Reviewer's report

Title: Inhaled Nitric Oxide for the Adjunctive Therapy of Severe Malaria: Protocol for a Randomized Controlled Trial

Version: 2 Date: 5 March 2011

Reviewer: Gray Heppner

Reviewer's report:

1. Will the study design adequately test the hypothesis?

Yes. This well-designed study will adequately test the primary hypothesis that adjunctive treatment with inhaled nitric oxide will reduce serum levels of angiopoietin-2 (Ang-2), the proposed marker of severe malaria disease, over initial 72 hours of hospital admission.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

Yes, but discretionary revisions are suggested to include greater detail in the protocol, especially for inclusion and exclusion criteria.

#1
Page 9 "Positive malaria rapid diagnostic test."
These tests significantly vary in performance parameters. Please address test selection, staff proficiency training in test use, and concomitant or retrospective requirement to confirm presence of asexual parasites in peripheral blood.

#2
Page 9 "Features of severe malaria."
Please be explicit if one or more features are required for inclusion.

#3
Page 10 "Severe malnutrition"
Please provide objective criteria for making this determination.

#4
Page 10 and 11.
"Treatment groups."
It is highly desirable to standardize treatment (Ugandan standard of care) within the trial (quinine versus artesunate), since their efficacy is known to be different, and the study might not be adequately powered to determine the incremental benefit of iNO in two versus one treatment groups.
"Outcome measures."
The method for determination of the primary study endpoint, Ang-2 concentration, should be stipulated and referenced in this section.

"Duration of Study Participation."
It would be helpful to stipulate that interim medical history would be collected, with special attention to severe intercurrent illness including cerebral malaria that might affect neurocognitive testing.

Interim analysis.
Agree with approach, but perhaps useful to clarify "no plan to stop the trial prematurely for efficacy or futility based on the primary or secondary trial endpoints....." by noting the exception of the planned use of the control chart for detecting excess mortality.

Secondary outcomes.
The protocol as presented makes reference to, but does not list, the cognitive and neurologic endpoints used for the secondary outcome analyses. Inclusion of such a list or named indices of performance/cognition would make the protocol complete.

3. Is the planned statistical analysis appropriate?
I defer to the study statistician.

4. Is the writing acceptable?
Yes.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

I declare that I have no competing interests.