Author’s response to reviews

Title: Detailed statistical analysis plan for the Target Temperature Management after Out-of-hospital Cardiac Arrest trial

Authors:

Niklas Nielsen (niklas.nielsen@med.lu.se)
Per Winkel (winkel@ctu.dk)
Tobias Cronberg (tobias.cronberg@skane.se)
David Erlinge (david.erlinge@skane.se)
Hans Friberg (hans.a.friberg@gmail.com)
Yvan Gasche (yvan.gasche@hcuge.ch)
Christian Hassager (christian.hassager@regionh.dk)
Janneke Horn (j.horn@amc.uva.nl)
Jan Hovdenes (jan.hovdenes@oslo-universitetssykehus.no)
Jesper Kjaergaard (jesper.kjaergaard@regionh.dk)
Michael Kuiper (mi.kuiper@wxs.nl)
Tommaso Pellis (thomas.pellis@gmail.com)
Pascal Stammet (stammet.pascal@chl.lu)
Michael Wanscher (michael.wanscher@regionh.dk)
Matthew P Wise (mattwise@doctors.org.uk)
Anders Åneman (anders.aneman@sswahs.nsw.org.au)
Jørn Wetterslev (wetterslev@ctu.dk)

Version: 2 Date: 14 August 2013

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

Thank you for providing us with the comments from the reviewers. The point-by-point response follows after this letter. Please find uploaded on your home page a revised version of the manuscript that we hope you will find improved, after being modified according to the reviewers suggestions. We would like to inform you that the TTM-trial is completed, with the last follow-up performed approximately one month ago. The database has been locked and the files are now with the statistician. We anticipate the - still blinded - results to be delivered to the author group within a week or so, and we plan for a submission within three weeks. Since the manuscript of the “Detailed statistical analysis plan” still was under review when we were close to the completion date, we uploaded a condensed version of the plan on clinicaltrials.gov, with permission from your editorial office. We believed it important to have the plan made public before any analyses were undertaken.

Due to technical problems (undelivered emails) we never received the decision letter from Trials, which postponed our ability to respond swiftly. We therefore hope and ask that the review process of the revised manuscript will be as quick as possible. Please notify us if there is anything that we could do to assist if needed.

Yours sincerely

Niklas Nielsen, MD, PhD

Dept of Clinical Sciences

Lund University, Helsingborg Hospital, Sweden
Authors response: We thank the three reviewers for their insightful comments and suggestions. We have tried to address all of them in this new version of the manuscript and we believe that the comments have helped us improve the clarity of the analysis plan.

Reviewer 1.
The manuscript (MS) submitted by Nielsen et al. describes the statistical considerations for a large multi-center study of outcome from cardiac arrest (CA) in adults. The author state that the study design and rationale has been published before (refs 3 and 4). Given the fact that study enrollment is completed and the database will be closed in less than two months, this is a timely publication of the statistical methods. It is, however, unknown – and not mentioned in this MS – if there were any changes to the statistical approach since the study was conceived. It is, however, mentioned in the MS that the current version of the protocol is 3.3 – suggesting that adjustments might have been considered even for the statistical approach to the data.

Authors response: Thank you for these comments. During the planning phase and the course of the trial there have indeed been changes, both to the protocol and to the statistical approach. We believe that it is not possible to give all the details in the current manuscript. The most important issue is that we report and fully disclose our statistical approach before we start the analysis process of the trial and before we break the randomization code.
It is most likely not to my task as a reviewer to comment on the design of this study which was discussed earlier. However, for completeness, it should be stated what the current guidelines are.

The MS is focused mostly on the statistical approach to the data and the rationale and practical conduct is addressed only briefly, with references to previously published works. Such an approach is of limited value to the reader who is not a statistician. It may be worth to reiterate in the introduction some important, yet statistical-oriented details, namely that the seminal clinical studies on hypothermia showed an effect with number needed to treat = 6. This was of course based on the selected patient population, namely ventricular fibrillation CA, i.e. shockable rhythm. This study, in contrast, enrolls all patients with presumed cardiac origin of CA. It is probably hypothesized (and there are references supporting this hypothesis) that therapeutic hypothermia will be less effective in CA with non-shockable rhythm, which leads to a larger number of subjects to be studied to be able to properly test the hypothesis stated in this MS.
Authors response: This is a valid point and was definitely missing in the first version of the manuscript. We have now given a short summary of the field with references to the two RCTs. Regarding the sample size, we will include a much larger population than previously investigated in cardiac arrest trials, and our risk reduction used in the sample size calculation is smaller than the risk reduction that was observed in the HACA and Bernard-trials. We have also used a clinical registry (INTCAR and Hypothermia Network) to simulate and estimate a mortality rate that is relevant to the study population. Non-shockable rhythms of presumed cardiac cause also have a better survival than all cause non-shockable rhythms. Finally we have used mortality/survival as our primary outcome which give benefit to the “standard” composite outcome of neurological function and survival status. We have in the Design article previously published discussed these issues. However, we fully acknowledge that a trial sample size always is a balance between feasibility, economics and statistics.

The MS text flows smoothly but at times I have doubts about what the message is. Some sentences are long, providing all-inclusive details – which results in the “lost in translation” phenomenon. The initial sentence of Section 2 that spans over 4 lines is a good example. Do we really to know all this in a single sentence? Please consider revising the text so it is more palatable. Similarly, in Section 10 there is a 5-line sentence which ends with the statement “this was the fundament for the order of outcomes”. Please consider revising.

Authors response: These sections have been revised and the long sentences are now divided into separate sentences. We hope that this revision has improved the clarity.

There are some sections that seem to be out of place, e.g. last sentence in Section 5 “Quality of life defined with Short-Form 36.” I believe this entry needs to be put into some context.
I am unsure about some terminology in this MS:

- If there is data missingness…
- Imputing missing values…

Unless these are established statistical terms (not known to me and not traditionally used in the scientific literature that I read), please consider revising, e.g. “Missing data will be treated as follows:”

Authors response: We believe that this is established statistical terms used in current literature and have thus kept it unchanged. Please see for instance:


I also suggest revising the following terms/typos:

Abstract: ACCORDING to A systematic review, previous trials…

Abstract: The TTM-trial is… trial of induced hypothermia OR NORMOTHERMIA in 950 adults….

Page 9 novel LBBB… rather NEW LBBB page 12 The multiplicity problem is further illuminated… rather addressed?

Page 13 Patients who did not meet… WERE randomized

Page 14 …delineate which events drive this difference.
Conclusion – needs to be revised. I suggest “This article describes principles of analysis used in the TTM-trial for the first publication of the main outcomes. Our approach aims to minimize the risk for data driven results and outcome reporting bias.”

(At least I think this is what you meant to say but please revise accordingly.)

Authors response: Thank you. These corrections are done according to the above suggestions.

Reviewer 2:

I have read this account carefully – I congratulate the authors for undertaking such an important study and for outlining the analysis and data presentation plan with such clarity and rigor.

The rational for the study is powerful, underscores major concerns with wholesale promulgation and uptake of several current guidelines, and will likely shape care in this area for a decade or more. It may be among the most important and most generalizable practical issues in medicine.

The key issues are the intention to treat analysis, the sequence of -and approach to- primary and secondary analyses and the plans to compare adjusted and unadjusted analyses as sensitivity to the potential for the presence of unmeasured confounders.

The study appears to be based on sensible effect sizes and seems adequately powered.

I suggest a clear statement that in the event of significant missing data (this is NOT anticipated), ‘raw’ (unadjusted, non-imputed) data and analysis be presented, if only in an appendix.
Authors response: Thank you for this important comment. This is now stated in the manuscript.

A small suggestion: consider adding a question to the spouse/life partner about the patient’s comparative mental state (in addition to the ‘self question’).

Authors response: This is a very good point and it is in fact already done, but was not specifically outlined in this manuscript since we will not be able to present it in the main publication of the trial, due to the complexity of the detailed neurological follow up battery (which includes several questions to spouse/life partner/relative). We have clarified this in the text.

I have no comment on the alternative options outlined for the sequence of analyses of the multiple secondary outcomes. However, I suggest that priority be accorded to definitions that are more solid/less nebulous (e.g. renal replacement therapy, seizures, specific bleeding vs. ‘sepsis’).

Authors response: Thank you for this comment. We realize that the description of the adverse events was not optimal. We have inserted a Table 1 with the adverse events collected in the trial.

Congratulations.

Reviewer 3

It was unorthodox to make survival, rather than functional outcome, the primary endpoint.
This is described adequately in the Discussion section, and the authors have appropriately chosen the more conservative (and therefore powerful) measure. They do not consider in the brief discussion, however, the possibility that survival differs between the groups but functional outcome does not.

Authors response: We have inserted a short line on that subject.

An outstanding feature of this trial is the standardization of prognostication and withdrawal of life support practices. It is a modern and inspired approach that removes the most important, and previously unconsidered, variable.

Authors response: Thank you for these comments!