.

- Thank you for these insightful comments, and for your views on the suitability of this paper for publication.
- The definition of complexity we use is indeed somewhere between the two different definitions Rogers proposes. For example, we cite specifically the MRC complex interventions definition (Craig et al., 2008) in our discussion. That said, you raise an interesting distinction between complexity and complicatedness in interventions. Both methods we present here may be used to assess complexity and complicatedness in the ways in which they manifest in interventions.
- We have addressed your additional comments in several different ways. First, we do this by highlighting the differences in execution and in question addressed by both approaches. To the extent that the two approaches we highlight answer different questions, there may well be somewhat of a disconnect. The degree to which these to approaches are commensurate or incommensurate is discussed in the section on ‘Implications for Research’. Second, we address your comments about synergy and redundancy by pointing out that interaction terms are key in understanding ‘interactive component models’ as applied in multiple interventions meta-analysis.