Author’s response to reviews

Title: Global Health Trials Methodological Research Agenda: Results from a priority setting exercise

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Author’s response to reviews:

Dear Editor,

I am pleased to resubmit the revised manuscript following reviewer comments. The authors would like to thank both reviewers for their constructive feedback.

Please find below a point by point response to the reviewer comments.
Reviewer #1: The authors are to be congratulated for this original and important research initiative. They performed an online 2-round survey amongst researchers working on trials in LMICs with the goal of identifying the top priorities for methodological research. The topics deemed most important for methodological research were: choosing appropriate outcomes to measure and training of research staff. These data may serve as a platform for ultimately improving clinical trials in these regions.

Please further specify the criteria for researchers selection: "...researchers with experience in LMIC trials" (?) "... Researchers were also identified through online searches of the ClinicalTrials.gov registry..."

>>>Clarification added to line 74:

‘…researchers who had designed, conducted or analysed trials in LMICs’

Clarification added to lines 77-79:

‘…The registry ClinicalTrials.gov was used to search for trials currently open to recruitment in LMICs. Researchers involved in these trials who had provided an email address were contacted.’

Reviewer #1: I suggest a flowchart diagram to better visualize the flow of responders throughout each step of the trial, from the initial selection to the ultimate questionnaire completion.

>>>A flow chart has been added as suggested and referred to in line 117.

Reviewer #1: Besides the limitations already mentioned, please consider a few other aspects that may have not been captured:

- priorities may differ between low vs. middle income countries
- respondents affiliations and their priorities may vary (eg. academic vs. public health vs private setting, etc)
‘Although LMICs share the same limitation of resource issues, it should also be noted that the specific needs of different regions within LMICs could vary; for this reason a wide spread of countries was included in the survey. An extension of this work, however, could target the priorities of specific countries or regions within LMICs.’

‘A variety of disciplines was represented in the survey but it could also be the case that priorities vary depending on respondent affiliations (for example, private vs public).’

Reviewer #2: I like this paper; it presents a clear piece of work and highlights some differences between the needs of the UK and LMICs with regard to prioritising methods research in trials.

I only have a few comments, none of them requiring substantial work to deal with.

Discussion

A point is made early on that the UK prioritisation exercise need not apply to LMICs. Quite so. How likely is it that the current work will apply to all LMIC though? There's quite a mix of countries included and I guess the needs of, say, sub-Saharan Africa might be different to, say, Asia or South America. Could the authors comment on this?

Reviewer #2: Methods (p4). Why were patients and public not involved? Their absence is mentioned in the discussion but it would be good to know why they were not considered, even if the answer is a pragmatic one about it being difficult to find ways to do it at present.

This was due to pragmatic reasons in that it would have been difficult to identify participants who had taken part in trials in LMICs however it would be useful to obtain their views; clarification has been added to lines 189-190.
Reviewer #2: Methods (p5). How did the steering committee deem topics as not applicable, vague or beyond the scope of the study? It would be nice to have a bit more on this, it sounds a bit arbitrary at present. I do think it would be good to have a few examples too (I know that the text says examples can be obtained from the author but I think some should be in the text, perhaps in a box or table).

>>>Some examples are given in the discussion but clarification and further examples have been given to lines 195-197; a spreadsheet of responses and grouping has also been added as a supplementary file: 'Those deemed not applicable were often too vague, for example, ‘trial logistics’, ‘statistical analysis’ and ‘improving trial efficiency’ or to do with a specific disease area, for example, 'HIV’, ‘malaria’; a full list of responses and groupings are provided as a supplementary file.'

Reviewer #2: Results (p7). 'Outcomes to measure. Some examples are developing the correct objectives for the study.' This was unclear to me. I expected 'Some example of xxx are developing..' to make things a bit clearer. This also led me to wonder how the responses were collapsed into the headings shown in Figures 1 and 2. I'm guessing that 'standardising outcome sets and identifying patient focussed end points' were responses that were collapsed by the study team under a heading of 'Choosing appropriate outcomes to measure'. It would be good to say a bit more about this process.

>>>Clarification added to line 147 and supplementary file added as above: ‘Some examples of topics falling within choosing appropriate outcomes to measure, given by respondents, were: developing the correct objectives for the study, standardising outcome sets and identifying patient focussed end points.’

Reviewer #2:

Minor revisions

Discussion (p8). ‘Potentially due to the fact that involvement in trials guarantees access to healthcare which outside of a trial setting could be limited in LMICs.' I guess this is because treatment in both arms might not be available outside the trial, whereas in, say, the UK, the comparator is very often routine care. Generally even in the UK or other high income countries, the intervention is only available in the trial. The authors might want to clarify this. Apologies if I've got the wrong end of the stick.
This was also highlighting a capacity issue in LMICs, it is not always possible to see a healthcare specialist and receive personalised care which would be guaranteed to those within a trial.

Clarification added to lines 181-183: ‘…potentially due to the fact that involvement in trials guarantees access to more personalised healthcare which outside of a trial setting could be limited in LMICs due to capacity issues or to the intervention not being available outside the trial.’

Reviewer #2: Discussion (p9). The authors might like to consider expanding a bit on how the priority list could be used. For example, how might someone in a LMIC take forward 'Choosing appropriate outcomes to measure' now that we now it is priority #1?

Lines 161-168 introduce the COMET initiative and suggest the involvement of LMICs in developing core outcome sets (clarification added to line 168: wording changed from ‘within this initiative’ to ‘in the development of core outcome sets’).

Short expansion also added to lines 175-176:

‘Research should now be done to find methods for training which are available and effective in LMICs.’