Author's response to reviews

Title: Pre-referral rectal artesunate in severe malaria: a fundamentally flawed trial

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Author's response to reviews:

Dear Editors-in-Chief of Trials:

We are submitting the third revised version of the paper "Pre-referral rectal artesunate in severe malaria: a fundamentally flawed trial" by Karim F Hirji and Zulfiqarali G Premji for continued consideration for publication in your journal.

We thank you for your comments on the last version of our paper. Our responses to them are as follows:

1. Flow Chart and the CONSORT Statement: First note that the CONSORT Statement (Moher et al. 2001) is not as consistent on this issue as it should be. Item 13 in the Table of the checklist of items (page 659) relating to participant flow starts at randomization stage while the Figure showing the flow diagram (page 660) and the explanatory point (Point 8, page 660) begin at the enrollment stage. In Table 5 of the paper which gives further explanation of the CONSORT Statement (Altman et al. 2001, page 678), the enrollment stage is present. That is the normal situation. But this paper has two illustrative examples of flow diagrams (Figure 2 and Figure 4) that do not include the enrollment stage. Both examples deal with matters occurring at or after randomization. Exclusion of the enrollment stage in a flow diagram is not specifically justified in any of the two papers.

Flow diagrams for rural malaria trials (as shown in the example we gave of Yeboah et al. 2010) include the pre-randomization (enrollment) stage. Gomes et al. do not state the exclusion criteria for their study; and their flow diagram omits the stage at which the relevant numbers would be noted. This, in our view, constitutes selective or partial reporting. We thus standby our statement on this issue.

2. Checking adherence to the CONSORT Statement: The instructions to authors of trial reports in the Lancet are very clear on this issue. These reports must follow the latest version of the CONSORT Statement. That means that someone involved in the review process (associate editor, editorial team or external referees) has to check that this key, substantive requirement is followed.
Suppose the law says that a car driver should drive on the left hand side. A traffic policeman has to uphold the law, and should cite an offending driver even though what he was told to do did not specifically mention this particular point of law.

What is the point of strong requirement for publication if it does not have with an enforcement mechanism for it? If the Lancet editors do not ensure adherence to the CONSORT Statement, they are violating their own clearly stated standard.

We therefore standby our interpretation on this issue.

3. Reporting Problems Only?

The following problems with Gomes et al. pertain to the design and conduct of the trial: (i) enrollment of clearly ineligible subjects (1110 or 6%); (ii) recruiters with no or little health background; (iii) varying periods of training (1 to 3 weeks); (iv) follow up window too wide; (v) variation in age range for recruited subjects; (vi) two centers not collecting data on time to clinic (key variable used in analysis); (vii) taking one slide in Africa and two in Bangladesh (which introduced diagnostic bias); (viii) many missing blood slides at one center; (ix) provision of different levels of support and care at different centers.

Problems that pertain to reporting but also may pertain to design and conduct. (i) Lack of clear statement of eligibility criteria. Different centers may have had or have applied quite different eligibility criteria making the paper a report of a single clinical trial difficult to justify. Not reporting them thus also hides a major design or conduct flaw. (ii) Absence of details about sample size calculations. Different centers may have used different assumptions, metrics and other details of this exercise. Not reporting them thus hides a design flaw and makes the use of a common analysis method difficult to justify. (iii) Not reporting center level details to enable a stratified ITT analysis. Perhaps the numbers of clearly ineligible and potentially ineligible cases (slide negative cases) varied highly between centers, showing a major problem of conduct at some center. Not reporting this also hides an implementation related flaw. Etc. Etc.

Purely analysis and reporting problems: (i) Not doing an overall analysis and stratified analysis; (ii) analysis based on relative risk rather than risk difference; (iii) analyzing too many improper subgroups; etc.

In our view, most of these problems are intertwined, not easy to separate as purely reporting problems or just problems with design and conduct. Given the extent of the serious problems we found, and the major impact they can have or had on the conclusions drawn from the trial, we feel that our verdict that this is a fundamentally flawed trial is a fair verdict.

Our basic view, for which we lack good evidence and therefore do not state in our paper, is that here we have two very different trials that have would drawn quite different conclusions but which are being reported as a single trial. The Bangladesh trial, possibly a good quality trial, seems to show that if adequate level of support and care is provided, rectal artesunate has no effect on survival
or permanent disability. The African trial, with extensive practical problems, seems to show a marginal benefit of rectal artesunate. But that is difficult to justify given the low level of support to given to the patients, and the nature and number of design and conduct related problems. Poor reporting glosses over the serious problems of design and conduct.

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In the light of all this, we have not made any changes to the present version of the paper. All the blue and red colored sections from the previous version now appear in the regular color.

We thank you and your editorial team for your continued kind assistance,

Sincerely,

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