Author's response to reviews

Title: Confronting diversity in the production of clinical evidence goes beyond merely including under-represented groups in clinical trials

Authors:

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

Thank you very much for your e-mail of April 30, 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 revision.

We are grateful for the excellent suggestions of the reviewer and handling editor, and have revised the original manuscript accordingly (in red). Below are our detailed responses (in italic) to their 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, May 30, 2013

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**Comments handling editor**

I would strongly urge the authors to improve the composition of their article: the manuscript is somewhat bloated and contains many grammatical and compositional problems. Authors, for example, rely heavily on passive tenses and constructions (e.g. "the diversity agenda has been pushed by...;") "increasing evidence shows..."). The article also makes various strange statements: is it really true the general goal of EMB is standardization of clinical decisions (seems more precise to say the goal of EBM is to ground medical decision-making in high quality evidence)? Use of the word "underlying" in the phrase "...concerns the generalizability of results from underlying trials" adds nothing. Also, authors may want to consider ways to dial back the emphatic tone (e.g. "it is imperative that this diversity is considered..."). Statements like this sound preachy [btw- passive tense again- considered by whom?]).

The problems above obscure the very important and carefully researched message. The article will have a wider audience if the authors can address some of the above issues. Look forward to seeing a revised manuscript.

Thank you very much for your comments and suggestions. We have now improved the composition of our paper. This relates in particular to the introduction and second section of the paper, which have now been re-arranged completely. In addition, a native speaker has edited the language of the paper. We hope that the revised paper meets your expectations. The sections that have been changed substantially are highlighted in red. Language changes have not been highlighted (as this would make the text unreadable).

**Review Catherine Kreatsoulas**

I strongly recommend that this paper be accepted however, it can be written more succinctly to clearly relay their message to your audience.

Your extremely valuable comments have helped us to improve the paper. Thank you.
Introduction
The primary goal of evidence-based medicine is to make clinically informed decisions based on evidence from clinical trials (mostly RCT’s) that prove a treatment/intervention to be efficacious. A secondary outcome of EBM is to standardize clinical decisions. This may seem nuanced but it is an important distinction.

Thank you for this comment. We have now adapted this first paragraph of the introduction according to your suggestions.

RCT’s were used to help determine causality. What do you mean by universal knowledge? You need another sentence to bridge the argument.

We have now reformulated the second paragraph of the introduction, and hope that the argument is clear.

I think the thesis statement should be refined to clearly outline the objectives of this study, reflecting the position of this paper.

We have revised the final paragraph of the introduction, and clarified the objectives as well as the outline of this paper, also in relation to the original report.

Framing the issue of diversity in the production of clinical knowledge
Should you mention some examples of these recommendations?
We gave two examples of recommendations as to how to improve inclusion of minority groups in trials. A further elaboration of these examples goes beyond the scope of our paper.

Heterogeneity vs. homogeneity is not clearly delineated in this paragraph. For example, in a statin trial, women, men and individuals of multiple ethnicities are recruited into the study, esp in multi-centred studies. How does your concept of heterogeneity differ? This needs to be clearly outlined.

Thank you for your comment. Also in light of the comments of the editor, we realised that this section was not clear enough, and contains some overlap with the introduction and the section on ‘methodological reform’. We have therefore rewritten this whole section. We hope this now meets your expectations.

Toward a methodological reform
This point is repeated from above. Avoid repetition to make more succinct, clear and convincing arguments.

We have rewritten the text in order to avoid repetition.

Define effect modification. Perhaps illustrate this concept with an example and how you envision effect modification should be handled. This is not an easy concept and you should not assume the reader will know what you are referring to.

We have now rewritten this section, and illustrated the concept of effect modification by an example.

This is an important point to make and should be supported with creating a priori subgroup, that are hypotheses driven, and appropriately powered to detect a predetermined effect size difference.

We have added your suggestions.

This is too broad of a term. Specifically define what you mean by "investiments".

Sentence has been rewritten.
The most important weakness of a subgroup analysis is being underpowered to determine if a true difference exists. This is not a case of "reliability" per se. Rephrase appropriately. We have rephrased this according to your comment.

I think you should read some of the interesting and innovative approaches proposed by Miguel Hernan and colleagues to further support this point. Thank you for this suggestion. We have now made a reference to these innovative approaches.

How might they modify the treatment effect? This point needs to be clearly explained as it is too vague right now. We have rephrased this sentence.

The authors should explore some of the EBM qualitative research literature. We are aware of this literature, but realised that the original text did not do justice to this rich literature. We therefore have rewritten this section.

**Institutional changes**
Define acronym (INVOLVE)
INVOLVE is not an acronym, as far as we know.

**Conclusion**
It is unclear if you are suggesting that studies use mixed method approaches or if guidelines should incorporate evidence acquired from quantitative and qualitative study designs.

Acknowledge how? By statistically accounting for diversity treatment outcome differences? A priori design measures? This statement should include some suggestions in how this "acknowledgement" should be attained. We have changed the text of the final section, in order to clarify both points.