Author’s response to reviews

Title: Electroencephalography (EEG) for neurological prognostication after cardiac arrest and targeted temperature management; rationale and study design

Authors:

Erik Westhall (erik.westhall@skane.se)
Ingmar Rosén (ingmar.rosen@skane.se)
Andrea O Rossetti (andrea.rosetti@chuv.ch)
Anne-Fleur van Rootselaar (a.f.vanrootselaar@amc.uva.nl)
Troels W Kjaer (neurology@dadlnet.dk)
Janneke Horn (j.horn@amc.uva.nl)
Susann Ullén (susann.ullen@skane.se)
Hans Friberg (hans.friberg@skane.se)
Niklas Nielsen (niklas.nielsen@med.lu.se)
Tobias Cronberg (tobias.cronberg@skane.se)

Version: 2 Date: 16 June 2014

Author’s response to reviews: see over
Dear Gerard Clunn,

We apologize for the obvious imprecision in our description of the study design. We are aware of your policy regarding retrospective studies and agree that the scientific interest in such protocol manuscript is minor.

After consultations with our statisticians and discussions among the trialists we would like to stress that the study design in our manuscript “Electroencephalography (EEG) for neurological prognostication after cardiac arrest and targeted temperature management; rationale and study design” is indeed prospective in all important aspects and we would appreciate if you could consider it once more for publication in BMC Neurology. We consider a pre-analyses publication of the protocol an important part of this study and vital for the interpretation of our data. Since EEG is the most used method for prognostication after cardiac arrest next to a clinical examination and this study is the first international trial on EEG-patterns and the first to use a newly developed classification and multiple international EEG-experts as interpreters, it is therefore likely to be of major impact to the field. We believe that this protocol will be much asked for and cited.

This EEG-study is by our opinion largely a prospective study although the prospective/retrospective terminology is difficult to apply for a diagnostic study:  
* A routine EEG was included in the study protocol of the TTM-trial at 12-36 hours after the intervention if the patient was still comatose.  
* We contacted all sites before start of the trial and gave technical recommendations on how to register the EEGs.  
* The presence of clinical seizures, use of sedative and antiepileptic drugs, glasgow coma scale on the day of the EEG-registration, etc, were prospectly documented.

After the inclusion and follow-up phase of the TTM was finished, we collected all EEGs and commenced the analyses phase but all EEG-interpretations are made by interpreters completely blinded for data on outcome. During the analyses, the statistician will be blinded for outcome data as well and the specific hypotheses have been pre-specified in this manuscript.

In the TTM-trial, we have followed the CONSORT-guidelines and the publication of protocol and statistical analyses plan have been a vital part of this much cited study. In addition, we recently published the protocol of a large TTM substudy on cognition with a similar analyses strategy as the EEG-trial in BMC Cardiovascular disorders.

We are sorry for not making the prospective nature of the study design clear to you in the earlier cover letter. We have made some minor corrections of the manuscript to avoid further misunderstandings.

Jhonell De Los Santos asked for additional information:

1. Ethical and Funding Approval Documentation: The TTM-trial has been ethically approved in all participating countries and the ethical approval document for Sweden and the consent form for Sweden has been sent to BMCSeriesEditorial@biomedcentral.com as well as funding approval documents from the largest funders of the TTM-trial: AFA(55900Euro), The Swedish Heart and Lung Association(33200Euro), The Swedish Research Council of the Swedish National Health System(ALF) (23700Euro).
2. Funding: The study is externally funded by governmental funding and non-commercial organizations. The funding from AFA is from a non-profit organization within this insurance company. The funders have not influenced the study design. The study protocol of the EEG-study within the TTM-trial has not undergone peer-review by the funders.

3. Study status: The EEG-study is an ongoing study. All 399 EEGs have been registered at the 36 sites. The collecting of EEGs from the sites are ongoing. No EEG-data has been analysed.

4. Related Articles: The EEG-data of the present study protocol has not been published or submitted to any journal. The main results of the TTM-trial has been published in N Engl J Med dec 5 2013.

With kind regards

Tobias Cronberg, MD, PhD
Erik Westhall, MD
Susann Ullén, PhD

Associate professor
Department of Neurology
Skane University Hospital
221 85 Lund
Sweden

Lund, June 3, 2014


