Author's response to reviews

Title: A tutorial on sensitivity analyses in clinical research: the what, why, when and how

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Author's response to reviews: see over
July 2, 2013

Dear Dr Taljaard

RE: MS: 7041318138686307 – A tutorial on sensitivity analyses in clinical research: The what, why, when and how

We thank you for your email with reviewers’ additional comments on our paper. The comments were very helpful. We have revised the paper in accordance with the reviewers’ suggestions Please find attached the revised version of the manuscript. We have highlighted all the changes in YELLOW.

We hope that we have adequately addressed all the issues. Below are the point-by-point responses to the reviewers’ comments.

We look forward to hear from you.

Sincerely,

Lehana Thabane, PhD
Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University
Response to reviewer’s comments

<table>
<thead>
<tr>
<th>Comment</th>
<th>Response</th>
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<tbody>
<tr>
<td>There are a few grammatical errors that I’m sure the editorial staff will address</td>
<td>We have revised the manuscript for grammar</td>
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<td>Section 1.2: I am not aware that sensitivity analyses are generally powered and thus the last sentence of the 1st paragraph is problematic for me. In my clinical trials experience, generally sensitivity analyses are only provided for the primary endpoint and key secondary analyses --- not for all endpoints. I think it would be helpful for the readers to provide a bit more guidance about how to decide which endpoints or outcomes and which issues require sensitivity analyses. – the statement “… if they are sufficiently powered” still remains in the paper and I think is misleading.</td>
<td>We have deleted the statement “if they are sufficiently powered”. Guidance on which outcomes should be used for sensitivity analyses is provided in section 3: Question 6; page 16.</td>
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<td>The 2nd example in Section 2.1 seems unusual. Usually there is greater ability to detect an effect if subjects have severe disease with an effective treatment (i.e., no floor effect). In this example, did one of the groups have a larger number of patients with high values?</td>
<td>In this example, patients with very high baseline levels of depressions were more difficult to treat, and the effect of the intervention in these participants was smaller. A significant reduction in levels of depression was detected when they were excluded.</td>
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<td>The first example in section 2.2 would benefit with more detail. How is the PP analysis set defined? How many subjects are excluded? Also, it may help the reader know that PP provides the best scenario for a treatment to be shown to be effective --- in the group of subjects who comply, while the ITT may provide a better estimate of effect in “real life” where there are subjects who comply and subjects who don’t.</td>
<td>We have also added more detail to the example: definition of PP and numbers excluded. See page 8, example 1. We have added this explanation to the introductory paragraph. See page 7, section 2.2, paragraph 2.</td>
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<td>Section 2.3 has several reasons for missingness that are no focused on RCTs (e.g., registries). The discussion of missing data mechanisms is much improved. However, could you provide an example of MAR, MCAR and non-ignorable</td>
<td>We have provided examples of MAR, MCAR and MNAR that are related to clinical trials. See section 2.3, pages 8-9.</td>
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<td>missingness from a clinical trials perspective?</td>
<td>We have provided more details for both examples. See section 2.4, page 11.</td>
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<td>Please provide more details for the example in Section 2.4.</td>
<td>We have revised the calculation. Instead of looking only at the number of RCTs among studies that report sensitivity analyses, we are also reporting the number of RCTS that report sensitivity analyses among all the RCTs. 18/64 of the medical papers where RCTs, of which only 3 reported sensitivity analyses. We agree that the number is surprisingly low, hence the “raison d’etre” of this paper. We have modified the text and added a footnote to table 1.</td>
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<td>Although you focus more on clinical trials, I believe that Section 1.3 is not informative because you report on only 3 RCTs. I think focusing solely on clinical trials for medical journals (over an expanded period of time) would help us have a more robust sense of the frequency of reporting on sensitivity analyses. It is hard to believe it’s only 20%. Most well-conducted and well-reported RCTs included an ITT and PP or AT analysis set --- a sensitivity analysis as defined in your manuscript.</td>
<td></td>
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<tr>
<td>• The references have not been edited to exclude meta-analyses and other observational studies</td>
<td>The reference list has now been updated. The references to meta-analyses and observational studies have been removed.</td>
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<td>Table 1. Note that you provide the number of publications with statistical analyses, not the number of statistical analysis (right?) Your footnote (&amp;) notes 3 + 6 studies which does not equal 13 provided in the table</td>
<td>This error has been corrected</td>
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