Author’s response to reviews

Title: Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis

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Author’s response to reviews:

1. First, it is not true (as has been stated in the abstract and article) that this is the first individual homeopathic treatment meta-analysis. At least two and possibly three previous meta-analyses have looked at individualized homeopathic subgroups.
   • Ours is the first systematic review and meta-analysis that has used rigorous and up-to-date methods to focus solely on RCTs of individualised homeopathic treatment. We have inserted a clarifying statement, with references, at the beginning of paragraph 3 of Introduction. The abstract has also been suitably amended.

2. The statement on page 3, line 95 that the other reviews have combined all forms of homeopathy is also not true. Several of the other meta-analyses did subgroup analysis that did distinguish between the different types of homeopathy.
   • In the main text, this is the first statement on the subject. The above amendments (#1) are located here.

3. Page 4, line 102 needs explanation. The authors say that previous meta-analyses were lacking but do not describe what that those lacking areas were. It does not appear that they've used anything different in this meta-analysis.
   • We are referring here to the meta-analysis by Linde & Melchart 1998, whose methods – by the authors’ own admission – were sub-optimal. We have removed the word ‘lacking’ and replaced the entire sentence with a more explicit statement. The Linde & Melchart paper has been critiqued by the University of
4. Page 4, line 121. Many experts in meta-analysis say that combining multiple clinical outcomes into a single measure is not appropriate. And yet that's what these authors have done. They need to more fully justify doing that given the heterogeneity of the studies.

- As for the previous studies of homeopathy RCTs that have adopted this approach, we recognise the cautionary limitations of pooling together the data from diverse medical conditions and outcome measures. Thus, a given pooled effects estimate here has no absolute meaning: it is a summary measure that enables statistical significance and ‘mean effect size’ to be attributed and interpreted, and in the context of our hypothesis that individually prescribed homeopathic medicines have specific effects. We have inserted a statement of this nature as a new paragraph in Discussion.

5. Page 5, line 133. There is some concern over the search strategy implemented in PubMed. NOT(animals[mh] NOT humans[mh])”I am not quite clear why this was done as well as some of the other terms. The authors should have chosen limiters rather than putting those terms into their search like random, etc. Also, homeopathy is a MeSH term and that should have also been chosen rather than the * terms for a more comprehensive search. The author should ensure all literature relevant was captured.

- The terms comprise a Cochrane Highly Sensitive Search Strategy and are identical to those detailed in our previous publication (Mathie et al 2013). We agree that the double ‘NOT’ seems unusual, but it has proven its worth in practice. Using the search terms again in PubMed (28 October 2014) identified a relevant list of 767 references. Unequivocally we have maximised literature capture, as evidenced by the scope of the databases interrogated and the total number of true RCT records obtained from them (Mathie et al 2013).

6. I was surprised to see that the Davidson et al. homeopathy systematic review on psychiatric disorders was not cited in this paper.

- Given the focus of the Davidson review on all placebo-controlled RCTs of homeopathy for psychiatric conditions, we did not judge it directly relevant in the context of our own systematic review. However, if the referee has identified a suitable location for its insertion, we shall be glad to do so.

7. Page 5, line 137. How did the authors know that the patients did not get a combined or mixed approached homeopathy - which is commonly done in practice?

- Our careful reading of the original RCT papers ensured we attributed a trial as individualised homeopathy only when that approach was clearly described.
8. Page 5, line 139. The fact that the practitioners were not blinded to the assigned intervention when selecting the studies for the meta-analysis opens itself to bias in the selection of studies. Homeopathic practitioners should not have been the ones allowed to select the studies.

• This is a misunderstanding of our term ‘the trial team’: we have changed this to ‘the trial’s team members’ to clarify we are referring to the original trialists, and not to our own review group.

9. Page 5, lines 144 to 147. While the Linde approach to selecting the main outcome measures is reasonable, the World Health Organization approach does not seem to have been validated. The authors need to justify its use here. Who did the selection of the outcomes and was it conducted in duplicate with a third reviewer confirming agreement? This needs to be detailed in the methodology.

• The WHO approach is a robust, internationally accepted, method to ensure that the selected outcome is the most important to the functioning and health of the patient, and so it ensures consistent selection of the most objective outcome per trial. We have inserted a statement of this nature in ‘Outcome definitions’, and we have clarified our consensus approach in ‘Data extraction’.

10. Page 6. The authors do not demonstrate that their selection and quality assessment approach is reliable. What was the Kappa between the two reviewers who are involved in this judgment? What was the percent disagreement needing third party resolution? How was that resolution obtained?

• Given our methods are founded closely on those of Cochrane, we have been guided in not using the kappa statistic by the cautionary words on this subject in the Cochrane Handbook:

  o ‘It is not recommended that kappa statistics are calculated as standard in Cochrane reviews, although they can reveal problems, especially in the early stages of piloting. Comparison of a value of kappa with arbitrary cut-points is unlikely to convey the real impact of any disagreements on the review. For example, disagreement about the eligibility of a large, well conducted, study will have more substantial implications for the review than disagreement about a small study with risks of bias.’

11. There is concern in the fact that the studies either rated as uncertain risk of bias or high risk of bias. I would think this be a red flag not to proceed with meta-analysis techniques and more so examine the gaps in the research methods to date to improve the research field. Those studies with uncertain or high ROB should not be trusted as much as the studies with low ROB. I appreciate the sensitivity analysis of the uncertain ROB to the high ROB but this
does not demonstrate much, what you want to see is that those studies do not differ from the low ROB studies, which you found none meeting that criteria.

• We are not sure whether the referee has noted our sub-group of three trials that we designated ‘reliable evidence’. Fig 4a, Fig 4b and Fig 5, and associated comments in Discussion and Conclusions, make it clear that our meta-analysis was robust to sensitivity analysis based on a range of study quality. High RoB trials themselves did not display a significant pooled effect; this fact is also reflected in Discussion.

12. Page 6. It's not clear how the research sponsorship was taken into account for the sensitivity analysis.
• We define this point in ‘Assessment of risk of bias’ and the findings are presented in sub-group analysis (Additional file 9). We are not sure how to make matters more clear.

13. Page 10, line 251. How did the authors determine whether a study was a pilot or not?
• To explain this important point, we have inserted a brief statement in ‘Summary of findings’.

14. Page 16, lines 407-408. This is very awkwardly worded and was also repeated in the abstract; what does it mean that these meta-analysis results "do not necessarily contradict" previous meta-analyses. That's a use of a double negative and should be changed. The sentence is very ambiguous. This is also conveyed in the abstract as well and is quite confusing to the reader as the author is stating (1) that this is the first of its kind and then (2) that this one is not necessarily contradicting previous meta-analysis of its kind. This needs attention.
• We have amended the offending phrase, and have clarified that we are comparing our related data to our newly published analysis of sub-groups of data that were not separately analysed by Shang et al (2005); reference to that new analysis has been inserted. Conclusions, in the main text and in the Abstract, have also been clarified.