Author’s response to reviews

Title: Intermediate Outcomes in Randomized Clinical Trials: An Introduction.

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Author’s response to reviews: see over
Minor essential revisions:

Abstract:
1. The first sentence of the abstract is too long and meaningless. It should be edited and split into two.
Done.
2. The purpose of the paper would be to inform researchers and not to argue, as can be seen from the conclusion.
Done.
3. There is an inappropriate use of quotation marks.
Done. I have deleted most quotation marks.
4. It would be better to conclude that ITT is not appropriate for dealing with missing intermediate outcomes.
Done.
5. Consider deleting all uses of “so called” from the manuscript.
Done. All “so called” have been deleted.
6. Intention to treat should be changed to intention-to-treat. It appears twice in the keywords.
Done.

Methods:
7. The first sentence is not referenced.
Done. It is referenced now.
8. RCT not spelled out at first use
Done.
9. Many other language issues need to addressed.
I have tried my best, changing several sentences across the manuscript.
10. Generally speaking this paper is an important one in its field, yet it doesn’t present its arguments in an attractive way. For example ITT is not described in sufficient detail and we get the overall impression that its only flaw is that it is used inappropriately.
I do recognize my style is not very attractive, but it is difficult for me to change it now.
The ITT approach has been described elsewhere in detail and I make reference to key papers.
I have tried to present a more balanced picture of what are the problems with ITT; there are problems related to misuse, and there are also conceptual problems.
11. Pragmatic trials are not mentioned in the introductory stages of the paper, but show up in the discussion as the crux of the matter. It is also useful to distinguish ITT analyses with imputation and without imputation.
The reviewer is definitely right. I have now presented pragmatic trials in the initial stages of the manuscript. I have also made clear that a full ITT analysis requires complete data, so missing data imputation is a must.
12. The authors’ description of PS makes it seem to be quite complex and requiring many assumptions to be met and yet no mention is made of statistical packages that can be used.
It is true that PS is more complex and requires several assumptions. I have now included in the manuscript a reference to a software in R, PSpack, described in 2004 by Frangakis (reference [30]); however I have not been able to locate it as the relevant website is not working (www.biostat.jhsph.edu/~cfrangak/pspack/pspack.pdf). I have not found any other software for PS analyses.
13. I would also disagree with the need for a significant explanatory component in public health. Historically, public health interventions are implemented without the need for an explanation. The famous example is that of John Snow shutting down the water pumps in the UK. He did not know of cholera. This said, the arguments can be more balanced in order to avoid antagonizing the audience it is intended for.
I have now presented a more balanced picture on the need of explanatory components in public health research.

**Level of interest** An article of importance in its field