Author's response to reviews

Title: Homeopathy for Allergic Rhinitis

Authors:

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Version: 3
Date: 18 April 2014

Author's response to reviews: see over
From,
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18th April 2014

To,
Dr. Mark Rogers,
Editor,
BMC Systematic Reviews

Subject: Resubmission after review MS: 6829843531197782

Dear Dr. Rogers,

Thank you for inviting us to resubmit the systematic review protocol, ‘Homeopathy for Allergic Rhinitis’ after addressing comments made by the reviewers and the editor. We wish to thank the reviewers for their helpful and generally positive comments. These have been addressed in detail (see table below).

We would like to call your attention to two key improvements. First, the English language limitation for this review protocol has been removed. Second, we have added Dr. Mathie as co-author. Dr. Mathie has extensive experience and expertise with homeopathy research.

As requested, I am submitting the revised manuscript with changes in track. Please do not hesitate to contact us for any further clarifications.

Yours sincerely,

Kushal Banerjee*, Ceire Costelloe, Robert Mathie and Jeremy Howick

*Corresponding Author
## Detailed reply to reviewer comments

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<th>S. No.</th>
<th>Editor’s Comment</th>
<th>Author Response</th>
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<tbody>
<tr>
<td>1.</td>
<td>Can you please ensure that your abstract is formatted correctly. This should be structured into separate sections: Background, the context and purpose of the study; Methods, how the study was performed and statistical tests used; Results, the main findings; Conclusions, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract.</td>
<td>Thank you for the opportunity to format this according to separate sections. The relevant headings have been added. Abbreviations have also been removed. The reference to a published guideline has been removed.</td>
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<td>2.</td>
<td>Systematic review registration, if your reports the results of a controlled health care intervention, please list your registry, along with the unique identifying number (e.g. Systematic review registration: PROSPERO CRD0123456789). Please note that there should be no space between the letters and numbers of your registration number.</td>
<td>The systematic review protocol has been registered on PROSPERO and the article has been amended to state this (page 4). I have ensured that there is no space between the letters and numbers of the registration number.</td>
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<td>3.</td>
<td>Please state that all authors have approved the manuscript in your author contributions section.</td>
<td>This statement has been added in the revised manuscript (page 19)</td>
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<td>4.</td>
<td>Please state clearly whether or not you have funding in the acknowledgement section. If there is no funding, please state this.</td>
<td>I can confirm that we have no funding for this review and that a statement to this effect has been added to the revised manuscript (page 20).</td>
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**Referee’s Comments**

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<tr>
<th>Referee 1:</th>
<th>This protocol appears to have been registered on PROSPERO. Please include the PROSPERO registration number.</th>
<th>Please see point 2.</th>
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<td>Referee 1:</td>
<td>A recurrent concern in homeopathy research is the potential for confounding and bias to influence results. The authors state that they will use the Cochrane risk of bias tool which has generic instructions for making judgments for each of the domains. I was wondering if the authors had considered giving a priori statements on how judgments for these domains will be applied in this particular review? e.g. what constitutes sufficient blinding for each form of homeopathy (classical, clinical, complex)?</td>
<td>We agree with this. We shall reflect the Cochrane risk- of –bias tool in the same way for each form of homeopathy: there is no reason to consider different criteria for participant blinding, for example, since we would require an explicit statement for each trial that test and placebo pills were identical in appearance, taste etc. How the form and quality of homeopathy impinge on a trial’s findings is a matter for model validity, and a method to assess this attribute of trial validity has been developed within the authorship of our group. Such assessment is taking place in another strand of systematic review in homeopathy.</td>
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<td>Referee 1:</td>
<td>Referee 2: Major issue - the definition of allergic rhinitis. This is done entirely on nasal and eye symptoms. This raises several</td>
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<td>Since the Cochrane risk of bias tool only rates the processes of randomisation and allocation concealment, rather than the outcomes of these processes, the authors may also want to assess the baseline comparability of treatment groups in terms of known prognostic variables.</td>
<td>The suggestion of this referee is reasonable. The number of sub-groups have been reduced and primary and additional analyses have been clearly defined (page 18). We have now added a statement clarifying that the sub groups may be insufficiently powered to detect statistical significance and that the analyses will be undertaken for the purpose of hypothesis generation only (pages 18).</td>
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<td>Comparability of groups at baseline is readily accommodated in Cochrane domain VI (other risk of bias). We will compare studies for prognostic variables - this will be presented descriptively in table format and we will (if we identify sufficient studies) carry out a crude and adjusted analysis (the adjusted analysis will include prognostic variables). We have now also stated that baseline comparability of treatment groups will be assessed in the section titled 'Measurement of Treatment Effect' (page 15).</td>
<td>The referee has identified an important concern in research involving allergic rhinitis. There is no single standard definition. However, patients are</td>
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<td>Referee 1: The decision to apply a fixed or random effect(s) model should depend on assumptions about whether the studies represent estimates of the same underlying effect or a distribution of effects, rather than some measure of statistical heterogeneity as currently stated.</td>
<td>This referee is correct in identifying a need for further clarification regarding the selection of a fixed or random effects model. Our statement regarding which model to select has been altered (page 16). We now state that both models will be applied. If fixed effect and random effects meta-analyses give identical results then it is unlikely that there is important statistical heterogeneity, and fixed effects modelling result will be presented. If the results vary possible causes of heterogeneity will be examined. This will inform which result should be reported - stable robust techniques with an underlying assumption of a fixed effect (which may be incorrect) or less stable, sometimes unpredictable techniques based on an underlying assumption of random effect (which may be more likely). I² testing will be performed to determine heterogeneity.</td>
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<td>Referee 1: The authors present a reasonably large number of subgroup and sensitivity analyses. Perhaps they should include a statement that their conclusions will acknowledge the potential for spurious statistical significance.</td>
<td>The referee is correct. The formatting, spaces and other typographical issues have been checked and corrected.</td>
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<td>Minor issue with changes in font size and paragraph spacing, and several instances of missing spaces between words</td>
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First, there is no requirement for nasal examination to exclude other diagnoses, such as a septal deviation, or nasal polyposis. Many of these symptoms may also be seen in sinusitis. Even so, it is not clear from the protocol how the reviewers will deal with the situation where not all of the listed symptoms are accounted for. This should be clarified.

12. **Referee 2:** Even so, it is not clear from the protocol how the reviewers will deal with the situation where not all of the listed symptoms are accounted for. This should be clarified.

We have now clarified that the presence of any one of the nasal symptoms will be essential for the diagnosis of AR but nasal blockage alone will not be sufficient for this diagnosis[2] (page 8). Please also see point 11 above.

13. **Referee 2:** Second, many of these symptoms can occur in non-allergic rhinitis and differentiation between allergic and non-allergic rhinitis can be very difficult, even when allergy tests are available. [Even a positive allergy test does not mean that one has allergic rhinitis.]

We disagree with this point. Although there is insufficient clarity in available literature regarding this, the presence of these symptoms and a positive response to skin prick or other allergy tests is widely used as a confirmation of allergic rhinitis. Please also see response to point 11.

14. **Referee 2:** It is recognized that the literature may not have presented diagnostic criteria that allow for an accurate diagnosis of allergic rhinitis and that the best[2] that one may be able to do is to rely upon symptoms. That may be acceptable, if the review were to be called Review of Homeopathy for relief of symptoms consistent with a diagnosis of allergic rhinitis[2], and it is the opinion of this reviewer that this is probably the best approach.

We disagree with this point made by the referee. Multiple reviews [3-6] on allergic rhinitis use the same guidelines/criteria for diagnosis and are considered to be reviews of ‘allergic rhinitis’ and not ‘symptoms of allergic rhinitis’.

15. **Referee 2:** Quality of available trials is poor. What hope is there of achieving an adequate require?

The authors plan to conduct a high quality, well designed systematic review. Sensitivity analyses will be conducted to determine if the findings are robust to the decisions made in the process of obtaining them.

16. **Referee 2:** In the same paragraph, the repeated use of this review[2] is a little ambiguous; the reader may be confused about whether the text refers to [10] or the proposed systematic review.

The sentences have been restructured to mitigate ambiguity regarding the review that is being referred to (page 5).

17. **Referee 2:** Types of interventions: the reviewers will reclassify the homeopathy type according to standard definitions[2][13,14] - these should be stated in the protocol

We thank the referee for this suggestion. We have now quoted the standard definitions and provided a relevant reference (page 10). Examples have been provided for each type of homeopathy.
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<th><strong>Referee 2:</strong> Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing? Yes.</th>
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<td>19.</td>
<td><strong>Referee 2:</strong> Is the planned statistical analysis appropriate? Yes, except that there are very many proposed sub-groups analyses, even though there is expected to be very few studies eligible for analysis. This seems unrealistic. I would urge a rationalization of this list, or a qualification, such as suggesting that specific sub-group analysis amongst those listed will be performed if the is sufficient data available. The number of sub groups have been reduced. We have made statements clarifying that such analyses will only be performed if sufficient data are available and that they are for hypothesis generation purposes only (page 18). Please also see point 9.</td>
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<td>20.</td>
<td><strong>Referee 2:</strong> Is the writing acceptable? Yes.</td>
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