Reviewer's report

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

**Version:** 1  **Date:** 20 May 2013

**Reviewer:** Tomas Drabek

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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.

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.

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.

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:”

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.

Page 18 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.)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

No competing interests.