Author’s response to reviews

Title: Pilot Randomized Trial of Therapeutic Hypothermia with Serial Cranial Ultrasound and 18-22 Month Follow-up for Neonatal Encephalopathy in a Low Resource Hospital Setting in Uganda: Study Protocol

Authors:

Nicola J Robertson (n.robertson@ucl.ac.uk)
Cornelia F Hagmann (corneliahagmann@london.com)
Dominique Acolet (d.acolet@imperial.ac.uk)
Elizabeth Allen (Elizabeth.Allen@lshtm.ac.uk)
Natasha Nyombi (nyombin@yahoo.com)
Diana Elbourne (Diana.Elbourne@lshtm.ac.uk)
Anthony Costello (cihdcostello@gmail.com)
Ian Jacobs (i.jacobs@ucl.ac.uk)
Margaret Nakakeeto (mnakakeeto@yahoo.co.uk)
Frances Cowan (f.cowan@imperial.ac.uk)

Version: 3 Date: 20 February 2011

Author’s response to reviews: see over
Dear Editors,

MS: 6530396444572873

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
Nicola J Robertson, Cornelia F Hagmann, Dominique Acolet, Elizabeth Allen, Natasha Nyombi, Diana Elbourne, Anthony Costello, Ian Jacobs, Margaret Nakakeeto and Frances Cowan

Thank you very much for the opportunity to respond to the reviewer comments. We have responded to each point in turn and made changes that can be viewed in the version with track changes. We also provide a copy with no track changes. We hope that the manuscript is acceptable for publication in Trials.

Reviewer replies

Reviewer: Keith Wheatley

Thank you very much for these helpful comments

1. The epidemiological evidence is now referenced
2. Yes – it is possible that patients included in this trial will also be analyzed as part of subsequent larger RCTs at some point, however we suggest that RCTs of therapeutic hypothermia are unlikely to be performed in the near future in a low resource setting such as this. We have explained this in more detail in the discussion.
3. Yes – we have included this comment that the pilot study may at some point in the future help with a sample size calculation.
4. I apologize for this mistake – it should read < 36 weeks
5. As 20,000 births per year occur at Mulago Hospital and perinatal asphyxia occurs in around 17 /1000 live births, we were able to exclude those families living >25km from the hospital and still recruit sufficient infants. This was done on the advice of the local staff who in previous trials found it very problematic following patients who lived this distance form the hospital.
6. We have removed the word “consecutive” as this was potentially misleading
7. We have changed the tense throughout to past tense
8. The number of data loggers will not be a problem in future trials as there would be sufficient resources for more of these temperature monitoring systems.
9. This was a typographical error which ahs now been corrected to oxygen
10. Thank-you. 14.6 is now defined as standard deviation
11. The word trend has now been removed
12. WE have now included the absolute difference
13. This was not an efficacy trial but a feasibility trial and so we did not adjust for severe NE in the analysis
14. Thank you for this comment. We have now expanded the discussion section on why a larger trial might not be warranted at the moment. We have discussed the future studies now on-going that have arisen out of this pilot study.

Reviewer: Alistair Gunn
Thank you for these comments.

Minor essential revisions:

Page 7, para 1. We have removed the potentially misleading statement about thrombocytopenia and arrhythmias.

Page 11, Results, para 1. We agree that this is potentially misleading and have removed this sentence.

We have strengthened the point that many standard care infants are actually being cooled and have also highlighted the fact that in the NICHD trial, standard care infants were hyperthermic. We emphasize that this is a very different situation to low resource settings.

P12 cranial ultrasound
We acknowledge the reviewer’s point here. We suggest that in experienced hands, cranial ultrasound findings can correlate with MRI especially in BGT injury. However, we have added a section here explaining more about the caveats of cranial ultrasound.

trivia
Thank you for pointing out these errors. We have corrected them all.

Yours sincerely

Nikki Robertson