Reviewer's report

Title: Variability in research ethics review of cluster randomized trials: Scenario-based survey in three countries

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Reviewer: Dave Wendler

Reviewer’s report:

Questions regarding the review and conduct of CRTs are important and the authors have done a good deal of work on this topic. The writing is clear, the methodology seems appropriate, and the authors note the relatively low response rate. Given how difficult it is to write short descriptions of complicated studies, I thought the descriptions of the 3 scenarios were clear and realistic.

I had 5 Major Compulsory questions/suggestions:

1. Because the Ottawa statement came out after the survey was conducted, I would suggest deleting it from this manuscript, and focusing on the results of the survey and their implications. Certainly, the authors might argue that the results suggest the need for guidance, note that some now exist, and cite the Ottawa statement. For example, it seems odd to find in the conclusion of the abstract and the paper that the Ottawa statement is or may be “a first step” toward providing the necessary guidance. The Ottawa statement might be that, but this is not a conclusion that follows from the present study.

2. The authors assessed respondents’ views on two questions relevant to the three CRTs: 1. The level of review needed; and 2. Which individuals qualify as subjects. The manuscript argues that respondents’ answers to these two questions highlight the need for more guidance on the ethics of CRTs. It might help the reader to explain the connection between the findings and this conclusion in more detail. The manuscript summarizes the results of the question regarding what level of review is needed in terms of large variability: half of the committees would require full review, the others would require less than full review (for the first two scenarios). However, the same data suggest that approximately 90% agreed that some level of review was needed in these two cases. And, in the case that seems to clearly merit full review, almost everyone endorsed this view. Thus, whether one describes the results as significant disagreement or significant agreement seems to depend on whether the important point from an ethical point of view is whether the first two studies undergo some review, or whether they undergo full review. While one might take different views on this, my inclination, at least for the first scenario, is that the ethically important distinction is no review versus some review, rather than the distinction between expedited view and full review. Given this possibility, it would help to provide more discussion of this issue and what the primary concern is.
3. The data show clear variability in which individuals are regarded as research subjects. However, one wonders whether the respondents all understood this question in the same way. Some might have been answering in the affirmative because they thought that some level of review was needed and this was the way to secure that end. This is suggested in the verbatim responses. For example, the respondent from the US who endorsed the more inclusive view seems to be saying that they want to make sure the content is right and this is the way to get that end. Thus, they may not be disagreeing with others who suggested that they were not subjects, but it was nonetheless important to get the content right. The manuscript mentions this point in a brief sentence at the bottom of page 16. I would suggest expanding on this point given its importance.

4. Page 5 notes that the perceived need for guidance was not diminished in committees that had more experience with CRTs, suggesting that the need does not diminish with experience. This is an important point given that CRTs are relatively new and one might wonder if the perceived need will fade as the committees get more experience. Thus, it might help to provide a few more details of the analysis here. Given that relatively few had much experience with CRTs, what was the exact test that was done and how strong were the results?

5. As mentioned previously, I would delete discussion of the Ottawa statement from this manuscript. To the extent it is retained, or presented elsewhere, it might be useful to consider how the statement would help with the scenarios in question. For example: Who would count as a research subject in the first scenario? The guidance mentions individuals who are affected which might suggest that everyone in the community is a subject, including young children? Whereas a focus on who is targeted seems to imply that many fewer individuals qualify as subjects.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
'I declare that I have no competing interests'