Author's response to reviews

Title: Eligibility determination for clinical trials: development of a case review process

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Author's response to reviews: see over
Dear Editors-in-Chief,

On behalf of my co-authors, we are grateful for the thoughtful review and comments provided by the reviewers of our submission: “Eligibility determination for clinical trials: development of a case review process.” We are confident that the review process has resulted in a higher quality submission.

We carefully considered editorial requests and each reviewer suggestion/comment. Our responses are outlined on the following pages. As requested, notable changes in the manuscript are highlighted using Track Changes.

We very much appreciate the opportunity to publish the work of our research center in Trials.

Sincerely,

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Editorial suggestions:

1. Please include the names of all ethical bodies that approved your study in the various centres involved, along with appropriate reference numbers, in the Methods section.

Response: Institutional review board and names and reference numbers were added to the Methods section on Page 5.

2. Please move your tables below the reference list.

Response: Manuscript was reformatted with all tables moved from additional files and added below the reference list. Tables were renumbered in the text to match these changes, as well. These changes were not highlighted with Track Changes.

3. Please upload your figures as separate files (as opposed to additional files) via the submission system.

Response: Figures are now labeled Figure 1, 2, 3, and 4 instead of additional files.

4. Please include an additional file title and legend section below your figure legend section.

Response: All tables (1-7) including titles and legends are included at the end of the manuscript and renumbered as suggested. Due to this suggestion and that of reviewer #2, there are no longer any additional files. These changes are not highlighted with Track Changes.
Reviewer # 1.

1. I note the additional files and table 1 providing details on the inclusion and exclusion criteria of the three trials. Is this the exact wording...? Please clarify in your manuscript.

Response: Tables 1, 2 and 3 include exact wording and this was clarified in the manuscript on pages 5 and 6.

2. Please provide more details in your manuscript as to who serves as the ‘moderator’?

Response: Additional details regarding the function of the moderator and who serves in this role are provided on page 8.

3. Please provide more details as to how the ‘poll’ is conducted during the meetings.

Response: Details on the polling process are provided on page 9. Text was added to the Discussion regarding limitations of verbal polling on page 16.

4. On page 9, the authors discuss that 72 participants were deemed eligible but decided not to participate or were later excluded. Do the authors have a breakdown of the numbers in each category? If so, please add to the manuscript.

Response: Additional details regarding a numerical breakdown were added on pages 10-11.

5. In table 2, do you have figures to add to the table that would provide more details as to why participants who were eligible did not ultimately enroll in the trial? If so, please add to your manuscript.

Response: We added itemized details regarding why eligible participants did not enroll on pages 10-11. In summary, participants either changed their minds about participation before randomization, or they failed the eligibility questionnaire conducted pre-randomization, typically due to a resolution of symptoms or for seeking other treatment for their condition.

6. Page 10 sentence beginning “Three of the 96 eligible”... The authors have listed three reasons for exclusion. Could you please clarify ... the number of patients that used each of the reasons given?

Response: Clarifications added. They can be found on page 12.

7. In your limitations section of your discussion, please discuss in more detail that there is room for exclusion and hence selection bias at the initial step where the study volunteers are screened at the baseline visit by (one) study coordinator.

Response: We added details on pages 6-7 to clarify that exclusions by study coordinators and clinicians during the automated eligibility screening process occurs only for objective criteria and not for those requiring clinical decision-making. Text was also added to discuss the limitations of this aspect of the process in the final paragraph on page 16.
Reviewer #2
1. Page 9, lines 186. 225 patients were ‘excluded’ through this process. Please provide more detail for each reason, with numbers.

Response: Text including more detail was added on page 10 and readers were more clearly directed to Tables 5, 6, and 7, which quantitatively present exclusion reasons. In addition, we added a flowchart (Figure 4) that presents some of these details visually for Trial 3.

2. Page 9, line 186-188. Of the 72 patients not allocated, how many refused consent and how many were excluded based on explicit criteria ascertained on response at interview?

Response: Additional details regarding a numerical breakdown were added on pages 10-11.

3. Page 10, Line 204. In this detailed list of exclusions, please explicitly indicate whether each of these reasons was an exact eligibility criteria listed by the study under consideration.

Response: All exclusion reasons were for exact eligibility criteria listed for the study. Text was added on page 12 to clarify this ambiguity.

3.a Please also explicitly report whether any of the patients who were enrolled were later reported to be inappropriate by the trials central office?

Response: Text was added on page 11 stating no participants were later reported to be inappropriately enrolled.

3.b How does your case review process conduct eligibility screening ‘better’ than a normal process?

Response: We do not know if the case review process described in our manuscript improves on the normal eligibility processes used in clinical trials. As we investigated for such processes to develop our own, we found little guidance in the literatures. Similarly, a recent systematic review on interventions to improve adherence to eligibility criteria in clinical trials failed to find any publications describing eligibility screening processes. Our goal with this manuscript is to offer an example of one such eligibility screening process, with the hope that other researchers will have this model as a resource and begin including descriptions of their processes in study protocols or primary manuscripts. Text was added to the discussion on pages 13 and 14 to address this point and to describe that this article represents a first step in describing systematic methods that specifically incorporate steps to mitigate selection bias where it is known to occur.

4. Page 10, Line 214. Please provide more detail overall with regards to the exclusion for ‘safety concerns’. It is very important to understand whether these exclusions were consistent with explicit study eligibility criteria or whether these were additional ‘safety’ judgements made by the panel.

Response: Text was clarified in the second and final sentences of the paragraph in question, located on page 12.

5. Tables for Trial 1 and Trial 2 can be moved to the main manuscript. Please also provide a similar table for all trials.
Response: All tables were moved to the main manuscript and relabeled. Table 4 summarizes eligibility determinations for the 3 clinical trials presented.


Response: Average time was added on page 12.

6.a This issue needs to be addressed in your Discussion. ...provide some measure of quantifiable ‘information gain’ that justifies these costs.

Response: See response to comment 3.b. Additional text was added to the Results on page 12 with the subheading “Resource Considerations” and to the discussion on page 16 to explain that some of the time allocated for this process involves training graduate students in a Master’s of clinical research program.

7. The opinions expressed in the first paragraphs of your Discussion are very interesting, but are not supported by any data or hypothesis tested in your Results...

Response: This methodological paper was not a hypothesis testing study. The goal of this manuscript is to offer an example of an eligibility screening process, thus providing researchers with a resource for eligibility determination procedures that specifically incorporate steps to mitigate selection bias where it is known to occur. Text was amended in the Discussion to more clearly address the issue and describe this important methodological concept. See also response to comment 3.b