Reviewer’s report

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

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Reviewer: Stephan Ehrhardt

Reviewer’s report:

Phaik Yeong Cheah and colleagues present a very interesting paper on the ethics of using a placebo control group. The problem is presented by using the example of the IMPROV study which treats vivax malaria patients with two primaquine regimens or placebo to clear hypnozoites.

Background:

In the first paragraph please be more explicit explaining the "double standards" discussion. While people working in both high and low resource setting are familiar this problem is not intuitive for every reader. Please try and be as specific as you can.

Second paragraph. I would start with a brief methodological part explaining why we like to have a control group in clinical trials (distinguishing a treatment effect from phenomena like regression towards the mean, secular trends, or course of the disease) and when we tend to believe that a placebo control is appropriate (no standard treatment available, clinical equipoise must hold).

Proposed considerations for evaluating whether using a placebo is ethical:

The authors propose the following considerations: disease burden and clinical relevance; need for a randomized controlled trial (RCT) and placebo; standards of care; risks of harm due to administration of placebo and harm benefit balance; clinical equipoise; double standards.

1. Disease burden. This basically means that the clinical problem is important. I am not convinced that this point adds much to the discussion. In what way is this important? The higher the burden, the lower the bar for the placebo use? Please be specific.

2. Need for an RCT and placebo. Here I would suggest to be a bit clearer. When we have an active control arm only, we can't tell if any of the treatments is effective. We can only infer how they perform relative to each other. To establish efficacy, a placebo arm is needed. And here is the methodological point. If efficacy has been established, comparative effectiveness trials (testing alternative interventions) are fine. But if efficacy is unclear we will need the placebo arm.
3. Standards of care. Interesting points!

4. Clinical equipoise. I would try and argue a little bit sharper. The equipoise (in terms of placebo use) is really in the question: Are we uncertain whether any primaquine (7 or 14 days) is better than placebo? The comparative effectiveness question (7 vs. 14 days) is important too (clinical equipoise is also critical in comparative effectiveness research) but not regarding placebo use.

5. Risk of harm from placebo administration and harm benefit balance. Relapse vs. hemolysis in G6PD study participants.

6. Double standards. This point is, analogue to the HIV story in the introduction, a bit unclear and needs revision. Please be explicit. First explain what exactly you mean by double standards. Then give an example (and this might be HIV in SSA), then translate this to the IMPROV study and explain why there is no double standard there.

Discussion:

The discussion starts with a summary of the considerations in the IMPROV context. Then follows a piece about the Declaration of Helsinki (which should be expanded a bit to help the reader understand what it is and why it has been established). Then the authors move on to the placebo/active comparison discussion. Here things become a little bit unclear. Placebo controlled trials are fundamentally different from comparative effectiveness trials. They try to establish if an intervention is better than no intervention (and better could mean more effective or safer, etc.). Comparative effectiveness needs to be grounded in proven efficacy. It compares the efficacy of two treatments relative to each other. This comparison only makes sense if these two treatments have an established efficacy (because A can be significantly better than B but both can still be worse/equal relative to placebo). Please put some thought into this.

The other study designs that are mentioned in this paragraph (page 10, third para) have different strengths and weaknesses which should be briefly mentioned. The "more innovative designs suggested for the Ebola trials" should be explained and pitted against RCTs regarding their scientific merit and also their ethics. A study is not automatically more ethical just because it has no placebo control. Also, ethical is not the same as acceptable. Sound ethical reasoning is one component of a studies acceptability in the local but also the larger scientific communities.

I am not sure I follow the point that "…it has been argued that placebo should not be used if there is high mortality such as in the case of the Ebola trials". I also don't see a reference here. What else should be used? Please explain. One might argue that especially if the condition is grim, good quality evidence is critical if (and this is key) there is true clinical equipoise. If there is no equipoise, no placebo should be given regardless of the prognosis of the patient or the severity of the condition.

The discussion on double standards lacks some context but this can be easily fixed once the definition of double standards has been established.
Finally: How does the non-inferiority design of IMPROV fit here? Please discuss if (and if so how) it affects your considerations in light of the current literature.

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.

I am able to assess the statistics

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