Author's response to reviews

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

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Author's response to reviews: see over
Editorial requests:

1) Please include a figure title and legend section after the reference list. The figures should not be included in the main body of the manuscript.

Done

Reviewer: Dave Wendler

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.

We thank the reviewer for the positive comments about our study and paper.

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.

We agree, and have deleted the last sentence in the conclusion of the manuscript as well as the sentence in the abstract referring to the Ottawa Statement.

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 is 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.

This is an excellent suggestion. While we agree that the distinction between some versus no review is probably most important, we maintain that the difference between full versus expedited review is important. We considered the respondents' classification of the type of review as an indicator for the level of risk the committee might associate with the proposed trial or the degree of vulnerability they may ascribe to participants, in addition to the level of scrutiny the trial may receive. In both scenarios 1 (public health intervention) and 2 (knowledge translation intervention), therefore, we believe the disagreement with respect to full versus expedited review raises the possibility of substantial variability between ethics committees that may lead to variation in subject protection and variation in study conduct between jurisdictions. We have made several modifications to the manuscript in response to this comment.

In the Abstract we have added the statement:
*The proper identification of human research subjects is a necessary requirement in the research ethics review process, to help ensure, on the one hand, that research participants are protected from harm and exploitation, and on the other, that reviews of CRTs are completed efficiently.*

We have added the following to the discussion:
*Although the majority of respondents in all three scenarios agreed that some type of review is required (as opposed to no review), variability in the type of review required is an important finding as it reflects fundamental differences among committees with respect to the perceived level of risk associated with each scenario and the perceived vulnerability of those who might be considered participants. The type of review may have implications with respect to the level of scrutiny a protocol will receive during the review process, the number of reviewers assessing a protocol, and the time required to complete the review process.*

We also state that (see response to the first point by reviewer 2):
*Although variability among ethics committees is not necessary morally problematic, these decisions have clear repercussions for the ability of research ethics committees to fulfill their purpose which includes protecting the rights and wellbeing of all research participants and to provide independent, competent, and timely review of the ethics of proposed studies.*

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.
We agree, although we believe that, if chairs are casting a broad net in terms of research subjects because they believe a study ought to be reviewed, this reflects a conceptual confusion where the Ottawa Statement may help to provide clarity. We state that:

*It is possible that those respondents who were broadly inclusive in identifying individuals who may be subjects in a CRT were doing so because they believed that the study required full ethics review and this would be one way to that end. Furthermore, although the need to seek informed consent is a separable issue, it is possible that chairs conflated the identification of research participants with the need to seek informed consent. The Ottawa Statement may help to avoid conceptual confusion by providing clarity on these important questions.*

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?

We thank the reviewer for this suggestion. We have added the details of these analyses to the manuscript. In particular, we state that:

*Responses were not significantly associated with experience reviewing CRTs: agreement with the need for guidelines was 84% versus 85% (p=0.82), and agreement that committees could be better informed 98% versus 91% (p=0.10) among committees with and without prior experience reviewing CRTs respectively.*

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.

The question of who is a research subject is extensively discussed in our background papers which are cited in the manuscript. In Table 5 we indicate who, in these three scenarios, might be considered research subjects based on interpretation of the Ottawa Statement.

**Reviewer: Sarah Edwards**

This paper presents new data to answer a well posed question and is, therefore, worth publishing. Any limitations of the methods used to collect these data are sensibly discussed by the authors, and the conclusions drawn from the evidence presented are sound.

We thank the reviewer for the positive comments on our manuscript.
I would suggest only two discretionary revisions before publication.

1. The first concerns whether the variability the authors identity and seek to iron out is always morally problematic. A discussion of this point would strengthen the authors' recommendations to use the Ottawa Statement. For analysis of the issue of differences between ethics committees see Edwards SJL., Ashcroft RA., Kirchin S. Are discrepancies between research ethics committees always morally problematic? Bioethics 2004; 18(4): 408-427.

We thank the reviewer for bringing this interesting article to our attention. We have referenced it in our discussion section. We state that:

Although variability among ethics committees is not necessary morally problematic, these decisions have clear repercussions for the ability of research ethics committees to fulfill their purpose which includes protecting the rights and wellbeing of all research participants and to provide independent, competent and timely review of the ethics of proposed studies.

2. The other point is minor: the terms individual- and cluster-cluster trials were first coined in Edwards SJL., Braunholtz DA., Lilford RJ., Stevens AJ. Ethical issues in the design and conduct of Cluster Randomised Controlled Trials. BMJ 1999; 318: 1407-1409. However, while the terms have become commonplace, their origin is rarely acknowledged in subsequent burgeoning literature.

We are grateful to the reviewer for pointing out this omission. We have added a cross-reference to the indicated paper (already cited) in the manuscript.