Reviewer’s report

Title: The ethics of using placebo in randomised controlled trials: a case study of a Plasmodium vivax antirelapse trial

Version: 1 Date: 31 Aug 2017

Reviewer: Stephan Ehrhardt

Reviewer’s report:

The authors have done a good job editing the paper. I believe it has more focus now without losing the strong points it already had.

I have a few recommendations for the authors.

1. Background, first para: "Randomization is the preferred method for assigning participants to a treatment arm since this ensures that the participants in the study groups are equally matched with respect to factors potentially influencing study outcomes."

Should read: "Randomization is the preferred method for assigning participants to a treatment arm because it substantially increases the likelihood that measured and unmeasured factors influencing the outcome are equally distributed across study arms." There is no guarantee that this happens. The likelihood generally increases with increasing sample size. "Matching" is a specific procedure to address confounding that does not fit here.

2. "Randomisation also helps to ensure that the results of the study reflect the effects of administered interventions and extraneous factors."

I am a bit unclear what exactly that means. If this refers to factors like regression to the mean, not the randomization but the presence of a control group prevents this.

3. "The studies caused a huge public outcry due to concerns that double standards of clinical care were being applied to individuals from the developed and developing world, in disregard of the right to equal access to optimal clinical care."

I suggest to avoid "huge public outcry" but tone this down a little bit.

4. Under "Risks of harm due to …": "In addition to the above considerations, it is important for any study to ensure that the ancillary care obligations are met and that ancillary risks are minimised. In the IMPROV study, treatment efficacy and patient safety are ensured by close monitoring over a twelve-month follow-up period following a schedule of visits and corresponding clinical and laboratory examinations.8 Although this could affect the
generalizability of the results, it is ethically necessary to ensure that risks to individual patients are minimised especially the risk of relapse and haemolysis."

I don't see how generalizability is compromised here. If the study findings can be transferred to other target populations there is generalizability. If not, generalizability is not given. I would delete the last sentence.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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