Reviewer's report

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

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Reviewer: Rolf Groenwold

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Major comments:
This manuscript could make an interesting overview of sensitivity analysis (SA) of randomized trials. It provides some guidance on what SA are and how to apply it. A lot of topics are touched upon, but not discussed in much detail. To be honest, I guess such general information is not really relevant. For example, when discussing missing data, the authors provide information that is redundant if one is familiar to methods for handling missing data, or is a too short introduction to the topic if one is not familiar to the topic.

Another key issue is that in the abstract it is indicated that this manuscript focuses on trials. Why then discuss observational research (section 2.9)? In fact, I think a distinction between trials and observational research is necessary here.

Where the distinction between observational research and trials comes into play, is how to interpretation / what to do with results from SA. Suppose SA of a trial shows that the ITT effect is significant, whereas the per-protocol isn’t. What to conclude then? And if it would be vice versa, what then? I guess a bit of discussion on how to interpret results from SA should be added to the manuscript.

This overview of sensitivity analysis is not comprehensive. For example, misclassification is not addressed, and if observational research is part of this overview, then SA of unmeasured confounding is an important issue.

Page 6. Regarding the review. I wonder whether the results of this review would change if secondary analyses are considered as a form of sensitivity analysis. In addition, sometimes the impact of certain assumptions or data points is so obvious that one would not even consider a formal sensitivity analysis, because the conclusion of that is known in advance. Is that taken into account here? Could the authors make a distinction in this review based on RCT and non-RCT analysis? For example, they consider an per-protocol analysis in addition to ITT analysis as a sensitivity analysis. I would expect that all trials published in these high-impact journal would report on a per-protocol analysis in a RCT.

Minor comments:
I think the structure of the abstract is a bit odd. What is written under ‘Discussion’ I would consider ‘Methods’. Same holds for the main text. Why indicate the
second part of the main text as ‘discussion’? There must be more informative headings available.

Page 6. “Therefore despite their importance, sensitivity analyses are under-used in practice and often misunderstood.” What is the basis for the second part of this claim?

Page 7. Regarding the protocol violations in trials. What is written there focuses on trials with a single endpoint, but in case of repeated measures outcomes more alternative sensitivity analysis can be thought of.

Page 9. Recently a relevant paper on handling of missing data in trials (and particularly about sensitivity analysis for that) was published (Little et al. N Engl J Med. 2012 Oct 4;367(14):1355-60). I miss a reference to that paper. In addition, with the examples, I think it is a bit odd to consider a method that is known to be flawed (LOCF) as a sensitivity analysis. Better examples are available (e.g., de Ruyter et al N Engl J Med. 2012 Oct 11;367(15):1397-406).

Page 11, examples: these examples do not add information to the paper; either make the examples more informative, or consider removing from the manuscript.

Page 11, 2.6. To what extent is multicenter data different from clustered data (as discussed in 2.5). I think the main analytical approach (and thus also sensitivity analysis) would be the same.

Page 13, second example. This example has nothing to do with baseline imbalance (as the authors also point out, this was a study with balanced covariates).

Page 14, example no. 4 (ref 65). This is a simulation study. I don’t think that is a nice example of how to apply SA in observational studies. Same holds for the example on page 15, ref 70.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'