Reviewer's report

Title: Therapeutic Hypothermia for Perinatal Asphyxial Encephalopathy in a Low Resource Hospital Setting in Equatorial Africa: Pilot Randomized Controlled Trial of Cranial Ultrasound and Neurodevelopmental Follow up at 18-22 months

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Reviewer: Alistair Gunn

Reviewer's report:

This manuscript is a straightforward report of a trial protocol. The basic protocol and initial trial data have been previously reported as stated clearly in the text, reference 22. However, the authors now provide much more detail, that should be of interest to others considering similar studies.

Other than this, I have no major concerns. The worry about introducing active cooling into already stretched and under-resourced neonatal care in the developing world is sadly legitimate, and appropriate RCTs are essential.

Minor essential revisions.

Page 7, para 1 (first para of Background). The statement about thrombocytopenia and arrhythmias is misleading. The effect on thrombocyte counts is I believe real, but small, and there is no overall evidence from meta-analysis that it is associated with increased risk of bleeding or requires correction. Only one, small pilot study from Southwestern found any such changes, that have not been replicated. The 'arrhythmia' associated with mild whole body hypothermia is sinus bradycardia. There is no evidence that this should be treated.

Page 11, Results, para 1, mid para. The statement that 'it is unclear whether endogenous hypothermia is neuroprotective' is not clearly correct. There is an extensive animal literature that hypothermia, whether induced by drugs or environmental temperature or active heat transfer after severe hypoxia-ischemia, is similarly protective. This evidence is sufficiently compelling that many centers in the developed world now routinely initiate passive cooling in outborn infants before transfer.

More generally I was very struck by the degree of passive cooling originally reported in reference 22, and I cannot help wondering whether this is not the major challenge facing trials of cooling in the developing world? --- that many infants are already being cooled, whether we know it or not. The authors acknowledge this point, but I wonder if it could perhaps be strengthened?

Page 12, 'cranial ultrasound'.

It is well known that, as recently presented by Terri Inder, U/S has limited sensitivity and resolution for HI injury. Similarly, I am not aware of any data relating evolution of clinical neurological signs to acute vs subacute vs chronic...
injury. Of course, I may well have missed such a study and would be most interested if there were any data. Thus, I am pessimistic whether these goals will be achieved. This section should be significantly toned down and appropriate caveats stating the limitations should be added.

Trivia.

page 2, abstract, discussion, 'these data' should probably be 'this trial', since no data are presented.

Page 5, aims. I find the statement in the middle of the aims that 'these aims have been achieved' etc, to be confusing on first reading, since it is not necessarily clear what 'these' refers to. I wonder whether it should be moved to the beginning of the aims, and rewritten clearly? e.g., something like, the first two aims have been, etc.

page 11 (discussion line 4) references should be merged.

please change 'endogenous' hypothermia with 'passive' throughout

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests