Author's response to reviews

Title: Confronting diversity in the production of clinical evidence goes beyond the mere inclusion of underrepresented groups in clinical trials

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Version: 2 Date: 27 March 2013

Author's response to reviews: see over
Dear Editor,

Thank you very much for your e-mail of March 4\textsuperscript{th} 2013, informing us that our manuscript entitled “Confronting diversity in the production of clinical evidence goes beyond the mere inclusion of underrepresented groups in clinical trials” might be considered for publication after suitable major revision.

We are grateful for the kind remarks and the useful suggestions of the reviewers and have revised the original manuscript accordingly. Below are our detailed responses (in italic) to the reviewers’ comments.

We hope that the revised manuscript can be accepted for publication in Trials.

Yours sincerely, also on behalf of the co-authors,

Karien Stronks
Amsterdam, March 27, 2013

\textbf{Review Stacie Geller}
\textit{Thank you very much for your positive review, and for pointing at grammatical errors. We have changed the manuscript according to your suggestions.}

\textbf{Review Catherine Kreatsoulas}
The study is relatively balanced and the standard of writing is acceptable, however I have three broad conceptual concerns, which I feel warrant further exploration and explanation before consideration for publication.

1. The role of subgroup analysis is only briefly mentioned and this needs to be discussed further since this is the recommended gold standard to address diversity in clinical trials, especially RCT’s. Stratifying a priori for the subgroup of interest and ensuring the study is adequately powered to detect a statistically significant difference in the subgroup can adequately study underrepresented subgroups within the larger context of the clinical question. For this paper, the role of subgroup analyses in their call of diversity needs to integrated or epistemologically differentiated from their call to diversity representation in clinical studies.

\textit{Thank you for pointing out the lack of attention in our paper to subgroup analysis. We fully support this gold standard to address diversity in clinical trials. It should be noted, however, that the outcome of subgroup analyses should be interpreted with caution, as they might lead to misleading results. In fact, our plea for exploring diversities that matter might help to compensate for the limitations of this strategy, as this will lead to explicitly formulated hypotheses, which is a prerequisite for a reliable subgroup analysis. We have now added this argument at p. 10. We would like to point out that we also refer to that argument in the original version, at p. 7 (middle of page, directly before section 'Towards a methodological reform'), in which we comment on the way diversity in conceptualised in our reasoning.}
2. The underlying hypothesis of this paper is not explicitly stated. The authors imply that individuals of different gender or ethnicity have inherent differences, which may not necessarily be the case! The issue of diversity should be framed in a balanced framework exploring the implications of what “lack of” diversity also implies. For example, it has been postulated by many investigators that there are differences in the symptomatic presentation of angina in men and women. However recent research indicates that angina symptoms in men and women are more similar than dissimilar. For years, women have been misled to expect different symptoms than men. There are many more such examples in the literature, including the hormone replacement therapy (HRT) story, where there are still vocal advocates to subject subgroup of women to HRT despite known and well establish harms.

We completely agree with the reviewer that individuals of different gender or ethnicity etc. might not always be inherently different from each other. This is exactly the reason why we, in the second part of the paper, propose strategies to explore diversities that matter. See also p. 8, where we, amongst others, state that “This is not to say, however, that all clinical trials should automatically study effect modification”. We have now incorporated a statement at p. 5 to acknowledge this in the first part of the paper as well.

3. Five methodologies are presented in how to incorporate a diversity approach however limitations associated with each of these approaches are not discussed. For example, the issue of post-hoc testing, correcting for multiple p-value testing, main effect vs. subgroup effect (particularly if the subgroup effects are in the opposite direction of the study main effects), differences and inadequate sample size are inherent limitations in the re-analysis of RCT’s –none of which are explored. Although recommending these five methodologies is a good start, why these strategies are not being overtly implemented warrants discussion and needs to be recognized. It is not a matter of ignorance; rather the limitations associated with each of these methodologies are prone to erroneous assumptions and interpretation and this aspect needs to be addressed.

We have now reread the way we presented the five approaches as to how to incorporate a diversity approach with the comment of the reviewer in our mind. We now realize that, without discussing the limitations of each strategy, it seems as if we consider these as perfect solutions, which simply need to be implemented to incorporate a diversity approach into clinical research. This is of course not true. Therefore, thank you for your suggestion also to acknowledge and discuss the limitations of these approaches. We have now extended this section in line with your suggestions.