Author’s response to reviews

Title: Fair Inclusion of Pregnant Women in Clinical Trials: an Integrated Scientific and Ethical Approach

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Author’s response to reviews:

Dear Dr Meurer,

Thank you for reviewing our manuscript and for your decision to accept it after we have made essential revisions.

Please find a detailed response to the reviewers comments below.

- Reviewer 1:

- One could suggest a phase II to phase III step using pharmacodynamic projections for pregnant women with modern computed model design.

This is an interesting suggestion, in particular since the literature is mostly silent on timing of trials that may speed up knowledge generation in the field of pregnant women. However, we have indicated in the background of the manuscript that the scope of our paper is confined to an analysis of fair inclusion related to phase III trials. As you may know, another paper of some of the authors of this group is currently under review at Trials. This paper discusses research designs (such as adaptive trial designs) and timing of trials in relation to fair inclusion (see also our reference 31). We have slightly elaborated on the sentence where we outline the scope of our paper to clarify why we do not touch upon computed model designs and other designs. " [do not
discuss] trial designs and models that may speed up knowledge generation in this field." line 151/152

- The breastfeeding woman should be included in the process as both pharmacodynamic status and risk for the new born constitute argues for a separate subpopulation.

This is also an interesting suggestion since breastfeeding women are similarly underrepresented. However, there might be subtle differences between breastfeeding and pregnant women. For reasons of consistency we have confined our paper to pregnant women. We have added a sentence about the scope in the background: "although our paper focuses primarily on the interests of pregnant women, the findings may also be of relevance to other underrepresented groups including breastfeeding women." [line 153/154].

We are looking forward to your response.

On behalf of all authors,

Indira van der Zande

TRLS-D-17-00586

Fair Inclusion of Pregnant Women in Clinical Trials: an Integrated Scientific and Ethical Approach

Rieke van der Graaf; Indira S.E. van der Zande, MA, MSc; Hester M. den Ruijter; Martijn A. Oudijk; Johannes J.M. van Delden; Katrien Oude Rengerink; Rolf H.H. Groenwold

Trials

Dear Ms van der Zande,

Your manuscript "Fair Inclusion of Pregnant Women in Clinical Trials: an Integrated Scientific and Ethical Approach" (TRLS-D-17-00586) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in Trials, once you have carried out some essential revisions suggested by our reviewers.

Their reports, together with any other comments, are below. Please also take a moment to check our website at http://trls.edmgr.com/ for any additional comments that were saved as attachments.

Once you have made the necessary corrections, please submit a revised manuscript online at:
If you have forgotten your username or password please use the "Send Login Details" link to get your login information. For security reasons, your password will be reset.

Please include a point-by-point response within the 'Response to Reviewers' box in the submission system and highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript. Please ensure you describe additional experiments that were carried out and include a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that your revised manuscript conforms to the journal style, which can be found in the Submission Guidelines on the journal homepage.

Please also ensure that your revised manuscript conforms to the journal style, which can be found in the Instructions for Authors on the journal homepage.

The due date for submitting the revised version of your article is 08 Dec 2017.

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Please be aware that we may investigate, or ask your institute to investigate, any unauthorised attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

We look forward to receiving your revised manuscript soon.

Best wishes,

William J Meurer, MD, MS
Reviewer reports:

Reviewer #1:

We thank the authors for this conceptual analysis and suggestions to improve pregnant women recruitment in research programs.

The aim of this paper was to analyze and evaluate when research with pregnant women can be considered as fair and what constitutes scientific reasons for exclusion. The authors performed a conceptual ethical analysis of fair inclusion and then looked at fair inclusion from an integrated ethical and methodological perspective by applying the NIH Policy document to pregnant women.

General comments:

This is a subject of interest as most of the drugs used in pregnant women have not been evaluated despite the different distribution volume and metabolism and despite the potential side effects on the foetus.

The article is well written by referents for these progressive thoughts.

I have two comments that could be shared with the authors:

- One could suggest a phase II to phase III step using pharmacodynamic projections for pregnant women with modern computed model design.

- The breastfeeding woman should be included in the process as both pharamcodynamic status and risk for the new born constitute argues for a separate subpopulation.

Reviewer #2: Dear author,

thank you for submitting your manuscript.

This paper is discussing very difficult ethical dilemma of pregnant women inclusion/exclusion for research studies.

I hope that your integrated approach will help us to include more pregnant women in clinical trials in the near future.
Please also take a moment to check our website at for any additional comments that were saved as attachments. Please note that as Trials has a policy of open peer review, you will be able to see the names of the reviewers. If your manuscript is published in the journal, the reviewer reports and your responses to the reviewers will be published alongside the article.

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES-HS) and American Journal Experts (http://bit.ly/AJE-HS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.