Author’s response to reviews

Title: Community-based interventions to prevent serious complications following spinal cord injury in Bangladesh: the CIVIC trial statistical analysis plan

Authors:

Robert Herbert (r.herbert@neura.edu.au)
Lisa Harvey (l.harvey@usyd.edu.au)
Mohammad Hossain (mohammad.s.hossain@sydney.edu.au)
Md. Islam (physio.shofiqul@gmail.com)
Qiang Li (qli@georgeinstitute.org)
Laurent Billot (lbillot@georgeinstitute.org)
NA The CIVIC Trial Collaboration (lisa.harvey@sydney.edu.au)

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Author’s response to reviews:

Professor Maura Marcucci
Associate Editor
Trials

10th December 2018

Dear Professor Marcucci,

Re: Revision of MS

MS number: TRLS-D-18-00593

Paper titled: Community-based interventions to prevent serious complications following spinal cord injury in Bangladesh: CIVIC trial statistical analysis plan

Thank you for the reviewers’ comments on our manuscript. We have addressed all of the comments and attached our itemised response.

Sincerely,
Professor Lisa Harvey

REVIEWER #1

Comment: This paper describes statistical analysis that will be conducted in the ongoing trial. This is good practice, the protocol of the trial is already published and now the authors are publishing the planned analysis. All the planned statistical analysis are sound and I recommend the authors for this good practice of thinking through the analysis before the end of the study. I recommend this study unreservedly.

Response: Thank-you for your positive comments.

REVIEWER #2

Comment: Very good paper. Just some points needed to be more clear.

Response: Thank-you for your positive comments.

Comment: On page 7, lines 2 -5: "The allocation sequence was ... command in Stata." It's Ok, but this does not inform us about the allocation ratio. Please provide more information about allocation ratio in this section. NB: It is in the flow chart that one can understand that is 1:1

Response: Thank-you for this comment. We have added text to the MS to clarify this issue. The new text states:

"Participants were randomised in a 1:1 ratio to an Intervention or Control group using randomly permuted blocks. The allocation sequence was stratified by level of lesion (paraplegia or tetraplegia) using the user-written ralloc command in STATA (Ryan, 1998)."

Comment: Page 10. Concerning your first outcome analysis. It not clear the co-variables that you want to adjust for and why. Please provide any explanation on that point.

Response: Thank-you for this comment. The primary analyses described on page 10 are not adjusted. The sensitivity analyses (page 11) will be adjusted for the stratification variable (level of lesion). Secondary analyses will be adjusted for the stratification and baseline variables. We have added text to the MS to clarify this issue. The new text states:

“The primary effectiveness analysis will compare time to death from any cause in the Intervention and Control groups. Kaplan-Meier survival curves will be compared using the log-rank test (two-tailed α=0.05).”
“The primary estimates of the size of the effect of the intervention will not be adjusted for covariates. Effect estimates will be expressed as:…”

“Between-group comparisons of secondary outcomes will be conducted using linear models, adjusting only for the stratification and baseline variables. In these models, the outcome will be a linear function of intervention and level of lesion (tetraplegia or paraplegia). For continuous outcomes, baseline scores will be included in the model to increase statistical precision and statistical power.”

Comment: On page 11, "Sensitivity analyses: Additional testing will be conducted using a Cox model adjusted for level of lesion (tetraplegia or paraplegia)". Since your randomisation sequence was done using level of lesion, and that "level of lesion" could not be a confounding variable anymore (if the randomisation was successfully done), what will be the aim of this sensitivity analysis?

Response: Thank-you for this comment. The purpose of this adjustment is not to adjust for confounding but to account for the potential correlations created by the stratification process (reference: Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med. 2012 Feb 20;31(4):328-40. doi: 10.1002/sim.4431. Epub 2011 Dec 4.).

In addition to the responses to the Reviewers’ comments, listed above, we made one further change to the manuscript. A new sentence was added (the last sentence in the manuscript) to explain that the efficacy analyses will provide some insights into the safety of the intervention. The new text states:

“Instead, the efficacy analyses will be used to provide insights into safety because the primary outcome and many of the secondary outcomes reflect adverse events.”