

# TRIAL PROTOCOL

**Target temperature management 33°C versus 36°C after out-of-hospital cardiac arrest,  
a randomised, parallel groups, assessor blinded clinical trial**

Short title: **Target Temperature Management After Cardiac Arrest**

Acronym: **TTM-Trial**

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**Abstract: Title:** Target temperature management after out-of-hospital cardiac arrest, a randomised, parallel groups, assessor blinded clinical trial. **Trial acronym:** TTM-trial (Target Temperature Management after Cardiac Arrest) **Background:** Experimental studies and previous clinical trials suggest an improvement in mortality and neurological function with hypothermia after cardiac arrest but the present data is inconclusive and the optimal temperature is not known. **Intervention:** Patients will be managed with 24 hours temperature control at 33°C versus 36°C according to randomisation. Temperature control will be delivered with temperature management equipment at the discretion of the trial sites. **Design:** Multicentre, international, randomised trial with 1:1 concealed allocation of 950 out-of-hospital cardiac arrest patients to temperature control for 24 h at 33°C versus 36°C with blinded outcome assessment. **Inclusion criteria:** Age  $\geq 18$  years, out-of-hospital cardiac arrest of presumed cardiac cause, unconsciousness (Glasgow Coma Score  $< 8$ ) after sustained return of spontaneous circulation (ROSC) (20 minutes of circulation). **Exclusion criteria:** Conscious patients, pregnancy, out-of-hospital cardiac arrest of presumed non-cardiac cause, cardiac arrest after arrival in hospital, known bleeding diathesis, suspected or confirmed acute intracranial bleeding, suspected or confirmed acute stroke, temperature on admission  $< 30^\circ\text{C}$ , unwitnessed asystole, persistent cardiogenic shock, known limitations in therapy, known disease making 180 day survival unlikely, known pre-arrest cerebral performance category 3 or 4,  $> 240$  minutes from ROSC to randomisation. **Primary outcome:** Survival to end of trial (at least 180 days). **Secondary outcomes:** Composite outcomes of all-cause mortality and poor neurological function (Cerebral Performance Category (CPC) 3 and 4 and modified Rankin Scale (mRS) 4 and 5) at 180 days. All-cause mortality and CPC and mRS at 180-days. Adverse events: Bleeding, pneumonia, sepsis, electrolyte disorders, hyperglycaemia, hypoglycaemia, cardiac arrhythmia, renal replacement therapy. **Tertiary outcomes:** Complete neurological recovery. Best neurological outcome during trial period. Quality of life according to SF-36. Biomarkers at 24, 48 and 72 hours.

## **List of abbreviations**

AHA	American Heart Association
CA	Cardiac Arrest
CABG	Coronary Artery Bypass Grafting
CPC	Cerebral Performance Category
CRF	Case Record Form
CRP	C-reactive Protein
CTU	Copenhagen Trial Unit
CVVH	Continuous veno venous Haemofiltration
DSMC	Data Safety Monitoring Committee
DNR	Do not resuscitate
ECG	Electrocardiogram
EEG	Electroencephalogram
eCRF	Electronic Case Record Form
ECRIN	European Clinical Research Infrastructures Network
ERC	European Resuscitation Council
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
IABP	Intra Aortic Balloon Pump
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
ILCOR	International Liaison Committee on Resuscitation
INR	International Normalised Ratio
IVRS	Interactive Voice Response System
LOS	Length Of Stay
MIH	Mild induced hypothermia
OHCA	Out-of-hospital Cardiac Arrest
PCI	Percutaneous Coronary Intervention

PEA Pulseless Electrical Activity  
RCT Randomised Clinical Trial  
ROSC Return of Spontaneous Circulation  
SAPS Simplified acute physiology score  
ScVO2 Central venous saturation  
SOFA Sequential organ failure assessment  
SvO2 Mixed venous saturation  
VF Ventricular Fibrillation  
VT Ventricular Tachycardia  
UCG Ultrasound cardiogram

## **Trial flow chart**

**Phase 1** (hospital admission to start of intervention): Patients with out-of-hospital cardiac arrest (OHCA), admitted to hospital and who are unconscious with sustained return of spontaneous circulation (ROSC) are eligible for screening. The inclusion window is 220 minutes: i.e. from 20 minutes after ROSC (defined as sustained ROSC) and to 240 minutes after ROSC. The patients' eligibility for trial inclusion is assessed according to inclusion and exclusion criteria. Patients are randomly assigned to intervention group. Baseline characteristics are obtained.

**Phase 2-intervention period** (start of intervention to end of intervention): Patients are sedated and mechanically ventilated. Patients are treated for 24 hours at target temperature with temperature management devices with external or internal temperature control to achieve a target core temperature of either 33°C or 36°C according to intervention allocation. Patients are rewarmed to a core temperature of 37°C during 8 hours.

**Phase 3** (from end of intervention period to 72 hours after end of intervention period) Sedation is stopped at 37°C. Normothermia of 37°C $\pm$ 0.5°C is maintained until 72 hours from ROSC in both treatment groups, if the patient still is comatose. Neurological evaluation is performed by blinded physicians at 72 h, or later, after end of the intervention period.

**Phase 4** (72 h after end of intervention period to 28 days after OHCA): Neurological status, according to the CPC-scale, and survival are evaluated every day in the intensive care unit and/or at day 1, 2, 3, 4, 5, 6, 7, 14, 21 and 28, and/or at hospital discharge, whichever comes first. If the patient is discharged from hospital, site personnel will contact the patient after end of phase 4.

**Phase 5** (day 28 to end of trial): Survival and neurological status are evaluated on day 90 and day 180. Evaluation is performed by a follow-up research nurse and/or behavioural

therapists blinded to the intervention allocation. Survival will be followed until end of the trial for all patients.

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## **Ethical approvals**

Australia: Health Ethics Review Committee Protocol No X11-0150 & HREC/11/RPAH/216 –  
“GI-CCT886

Czech Republic: Ethics committee of the General University Hospital of Prague, c/j 193-11 S  
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Denmark: De vitenskabetiske Komiteer i Region Hovedstaden, H-1-2010-059

Italy: Comitato Etico Indipendente, Hospedaliara S Maria degli Angeli Pordenone, No 9

Luxembourg: Comité National d’Ethique de Recherche CNER No 201007/05 Ver 1.0

The Netherlands: Medisch Etische Toetsingscommissie MEC 10/107 # 10.17.0921

Norway: Regional komité for medisinsk och helsefaglig forskningsetikk Sør-øst C Ref  
2010/384

Sweden: Regional Ethical Review Board Lund, Protocol 2009/6 Dnr 2009/324 (TTM-Trial)

Switzerland: Comité d’Ethique de Recherche CER 10-254 (NAC 10-088)

United Kingdom: Cardiff and Vale Research Review Service, Project ID 10/AIC/4927,

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## **1. Introduction/background**

The brain of a patient resuscitated after cardiac arrest (CA) may have suffered ischaemia and when the spontaneous circulation is re-established, the subsequent reperfusion may cause further damage.<sup>1</sup> Brain ischaemia and the reperfusion injury lead to tissue degeneration and loss of neurological function, the extent dependent on duration and density of the insult. Temperature control and mild induced hypothermia (MIH) (33-36°C) mitigate this damage in the experimental setting<sup>2-6</sup> and clinical trials have shown promising results in improving neurological function and survival.<sup>7, 8</sup>

### **1.1 The condition/population**

In Europe approximately 40 patients per 100,000 inhabitants per year suffer from out-of-hospital cardiac arrest (OHCA).<sup>9</sup> Mortality after OHCA is high and for patients hospitalised alive, the survival has been reported to vary between 34% and 56%.<sup>10-13</sup> Further, the frequency of persistent neurological deficits varies considerably.<sup>10, 13-17</sup> At admittance to hospital the body temperature of resuscitated OHCA patients is reported to be around 36°C,<sup>18, 19</sup> but it is then often gradually rising. Elevated body temperature is common during the first 48 h after CA<sup>20, 21</sup> and is associated with worse outcome.<sup>18</sup> The post-resuscitation period was previously regarded as the missing link in the chain of survival, but during the last years this has changed.<sup>22</sup> Research has focused on the use of temperature control with MIH, but the general care of CA patients has improved with standardised active intensive care<sup>23</sup> and attention to coronary reperfusion and circulatory support.<sup>24, 25</sup>

### **1.2 Preclinical data**

The post-ischaemic period is complicated by hyperthermia induced by generation of pyrogens in the brain but also hyperthermia secondary to infection. Fever occurring during the first 48 hours after global ischaemia may be detrimental<sup>26</sup> and is in considerable disfavour of an optimal cerebral metabolic rate of oxygen.<sup>27</sup> Bringing temperature to normothermia diminishes brain damage in the experimental setting.<sup>26</sup> The development of ischaemic

neuronal damage is a complex process, involving multiple mechanisms acting synergistically or in series. After an early contribution of excitotoxicity and free radical oxidative stress, inflammation, calcium imbalance, modification of gene transcription and apoptosis appear to contribute to damage in experimental models.<sup>1</sup> MIH with decreased body and brain temperature effectively diminishes brain damage in animal models of cardiac arrest ischemia.<sup>2-6</sup> The protective action of mild hypothermia is probably multifactorial affecting multiple detrimental mechanisms<sup>28</sup> which may account for its efficacy as a protective intervention: lowered cell metabolism, diminished excitotoxicity, less calcium overload, less inflammation, modified gene expression and anti-apoptosis.

### **1.3 Clinical data**

The process of translating MIH into clinical practice is supported by animal experimental data. The results from two clinical trials have changed current guidelines and MIH is now recommended as a treatment for adult OHCA patients who are unconscious when resuscitated after a primary cardiac rhythm of ventricular fibrillation or tachycardia.<sup>29, 30</sup> Guidelines also have an addendum that MIH might be beneficial for in-hospital cardiac arrests and for cardiac arrest with other primary rhythms.<sup>30</sup> However, there are no trial data or references to support these latter statements. We have conducted a systematic review showing that the GRADE level of the quality of evidence, to support the adoption of the guidelines, is “low”.<sup>31</sup> The implementation of MIH varies between countries and continents and in many places MIH is not utilised but in some it has become standard practice.<sup>32-36</sup> In surveys physicians state lack of firm evidence, lack of resources and equipment, and too technically difficult, among others, as reasons for not implementing MIH.<sup>33, 36, 37</sup> There has been criticism of the rapid inclusion of MIH into clinical guidelines.<sup>38-40</sup> However, when read carefully, the RCTs conclude that further studies to support MIH are essential and the guidelines state that the optimal target temperature is not known.<sup>7, 8, 30</sup> Recently a Cochrane report was published supporting the use of MIH but this study did not evaluate possible design errors, the risk of random error and reported selectively on the risk of bias.<sup>41</sup> Also

possible adverse events as infection, arrhythmia, coagulopathy and electrolyte/metabolic disorders have been poorly studied and reported in previous trials. In a meta-analysis there was a trend towards more adverse events in the hypothermia group, but the difference was not statistically significant, maybe because of a limited sample size.<sup>42</sup>

In conclusion, the evidence for MIH per se compared to no temperature treatment is of low quality, the optimal core temperature for post cardiac arrest care is not known and observational evidence supports the theory that temperature management may be of great importance.

#### **1.4 Experimental intervention and control intervention**

The trial will investigate whether target temperature management (TTM) of two different regimens affect survival and neurological outcome; TTM of 33°C (TTM33) and TTM of 36°C (TTM36) for 24 h after resuscitation from OHCA.

Target temperature management will be instituted on CA patients who are unconscious after ROSC. Patients will be mechanically ventilated, sedated (propofol/fentanyl or midazolam/fentanyl depending on haemodynamic stability) and when necessary paralysed with neuromuscular blocking agents to reduce shivering and subsequent heat-generation and energy consumption. The core body temperature will be set as quickly as possible at the predefined target temperature, according to intervention allocation, with 4°C intravenous solutions,<sup>43</sup> ice-packs<sup>8, 44</sup> and commercially available cooling devices<sup>45</sup> at the discretion of the treating physician. The target core temperature is then maintained for 24 h. After the maintenance period core temperature is gradually raised to normothermia of 37°C during 8 hours with a rewarming rate of 0.5°C/hour in both groups. Body temperature is then maintained at normothermia 37 ±0.5°C until 72 hours from sustained ROSC in both treatment groups, as long as the patient is in the ICU, using pharmacological treatment and temperature management systems when applicable.

## 1.5 Regimen rationale

Target temperature of 33°C (TTM33): Animal data and previous clinical data indicate that MIH is beneficial after CA. There are no conclusive studies indicating what level of temperature management that has the highest yield after CA. Animal data and previous clinical trials suggest a benefit of MIH of 32-34°C.<sup>7, 8, 46</sup>

Target temperature of 36°C (TTM36): Both animal experiments and clinical data show that brain temperature is gradually rising after CA and that this temperature increase is associated with worse outcome<sup>13, 18, 20, 21, 47</sup>. In the experimental setting brain damage is diminished by bringing temperature back to normothermia<sup>26</sup>. In other types of brain damage (stroke and traumatic brain injury) fever is also associated with worse outcome<sup>48, 49</sup>.

According to the international guidelines fever should be avoided for the first 72 h after CA<sup>29</sup>. It may be so that inducing controlled normothermia and sub-febrile temperatures to CA patients is sufficient to protect the brain from injury. Although elevated temperature and poor outcome are related in a purely associative manner and not proven causative, we argue that a sub-febrile temperature comparator is essential. To be absolutely sure that trial patients are not exposed to temperatures over 37°C and possibly associated harm during the first 24 h we have decided to choose a target temperature of 36°C for the control patients.<sup>31</sup> Also, the cardiac arrest patients admitted to hospital with a cardiac cause of arrest have initial median temperatures of 36°C,<sup>19</sup> why it seems reasonable to keep the comparator temperature at an unadjusted level, not warming or cooling the population.

Duration of intervention: There are no conclusive studies indicating what duration of temperature control that has the highest yield after CA. The previous randomised studies used 12 and 24 h respectively. Data from preliminary studies on stroke and traumatic brain injury indicate that the risk of adverse effects increase when MIH is applied for more than 24 h. Thus we have chosen a target management maintenance duration of 24 hours.

Mode of delivering the interventions: Reports indicate that both external and intravascular cooling methods are feasible and that they maintain temperature with high accuracy. There are no randomised studies so far indicating that any of the treatments should be superior. To

minimise economic burden we will allow trial sites to use temperature management system at their discretion. Each trial site will need to describe the temperature management of each patient included in the trial, before randomisation and need to report any amendments during the trial period.

Comparison with other trials: The majority of patients randomised to MIH after CA was treated at 33°C for 24 h (approximately 150 patients). When using the same temperature range and time limits we intend to minimise the clinical heterogeneity in future meta-analyses.

## **1.6 Risk/benefits**

The published randomised studies and the meta-analyses performed on those studies indicate that the number needed to treat for OHCA patients are 6-7 for better neurological outcome and also survival, however, there were substantial risks that the effects were over-estimated. Adverse events with infection, coagulopathy, electrolyte disorders and arrhythmia are common in MIH-treated patients, but also in non-MIH-treated CA patients and in patients' unconscious of other causes. The impact on survival of these adverse events is not evaluated. There was a trend towards more adverse events in the MIH-group in one of the meta-analyses<sup>42</sup> and more bleeding in association with angiography in one observational study<sup>19</sup>. MIH-treatment may mandate deeper sedation/analgesia and possibly also muscle relaxants to avoid shivering. If shivering is not treated adequately it might increase energy expenditure. Normothermia is not associated with any risks of adverse events in comparison with MIH. TTM36 will avoid many of the potential adverse events as infection, bleeding and metabolic/electrolyte disorders, but it may be equally or more associated with shivering. Possible benefits of TTM36 are, if it is equally beneficial, or superior, in terms of survival and neurological outcome that patients might be spared some of the additional risks of adverse events that MIH may impose. Possible risks with TTM36 are that this treatment is inferior to TTM33 in terms of survival and neurological outcome. Interim-analyses are planned to counteract these potential differences in risks and benefits.

## 1.7 Ethical considerations

### 1.7.1 Ethical justification

Increased temperature is common 48 hours after cardiac arrest<sup>20, 21</sup> and is associated with worse outcome.<sup>13, 18, 49, 50</sup> Current guidelines advocate that hyperthermia should be avoided in the post cardiac arrest phase until 72 hours after cardiac arrest and that a group of cardiac arrest (unconscious OHCA patients with initial rhythm VT and VF) patients should be treated with MIH.<sup>51</sup> The guidelines for MIH are mainly based on two RCTs.<sup>7, 8</sup> There are in total five trials evaluating MIH after cardiac arrest.<sup>7, 8, 52-54</sup> There are objections to the design of and potential risks of bias associated with everyone of these trials: no data on pre-arrest neurological function or post-arrest/pre-randomisation level of consciousness were presented why important predictors of outcome were not assessable (risk of baseline differences), there were baseline differences in reported variables between groups (sex, diabetes, bystander CPR), there were no data on reasons for withdrawal of active therapy or assessment of neurological function/prognosis, and temperature was poorly controlled in the control arms allowing febrile temperatures. The largest trial, contributing with the majority of the randomised patients, included only 8% of the screened patients after OHCA who had return of spontaneous circulation (ROSC) after cardiopulmonary resuscitation. This trial was terminated early without a pre-defined power analysis and without adjusting p-values, intervention effect estimates or confidence intervals hereof for early stopping.<sup>7</sup> One trial had a quasi-randomisation procedure allocating after odd and even dates, which preclude allocation concealment as well as adequate generation of allocation sequence and produces high-risk of bias. Further, it had an unplanned adaptive design with an interim analysis after 80% of the total sample size without adjusting levels of significance. The trial also evaluated outcome at hospital discharge based on whereto patients were discharged (home or to a nursing facility) and the final significant result for a good neurological outcome was conditional on one single patient.<sup>8</sup> One small trial evaluated MIH in combination with continuous veno-venous haemofiltration but this trial was terminated early; there was no

difference between allocation groups in terms of death or neurological outcome.<sup>53</sup>

Additionally two minor inconclusive RCT has been published in the field of MIH after OHCA, one only in abstract form.<sup>52, 54</sup> Two meta-analyses based on the two RCTs have been published with no additional findings,<sup>42, 55</sup>. Recently a Cochrane report was published supporting MIH, but this study did not evaluate possible design errors, the risk of random error and reported only selected risks of bias. It relied exclusively on fixed effects meta-analysis and included the quasi-randomised trial in the main analysis.<sup>41</sup> However it included a passage about the presence of fever in the control groups: “The control groups differed with regard to fever control. Mean body temperature 12 hours after start of cooling in the “normothermia group” was around 37.6°C in the HACA-trial<sup>7</sup> and 37.4°C in the Bernard - trial<sup>8</sup>. The Hachimi-idrissi-trial<sup>52</sup> did not report on the body temperature of the control group. It is known that for each degree rise in temperature over 37 degrees Celsius, the risk of an unfavourable neurologic outcome increases, with an odds ratio of 2.26.<sup>18</sup> If this is true even for smaller temperature differences, the beneficial effect of therapeutic hypothermia might at least partly be due to an antipyretic rather than a hypothermic effect. It is questionable whether a strict temperature control would have the same effect as mild hypothermia - as shown in a study of fever control in patients in a neurologic intensive care unit, where no difference in outcome was found with fever control.<sup>56</sup>” However, the temperature was higher at 24 hours after start of intervention in the HACA-trial and the fever control trial mentioned was not designed to evaluate outcome. We performed a systematic review including design, systematic and random error that in addition to randomised trials also evaluated data from observational studies. The conclusion was that there was a non-negligible risk of spurious findings and over-estimated intervention effects. Using GRADE the quality of the evidence was “low”.<sup>31</sup> Trial Sequential Analysis<sup>57, 58</sup> showed that there still is an information gap of between 600 and 800 patients to confirm or reject the intervention effect when the cumulative meta-analysis is adjusted for repetitive testing on accumulating data in the perspective of a realistic intervention effect and information size (see appendix) even if the previously performed trials had been of impeccable design. Further, whether there is an optimal target

temperature for post cardiac arrest patients is not known. Moreover, two sub-febrile temperatures have never been tested for effect on survival and neurological outcome after OHCA. We therefore conclude that there is clinical equipoise to evaluate both the concept of MIH versus no target temperature management but also to the concept of target temperature management with two sub-febrile temperatures, allocating participants to 33°C and 36°C.

### **1.7.2 Informed consent**

This trial will be conducted according to national and international standards of good clinical practice. This protocol and any amendments will be submitted to the ethics committee for review and formal approval to conduct the trial. Written information and the consent form will be subjected to review and approval by the ethics committee.

Eligible patients are unconscious and unable to give informed consent in the acute setting. Current guidelines recommend MIH, or avoidance of hyperthermia, and that temperature control should be commenced as soon as possible after admission to hospital according to guidelines. Therefore randomisation ought to be justified before informed consent could be obtained according to the declaration of Helsinki Section 2.5. Patients regaining consciousness will be asked for informed consent. The consent form will be provided with written and oral information on this trial to be able to make an informed decision about participation in this trial. The consent form must be signed by the participant or legally acceptable surrogate and by the investigator seeking the consent. According to the Swedish, Norwegian and Luxembourgian ethical approval legal representatives should not be asked for proxy consent at hospital admission. They should however be informed that temperature management is studied on the patient and that the results from this trial will be evaluated. This may not be the procedure in other participating countries and to ensure the possibility of immediate inclusion and randomisation, which is mandatory for trial participation, a delayed consent procedure may be arranged.

## **1.8 Trial conduct**

This trial will be conducted in compliance with the protocol approved by the competent authorities, and according to good clinical practice standards. No deviation from the protocol will be implemented without the prior review and approval of the ethical committees except where it may be necessary to eliminate an immediate hazard to the trial participants. In such a case, the deviation will be reported to the regulatory authorities without delay.

## **2. Trial objectives and purpose**

Primary objective: To evaluate whether there is a difference in survival to 180 days or longer with a target temperature management at 33°C compared to a target temperature of 36°C, in patients unconscious after out-of-hospital OHCA.

Secondary objective: To evaluate whether there is a difference in the composite outcome of all-cause mortality and poor neurological function at hospital discharge and at 180 days with a target temperature management at 33°C compared to a target temperature of 36°C, in patients unconscious after out-of-hospital OHCA. To assess quality of life at follow-up. To investigate biomarkers for prognostication of neurological outcome. To assess safety with target temperature management with regard to infection, cardiac arrhythmia, electrolyte disorders and bleeding.

## **3. Trial design**

### **3.1 Trial design**

Multicentre, international, randomised trial with 1:1 concealed allocation of OHCA patients to target temperature managements at 33°C or 36°C for 24 h, with blinded outcome evaluation. Sample size: 950 patients.

### **3.2 Randomisation**

Trial sites will have access to Internet based randomisation to allow for immediate allocation and to ensure adequate allocation concealment and adequate generation of allocation sequence. Each patient will be assigned a unique trial and randomisation number.

Randomisation will be generated into dynamic blocks and stratified for trial site.

### **3.3 Trial intervention**

The intervention is an emergency procedure and temperature management should be commenced as soon as possible after sustained ROSC, screening and randomisation.

Patients will be managed with 24 hours temperature control at a target temperature of 33°C or 36°C according to intervention allocation. Temperature management will be delivered with commercially available equipment at the discretion of the trial sites. The type of equipment used for a specific patient will be registered prior to randomisation. To facilitate cooling, when applicable, and to stabilise the circulation patients may be treated with crystalloid infusion (4°C or room temperature according to treatment arm) at the discretion of the treating physician.<sup>43</sup>

### **3.4 Blinding**

Because of inherent logistical problems with blinding of temperature management the immediate caregivers will be unblinded during phase 2. Measures will be taken ensuring that the information about allocation will not spread from the immediate group of caregivers. A team of blinded external physicians will evaluate the patient at 72 hours after the intervention period is completed and report their recommendation on further life-sustaining treatment, together with the specialist in intensive care medicine who will have to retain his/her knowledge of allocation group. Further life-sustaining treatment will be delivered according to standard procedures and withdrawal of active intensive care will be at the discretion of the treating physician. Patients and their legal representatives will only be informed that they have received target temperature management. Outcome assessors will be blinded to the allocated intervention. The steering group and the management group will be blinded to the type of intervention during the entire trial period, when handling the trial database.

### **3.5 Duration and trial procedure**

The patients in the trial will primarily be followed until 180 days from the CA. Mortality will be recorded for the entire trial period. Patients regaining consciousness will be informed and asked for consent for trial participation and further follow-up.

**Phase 1** (hospital admission to start of intervention): Patients with out-of-hospital cardiac arrest (OHCA), admitted to hospital and who are unconscious with sustained return of spontaneous circulation (ROSC) are eligible for screening. The inclusion window is 220 minutes: i.e. from 20 minutes after ROSC (defined as sustained ROSC) and to 240 minutes after ROSC. The patients' eligibility for trial inclusion is assessed according to inclusion and exclusion criteria. Patients are randomly assigned to intervention group. Baseline characteristics are obtained.

**Phase 2-intervention period** (start of intervention to end of intervention): Phase 2 starts when the first measure to achieve the assigned target temperature is taken. Patients are sedated and mechanically ventilated in both allocation groups. Patients are treated for 24 hours with temperature management devices with external or internal temperature control to achieve a target core temperature of either 33°C or 36°C according to intervention allocation. Patients are rewarmed to a core temperature of 37°C during 8 hours.

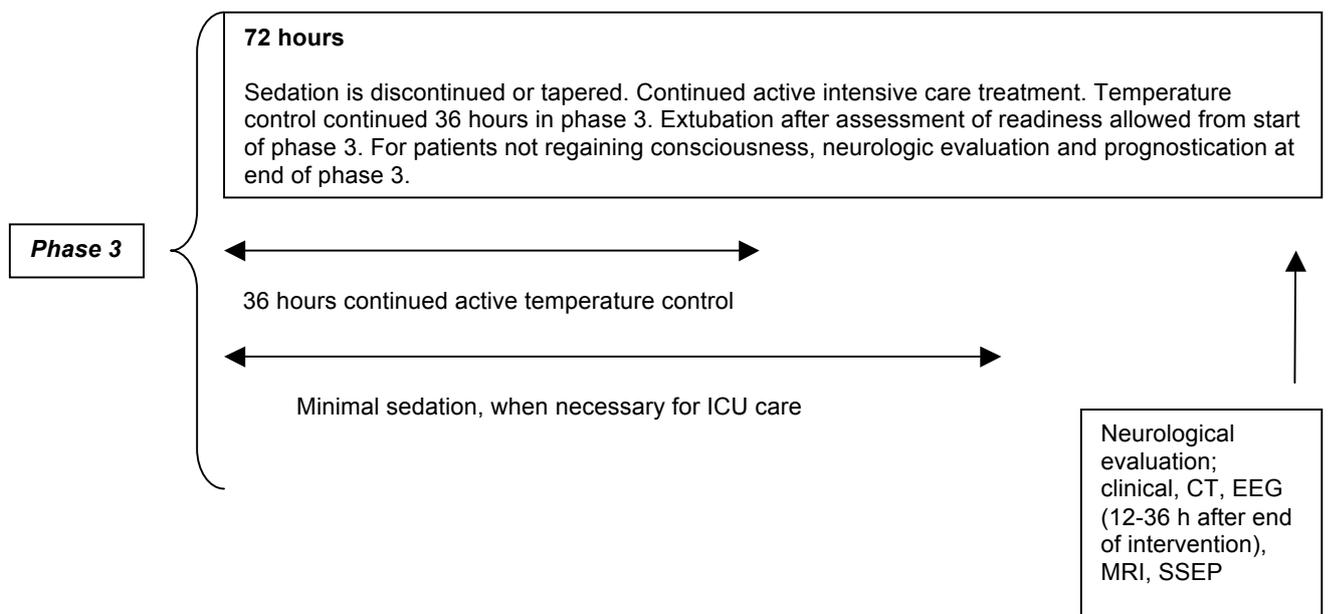
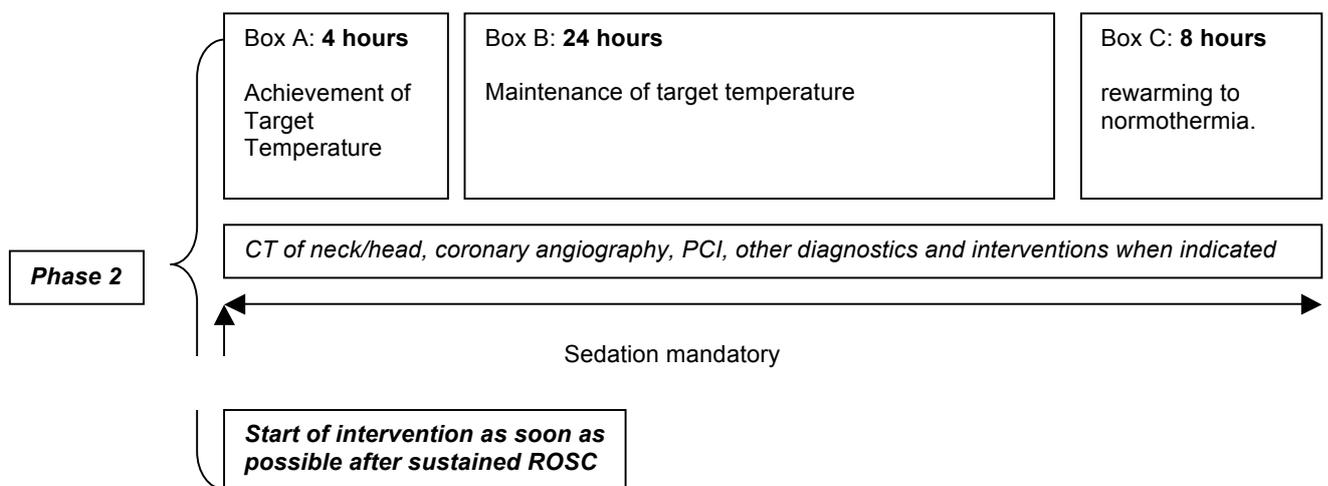
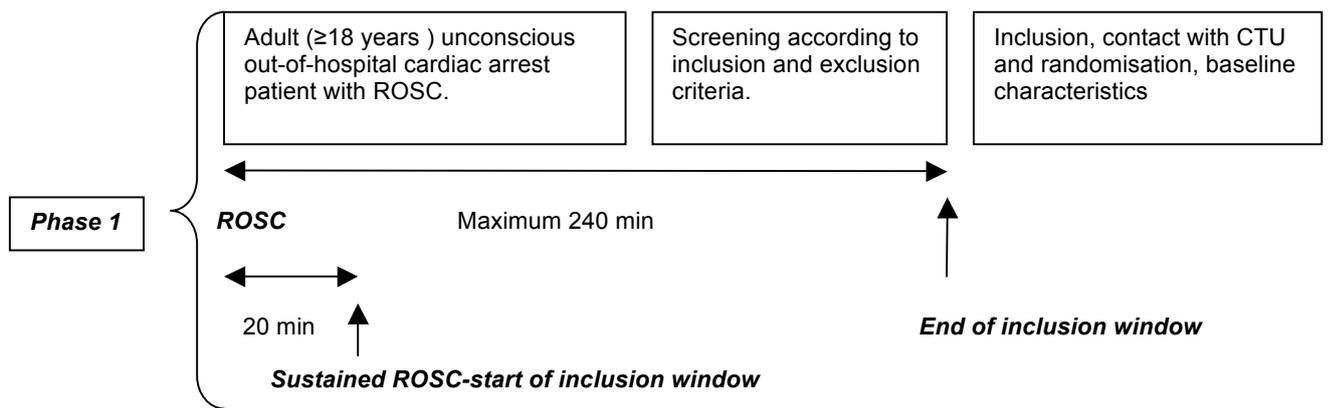
**Phase 3** (from end of intervention period to 72 hours after end of intervention period) Sedation is stopped or tapered at 37°C. Normothermia of 37°C $\pm$ 0.5°C is maintained until 72 hours from *cardiac arrest* in both treatment groups if the patient still is in intensive care, is comatose or sedated. However extubation should be attempted at the earliest possible time during this phase if applicable and based on standard procedures for discontinuation of mechanical ventilation. Neurological evaluation is performed by blinded physicians at 72 h or later after end of intervention period.

**Phase 4** (72 h after end of intervention period to 28 days after OHCA): Neurological status, according to the CPC-scale, and survival are evaluated every day in the intensive care unit and/or at day 1, 2, 3, 4, 5, 6, 7, 14, 21 and 28, and/or at hospital discharge, whichever comes first. If the patient is discharged from hospital, site personnel will contact the patient after the end of phase 4.

**Phase 5** (day 28 to end of trial): Mortality and neurological status are evaluated on day 90 and day 180. Evaluation is performed by occupational therapists/research nurses blinded to the intervention allocation. Survival will be followed to the end of trial

### **3.5.1 Detailed time schedule for intervention period (phase 2)**

From registry data we know that there is a great variability in how fast target temperature can be achieved. In order to optimise comparability between allocation arms, the intervention period will be divided into three definite time boxes. Box A, 4 hours (Period to achieve target temperature), Box B, 24 hours (Period to maintain target temperature), Box C, 8 hours (Period to restore normothermia). Total intervention period is thus 36 h in both groups. Patients allocated to TT36 will achieve target temperature and normothermia earlier but will not proceed to the next Phase until all time boxes are fulfilled. Patients that need more than 4 hours to achieve target temperature will anyway enter box B and C at 4 and 28 hours from start of intervention.



### 3.6 Neurological evaluation and withdrawal from active intensive care

All patients in the trial will be actively treated until 72 hours after the intervention period, i.e. 108 hours after start of treatment (end of phase 3), when neurological evaluation will be done on patients not regaining consciousness. Exceptions from this rule are 1) patients with myoclonus status<sup>#</sup> in the first 24 hours after admission and a bilateral absence of N20-peak on median nerve somatosensory evoked potentials (SSEP), 2) patients who become brain dead due to cerebral herniation and 3) because of ethical reasons described below. External blinded physicians will evaluate the patient at the end of phase 3 and make a statement on neurological prognosis. At that time-point limitations in and withdrawal of therapy could be instituted by the treating physicians according to trial guidelines. The neurological evaluation will be based on clinical neurological examination (including GCS, pupillary and corneal reflexes), SSEP and EEG. Biomarkers for brain damage will not be used for operational prognostication.

Findings allowing for discontinuation of active intensive care:

- 1) Brain dead due to cerebral herniation.
- 2) Severe myoclonus status<sup>#</sup> in the first 24 hours after admission and a bilateral absence of N20-peak on median nerve SSEP.
- 3) After 72 hours: persisting coma with a Glasgow Motor Score 1-2 and bilateral absence of N20-peak on median nerve SSEP.
- 4) After 72 hours: persisting coma with a Glasgow Motor Score 1-2 and a treatment refractory status epilepticus\*.

# Generalized myoclonic convulsions in face and extremities and continuous for a minimum of 30 min.

\* Status epilepticus defined by EEG as sequences (>10 sec) of repetitive epileptiform discharges with an amplitude >50µV and a medium frequency  $\geq 1$ Hz, constituting >50% of a 30 minute period in a patient with or without clinical manifestations. Treatment refractory defined as unresponsive to treatment with propofol, midazolam or pentothal to a slow suppression burst pattern for 24 h in combination with at least one intravenous antiepileptic substance (including valproate and/or fos-Phenytoin) in adequate dose for at least 24h. Free use of further antiepileptic substances and combinations at the discretion of the attending physician.

Patients with Glasgow Motor Score 1-2 at 72 h after the intervention period who have retained N20-peak on the SSEP, or in hospitals where SSEP is not available, should be re-

examined daily and the limitations/withdrawal of intensive care considered if GCS-Motor does not improve and metabolic and pharmacological affection is ruled out.

Recommendations and decisions on life sustaining treatment will be recorded.

Active treatment may be withdrawn prior to 72 hours after the intervention period for ethical reasons (for instance: previously unknown information about disseminated end-stage cancer or refractory shock with end-stage multiorgan failure), however assumptions of a poor neurological function will not be the sole reason for withdrawal of active treatment prior to 72 h after the intervention period (exception: brain death and early myoclonus status including a negative SSEP). The most important aspect is that the reason for withdrawal will be collected and reported.

### **3.7 Discontinuation of individual participants**

Discontinuation of intervention: A patient will be rewarmed from a target temperature of 33°C if *the intervention is suspected to cause* the patient uncontrolled bleeding, life threatening arrhythmia or refractory cardiogenic shock, at the discretion of the attending physician. The patient will continue in the trial and will be treated at 36°C but analysed by intention-to-treat. The reason for withdrawal will be collected and reported.

### **3.8 Intervention accountability**

The trial site investigator is responsible for:

- 1) Screening and listing eligible patients
- 2) Performing stratified randomisation
- 3) Achieving temperature control to target temperature according to the allocated intervention
- 4) Maintaining temperature control and intensive care therapy according to international and national standards guided by the trial clinical protocol.
- 5) Collection and reporting of data according to trial protocol and case record forms.
- 6) Achieving informed consent in writing from patients that regain consciousness.
- 7) Performing and reporting follow-up according to trial plan

### **3.9 Data collection**

Data will be entered into an electronic web-based case record form from patient notes by site personnel under the supervision of the trial site investigator. The trial site investigator must sign all eCRFs before finalisation. The software for the web-based form will be provided by Expert-Maker, Lund, Sweden. From the electronic forms the trial database will be established after data export, in a relevant data-format, to the data manager at Copenhagen Trial Unit.

The sponsor supplies a standard description of all laboratory units of measurement, which have influence on the data. To the extent that a trial site uses different unit of measurement, it must submit a correction list to the data centre and the sponsor and, if necessary, have its data capture module modified accordingly or use conversion tables.

Data not obtainable will be registered as missing and measures to obtain data should not delay intervention or concomitant treatment (i.e. central line not in place at the time of data collection).

#### **3.9.1 Pre-randomisation characteristics**

Screening form: Inclusion criteria (Y/N) Exclusion criteria (Y/N). National identification number, sex, age, type of temperature management system that will be used (intravascular, surface cooling).

Randomisation form: Randomisation number, consequences from the randomisation.

#### **3.9.2 Baseline characteristics**

(all obtained from emergency medical services/ ambulance/ hospital notes):

*Pre-hospital data:* Scene of arrest: place of residence/public place/other; witnessed arrest

Y/N; bystander CPR Y/N; first monitored rhythm at arrival of EMS personnel:

asystole/PEA/VF or non-perfusing VT/if unknown: shockable or non-shockable rhythm; time

from emergency call to arrival of EMS personnel; estimated time from arrest to basic life

support; estimated time from arrest to advanced life support; use of active compression-

decompression device: no/yes, manual/yes, mechanical; number of defibrillations; time from arrest to first defibrillation (if applicable); total amount of adrenaline (in mg), use of atropine, amiodarone, calcium, magnesium, any buffer solution administered Y/N, time from arrest to ROSC; patient intubated on scene/in ambulance/in emergency department, seizures before arrival to hospital.

### **3.9.3 Data at admission to hospital:**

- estimated height in cm, estimated weight in kg,
- co-morbidities (previously admitted for or on chronic treatment for): heart failure Y/N, acute myocardial infarction Y/N, arrhythmia Y/N, arterial hypertension Y/N, stroke Y/N, transitory cerebral ischaemia Y/N, epilepsy Y/N, other neurological disease Y/N, diabetes Y/N, asthma or chronic obstructive pulmonary disease Y/N, renal impairment Y/N, liver impairment Y/N, haematological malignancy Y/N, other malignancy Y/N, alcohol abuse Y/N, drug abuse Y/N, AIDS Y/N, previous PCI Y/N, previous CABG Y/N, previous valvular surgery.
- First recorded tympanic temperature (bilateral, highest value)
- Glasgow Coma Score sub scores, pupillary and corneal reflexes
- Any sign of spontaneous breathing/agonal breathing/gasping at admission
- Blood gas (alpha stat) and FiO<sub>2</sub>: pO<sub>2</sub>, pCO<sub>2</sub>, BE, pH, lactate
- Blood glucose
- Troponine T
- Pro-BNP
- ECG findings (normal, abnormal: acute STEMI, abnormal: LBBB, abnormal: other)
- Pre-arrest CPC from next of kin (when available)
- Cardiogenic shock Y/N

#### *Hourly during phase 2.*

- Core temperature

*During phase 2 at 0, 4, 12, 20, 28, 32 and 36 hours:*

- Blood glucose and dose of insulin
- Heart frequency
- Mean arterial pressure
- PaO<sub>2</sub>, FiO<sub>2</sub> and mean airway pressure

*During phase 2 at 0, 4, 12, 20, 28, 32 and 36 hours:*

- Central venous or mixed venous oxygen saturation and arterial or venous lactate concentration.
- Blood gas

*After the first 24 hours*

- Simplified Acute Physiology Score (SAPS) III (raw data)

*Daily during day 1-7 of ICU stay:*

- Sequential Organ Failure Assessment (SOFA) sub scores. Lowest Hb, pH, BE, Trc, Magnesium, Phosphate, Potassium, ScVO<sub>2</sub> (or SvO<sub>2</sub>) during 24 hour period, highest INR, Krea, CRP, lactate. Maximum value of Troponin T during the first 72 hours.
- GCS subscores.
- Highest body temperature and accumulated duration of body temperature >38°C
- Need of vasopressor/inotropic medication
- Need for pacing
- Need for mechanical circulatory assistance
- Mechanical ventilation
- Daily volumes of blood products, net fluid balance excluding perspiratio insensibilis
- Adverse events according to list

- If trial intervention has been discontinued, time of discontinuation and specified reason
- If active intensive care is withdrawn, specify reason
- Do not attempt resuscitation order Y/N
- If dead, specify presumed cause from death certificate: cardiac, cerebral, other

*Daily from day 8 to ICU discharge:*

- Patient comatose Y/N
- Mechanical ventilation Y/N
- Renal replacement therapy Y/N
- Presence of pneumonia and sepsis
- If active intensive care is withdrawn, specify reason
- Do not attempt resuscitation order Y/N
- If dead, specify presumed cause from death certificate: cardiac, cerebral, other

*At prognostication:*

- Results and time of SSEP (n20 present bilaterally/n20 present unilaterally/n20 absent) and EEG
- Clinical neurological examination
- Recommendation of evaluation team: continue active intensive care/do not escalate active intensive care/withdraw active intensive care

**3.9.4 At ICU discharge:**

- Time and results of EEG/MRI/CT/Echocardiography/Angiography, if performed
- Time of thrombolysis/PCI/open-heart surgery, if performed
- Time when obeying commands, if applicable
- CPC and GCS at discharge
- Best CPC during ICU stay

- Discharge facility (coronary care unit/general ward/other ICU/dead)

### **3.9.5 In the ward/coronary care unit**

- UCG at hospital discharge (EF-normal, moderately impaired, severely)
- Pro-BNP at hospital discharge
- CPC at hospital discharge
- Discharged to: nursing home/rehabilitation unit/other hospital/home/dead
- If dead, presumed cause of death: cardiac/cerebral/other

### **3.9.6 90 days after randomisation:**

- Survival status obtained from hospital or civil registries
- If the patient is deceased, date of death, presumed cause of death:  
cardiac/cerebral/other
- Date of hospital discharge as obtained from hospital notes or registries
- Telephone call to obtain value of CPC

### **3.9.7 180 days after randomisation:**

- Survival status obtained from hospital or civil registries
- Neurological outcome according to the CPC scale
  - CPC 1-conscious, no or minor neurological disability, can work at least part time
  - CPC 2-conscious, moderate neurological disability, can work in sheltered environment, independent
  - CPC 3-conscious, severe neurological disability, dependent
  - CPC 4-coma or vegetative state
  - CPC 5-dead.
- Neurological outcome and Quality of life tested with:  
Mini Mental Test, IQCODE, Modified Rankin Scale, Short Form 36, Two questions

- Interventions performed after discharge from ICU, type and time: CABG Y/N, PCI Y/N, ICD Y/N, other cardiac resynchronization therapy Y/N

### **3.9.8 Investigations and blood samples per protocol**

Most investigations and interventions are performed at the discretion of the treating physician. However a few investigations are strongly recommended by the protocol: ECG will be taken at admission, when target temperature is achieved, at 24 h, at return to normothermia, at 72 h and at 180 days.

In unconscious patients:

- EEG 12-36 h and SSEP 48-72 h after the end of the intervention period.
- Biomarkers at 24, 48 and 72 hours after ROSC (central biobank).

## **4. Selection and withdrawal of participants**

### **4.1 Inclusion criteria**

1. Age  $\geq 18$  years.
2. OHCA of presumed cardiac cause.
3. Sustained ROSC<sup>#</sup>.
4. Unconsciousness (GCS <8) (patients not able to obey verbal commands) after sustained ROSC.

<sup>#</sup>Sustained ROSC: Sustained ROSC is when chest compressions have been not required for 20 consecutive minutes and signs of circulation persist<sup>59</sup>

### **4.2 Exclusion criteria**

1. Conscious patients (obeying verbal commands)
2. Obvious or suspected pregnancy
3. In-hospital cardiac arrest (IHCA)

4. OHCA of presumed non-cardiac cause, e.g. after trauma or dissection/rupture of major artery OR Cardiac arrest caused by initial hypoxia (i.e. drowning, suffocation, hanging).
5. Known bleeding diathesis (medically induced coagulopathy (e.g. warfarin, clopidogrel) does not exclude the patient).
6. Suspected or confirmed acute intracranial bleeding
7. Suspected or confirmed acute stroke
8. Unwitnessed asystole
9. Known limitations in therapy and Do Not Resuscitate-order
10. Known disease making 180 days survival unlikely
11. Known pre-arrest CPC 3 or 4
12. >4 hours (240 minutes) from ROSC to screening
13. Systolic blood pressure <80 mm Hg in spite of fluid loading/vasopressor and/or inotropic medication/intra aortic balloon pump<sup>#</sup>
14. Temperature on admission <30°C.

# If the systolic blood pressure (SBP) is recovering during the inclusion window (220 minutes) the patient can be included.

Since post resuscitation care and intervention are regarded as emergency procedures and should not be delayed, there should only be taken normal measures (previous in house chart records, history from emergency medical services) to assess 5, 9, 10 and 11.

#### **4.3 Participant withdrawal**

A participant is free to withdraw his/her informed consent from the trial at any time after regaining consciousness. A patient will be withdrawn from the trial if this patient withdraws consent. The reason for withdrawal will be collected and reported. The patient will be asked to specify which aspects of the trial he/she is withdrawing consent and participation from: attending the follow-up visits, diagnostic testing, inclusion of their data (including survival

data) in a database, registry, or publication. The patient making the withdrawal will be asked for permission to use data obtained prior to withdrawal and to obtain data for the primary outcome measure. If this is achieved the patient will be included in the final analyses. If the patient declines, all data from that patient will be destroyed.

## **5. Experimental interventions**

Target temperature 33°C (TTM33): Patient will be managed at 33°C with either intravascular heat-exchange catheters or external temperature management systems. Fluid therapy will be guided by standard procedures for haemodynamic support (fluid responsiveness, urinary output, haemodynamic and laboratory values, echocardiography etc). If a patient has a temperature between 30 and 33°C, the patient will be actively rewarmed to 33°C with 0.5°C/h.

Target temperature 36°C (TTM36): Patients will be managed at 36°C with either intravascular heat-exchange catheters or external temperature management systems. If a patient has a temperature between 30 and 33°C, the patient will be actively rewarmed to 33°C with 0.5°C/h. If a patient has an initial temperature 33-36°C, the temperature will be followed and the patient will be allowed to spontaneously rewarm and temperature management will be instituted when the core temperature is 36°C. Fluid therapy will be guided by standard procedures for haemodynamic support (fluid responsiveness, urinary output, haemodynamic and laboratory values, echocardiography etc).

There will be comprehensive guidelines for respiration, circulation, sedation, temperature management, vital parameters, electrolyte and metabolic disturbances, shivering, anti-shivering drugs, concomitant cardiac treatment, neurological prognostication and decisions on withdrawal of therapy. However the specific care of the patients are at the discretion of the treating physician.

### **5.1 Concurrent medication/treatment**

Computed Tomography of brain/head/neck will only be performed on indication, not as a routine screening after admission. Patients will be treated with standard therapies for cardiac diseases. Thrombolysis, angiography, percutaneous coronary interventions and/or open-heart surgery will be performed according to current guidelines at the discretion of the caregiving physicians. Necessary cardiac interventions should not be delayed by the trial intervention, but efforts should be made to keep the allocated temperatures during treatment.

### **5.2 Monitoring for compliance of treatment**

Temperature management will be followed with continuous core-temperature (bladder) measurements during phase 2 and 3. In oliguric patients core temperature will be followed with esophageal or intravascular temperature measurements. Initial temperature at admission will be tympanic, bilaterally, with highest value recorded.

## **6. Assessment of outcome measures**

### **6.1 Primary outcome**

- Survival to time of last follow up (end of trial) which will be at least 180 days from randomisation

### **6.2 Secondary outcomes**

- Composite outcome of all-cause mortality and poor neurological function (CPC 3 and 4) at 180 days.
- Composite outcome of all-cause mortality and poor neurological function (mRS 4 and 5) at 180 days.
- All-cause mortality at 180 days.
- CPC at 180 days
- mRS at 180 days

- Safety measures: Bleeding, pneumonia, sepsis, electrolyte disorders, hyperglycaemia, hypoglycaemia, cardiac arrhythmia and the need for renal replacement therapy.

For interim analyses there will be used an alternative time point of 90 days instead of 180 days for the primary and selected secondary outcomes. According to data from the Hypothermia Network Registry there is very little difference in mortality at 90 and 180 days.

### 6.3 Tertiary outcomes

- Complete neurological recovery\*
- Neurological function (MMSE, IQCODE, two questions; see below) and Quality of life at 180 days
- CPC at hospital discharge
- Best neurological outcome during trial period according to the CPC-scale.

\*Survivors with complete recovery defined by: MMSE  $\geq 27$  (or  $\geq 19$  on MMSE-Adult Lifestyle Functioning Interview by telephone interview), modified Informant Questionnaire on Cognitive Decline in the Elderly  $\leq 78$ , answer “No” to question 1a or “No” to question 1b, answer “Yes” to question 2.  
1a. “In the last 2 weeks, did you require help from another person for your every day activities?” (If yes, 1b. “Is this a new situation following the heart arrest?”) and 2. “Do you feel that you have made a complete mental recovery after your heart arrest?”

### 6.3 Efficacy variables

- Survival from national databases and/or hospital records
- Neurological outcome according to the CPC scale<sup>60</sup>
  - CPC 1-conscious, no neurological disability
  - CPC 2-conscious, moderate neurological disability, can work
  - CPC 3-conscious, severe neurological disability, dependent
  - CPC 4-coma or vegetative state
  - CPC 5-dead.
- Modified Rankin Scale

- Mini Mental State Exam (MMSE)
- IQCODE
- two simple questions\*
- Short Form 36 (SF-36)

\*1a. “In the last 2 weeks, did you require help from another person for your every day activities?” (If yes, 1b. “Is this a new situation following the heart arrest?”) and 2. “Do you feel that you have made a complete mental recovery after your heart arrest?”

## **6.4 Method and timing**

Blinded efficacy variables will be recorded at hospital discharge and at 90 and 180 days.

Follow up will be performed at a hospital visit, but if the patient is unable to attend, a visit may be performed in the patients place of residence or with a telephone follow-up. Unblinded efficacy variables will be recorded at ICU discharge by the initial caregivers.

## **7. Assessment of safety and harm**

The OHCA population admitted to intensive care is a very seriously ill group of patients. Most adverse events may be of a potentially serious nature, but are often common in this patient group, with or without temperature intervention. Cardiac arrest patients and patients unconscious of any other reason are at great risk of developing adverse events. Adverse events will be recorded daily according to 7.1. The RCTs on MIH and observational data show that pneumonia, electrolyte disorders and arrhythmia are common but bleeding and septic shock rare events. There was a trend towards more sepsis in the MIH-treated group in one of the RCTs.

The potential adverse effects of the intervention disappear when temperature is re-established at normothermia (<36°C).

### **7.1 Safety variables-adverse events (AE)**

Bleeding: Bleeding from nose, gastro-intestinal tract, oral cavity, genitals, insertion sites, intra muscular, other .

Major bleeding: Uncontrolled bleeding (>1 unit of blood/10 kg/1h), bleeding causing fatality; symptomatic bleeding in critical organ e.g.: intracranial, intraspinal, intraocular, intraarticular, pericardial; other bleeding e.g.: retroperitoneal, muscular, solid organ, thoracic with Hb ↓ >50g/L (5 g/dl, 3,1 mmol/L) and req. >2 units of transfused blood.

Infection: Severe sepsis\*, septic shock\*, pneumonia#, other

\*Sepsis :

Infection is the inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

The Systemic Inflammatory Response Syndrome (SIRS) is diagnosed when the patient exhibits two of the following four abnormalities, only applicable in phase 3:

\* Temperature > 38°C or < 36°C.

\* Heart rate > 90 beats min<sup>-1</sup>.

\* Respiratory rate > 20 breaths min<sup>-1</sup> or PaCO<sub>2</sub> < 4.3 kPa or need for mechanical ventilation.

\* White blood cell count > 12 000 cells mm<sup>-3</sup> or < 4000 cells mm<sup>-3</sup> or > 10% immature cells (band forms).

Sepsis is SIRS resulting from infection. Severe sepsis is sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status.

Septic shock is sepsis with hypotension (systolic blood pressure < 90 mmHg or a reduction of > 40 mmHg from baseline) and perfusion abnormalities (see severe sepsis above) or the requirement for vasoactive drugs despite adequate fluid resuscitation in the absence of other causes for hypotension.

# Pneumonia

The diagnosis of pneumonia is based on the following criteria:

1. New or progressive consolidation on the chest radiograph.
2. Fever
3. Leucocytosis
4. Purulent tracheobronchial secretions

Renal impairment: Need for continuous renal replacement therapy (CRRT) or intermittent haemodialysis (IHD)

Electrolyte disorders: Hypokalaemia (<3.0 mmol/l), hypophosphataemia (<0.7 mmol/l), hypomagnesaemia (<0.7 mmol/l),

Metabolic disorders: Sustained hyperglycaemia (>10 mmol/l > 4 h) , hypoglycaemia (<3.0 mmol/l)

Arrhythmia: VF, VT, tachycardia >130/min, bradycardia <40/min, atrial flutter, atrial fibrillation, need for pacing, circulatory collapse mandating CPR

Seizures: Tonic-clonic, myoclonic, electrographic status epilepticus

Shivering

Other adverse event potentially associated to intervention? Specify.

## **7.2 Method and timing**

Safety variables will be recorded continuously during the first 7 days, when the patient is in the intensive care unit.

## **7.3 Adverse events reporting and follow-up**

### **7.3.1 Adverse events (AE)**

Safety variables will be reported daily according to 7.1 (within 24 hours from awareness of adverse event) through the electronic case record form if they appear.

### **7.3.2 Serious adverse events (SAE)**

For every adverse event reporting in the eCRF there will be an additional question: Has there during the last 24 h been any serious adverse event? An SAE is an AE that results in death, is life threatening, requires prolongation of hospitalisation or results in significant disability/incapacity. Uncontrolled bleeding (>1 unit of blood/10 kg/1h), bleeding causing fatality, intracerebral bleeding, septic shock and life threatening arrhythmia mandating CPR will always be considered serious adverse events.

### **7.3.3 Suspected unexpected serious adverse reaction (SUSAR)**

For an SAE noted on the question “Other adverse event potentially associated to intervention? Specify”, there will be an additional question: was this a suspected unexpected serious adverse event? A SUSAR is an SAE, the nature or severity of which is not consistent with the applicable literature on temperature management.

### **7.3.4 Severity of adverse event**

- Mild: transient symptoms, no interference with participant's daily activities, tolerable.
- Moderate: marked symptoms, moderate interference with the participant's daily activities, but still tolerable.
- Severe: considerable interference with the participant's daily activities, unendurable.

### **7.3.5 Relationships of adverse event to clinical trial intervention**

- Probable: good reasons and sufficient documentation to assume a causal relationship.
- Possible: a causal relationship is likely and cannot be excluded.
- Unlikely: the event is most likely related to aetiology other than the trial intervention.
- Unknown: causality is not assessable, e.g., due to insufficient evidence, conflicting data, or poor documentation.

### **7.3.6 Recording of adverse events**

Adverse events will be recorded daily in a prespecified form in the eCRF. At each assessment all adverse events, SAEs and SUSARs either observed by the investigator or other caregivers must be recorded by the investigator and evaluated. The adverse events will be reported in the electronic adverse event form at the latest 24 hours from awareness of the adverse event. Each SAE and SUSAR requires that the investigator to fill in the adverse event form (included in the eCRFs). The following variables will be recorded:

- Description of event
- Onset and end of event
- Severity
- Relation to intervention
- Action taken
- Outcome

### **7.3.7 Type and duration of the follow up of participants after adverse events**

Any adverse event, occurring during the trial, will be treated according to established standards and the patient will be followed until the event has disappeared or until the condition has stabilised. A report on the patients' clinical course will be submitted to the principal investigator, trial monitor or the CTU.

### **7.3.8 Management and analysis of adverse events**

The management and analysis of adverse events are described in the Charter for the DSMC in the appendix.

## 8. Statistical plan and data analysis

There will be a statistical analysis plan published well before the scheduled interim analysis.

Rationale for mortality/survival being the primary outcome: based on previous trials the relative risk reduction was smaller for mortality compared to neurological function. When powering the analysis for detecting a plausible intervention effect on mortality the primary secondary outcome (neurological function) will benefit, increasing the chance of detecting a difference. Also, mortality is a outcome measure minimising evaluation bias and, compared to neurological function, it is not prone to competing risks.<sup>61</sup> A survival analysis will be superior with respect to trial power if there are changes in the control event rate.

Rationale for including patients with non-shockable rhythms: It is reasonable to assume that the potentially neuroprotective effect of hypothermia would be equal regardless of initial rhythm inflicting the cardiac arrest. However, patients with cardiac arrest of non-cardiac cause with non-shockable rhythms have a very poor prognosis why we abstain from including this patient group. The baseline risk would have increased substantially and the sample size would have increased accordingly. On the contrary, cardiac arrest patients with a cardiac cause of arrest and non-shockable rhythms have a fair prognosis and when combining patients with cardiac cause of arrest with and without shockable rhythms we find a mortality of 44% and a poor neurological outcome of 48% in hypothermia treated patients in the Hypothermia Network Registry. These numbers combined with an *a priori* stipulated relative risk reduction of 20% would be optimal regarding sample size.

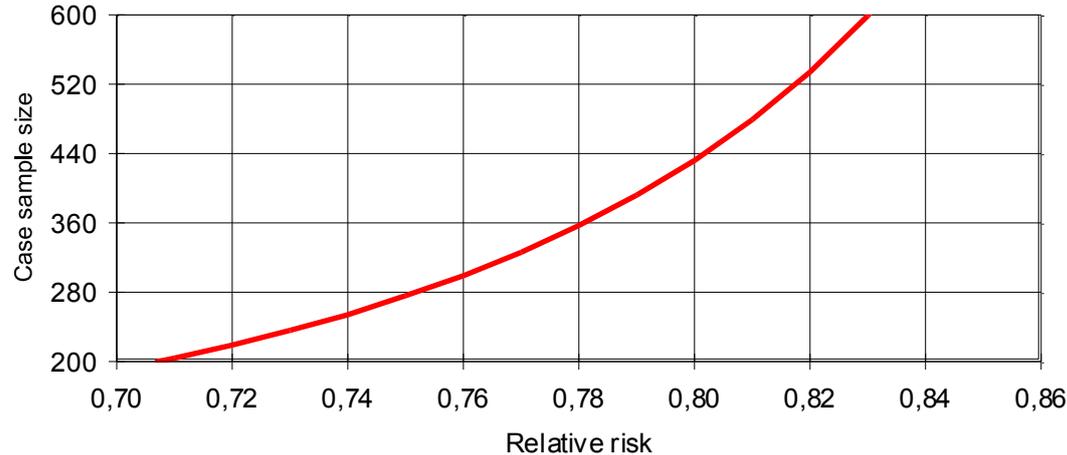
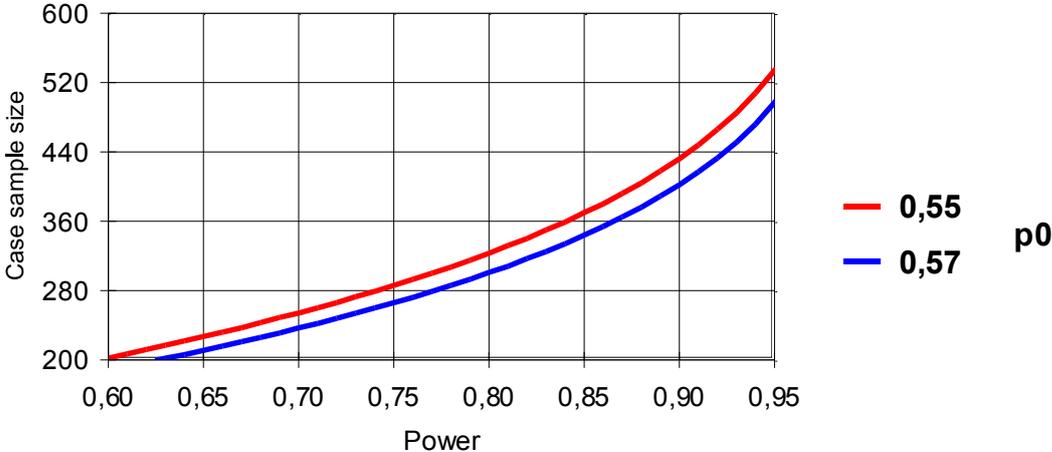
Rationale for not including patients with in-hospital cardiac arrest: There are numerous reports indicating that in-hospital cardiac arrest is a entity very different from out-of-hospital cardiac arrest with different time aspects of the arrest, different chances to achieve ROSC and different long-term survival.<sup>62</sup> There is an underlying reason for the hospitalisation that will affect the natural course of the in-hospital cardiac arrest. Also, there are reports indicating the great difference in the reason for the observed mortality, with a neurological

cause in the majority of out of hospital cardiac arrests (70% for out-of-hospital vs. 30% for in-hospital).<sup>63, 64</sup>

### **8.1 Sample size estimation**

Sample size: As the primary outcome survival to 180 days or more is chosen. We are planning a trial with 1 control per experimental participant, an accrual interval of 27 months, and additional follow-up after the accrual interval of 6 months (last patient followed for 6 months). We estimate the median survival time in the 36 degree Celsius group to be 5 months. If the true hazard ratio (relative risk) of experimental participants relative to control participants is 0,80 we will need 450 experimental participants and 450 control participants to be able to reject the null hypothesis that the experimental and control survival curves are equal with power=90%. The Type I error probability associated with this test of this null hypothesis is 0,05. That is: we need at least 900 patients with complete follow-up on survival. In previous trials on CA the loss to follow up has been minimal. However we will calculate with a loss of 5%. If we want to have at least 900 patients with complete follow-up we should include 950 patients if we accrue patients for 27 months and want to detect or reject a hazard rate (HR) of 0.80. A HR of 0.80 is equivalent to a 6 months median survival in the 33 degree temp. group versus a 5 months median survival in the 36 degrees temp. group assuming proportional hazards in the two groups during the observation time. According to Trial Sequential Analysis based on the published RCTs the sample size needs to be at least 600 patients to show a significant relative risk reduction of 20% for all-cause mortality within 6 months, with a power of 90% (beta 0.10) and a two sided significance level of 0.05 (alpha). See appendix I for different scenarios according to the published trials. Of note is that all published trials actually are trials with high-risk of bias making the TSAs difficult to interpret. A power of 90% is important. If we find no statistical differences between the intervention groups we have to be confident that this is a finding with a reasonably high probability, that the trial is powered to detect a difference if it is present and that true effects are so small that they are of limited clinical significance. A power analysis of a reasonable relative risk

reduction of 20% (mortality 57% vs. 46%) and a power of 90% made without TSA would give us a sample size of 800 individuals not calculated for losses to follow-up. Alternatively to detect or reject a relative risk reduction of 20% in mortality from 55% to 44% and a power of 90% requires a sample size of 856 participants. The relation between power, control group event proportion, and sample size in the experimental group are shown in the graphs below. Based on these assumptions we have decided on a sample size of 950 patients.



**8.2 Statistical methods**

The primary outcome of survival will be analysed after a minimum of 180 days of follow-up with Cox regression ("proportional hazards method after control that the assumption of

proportional hazards is fulfilled") analysis and the primary analysis will be an analysis for the effect of intervention adjusted for the stratification variable "site". The secondary analysis will be a multivariate Cox regression analysis adjusting for design variables (stratification variables, initial rhythm, time to ROSC, age, gender, presence of shock) The analyses will be performed after the intention-to-treat-principle.

### **8.3 Significance**

A two-sided significance level of 0.05 will be applied to primary and secondary outcomes.

### **8.4 Interim analysis**

There will be an independent DSMC arranging an independent statistician to conduct primarily a blinded interim analysis after the last of half of the included participants (475 patients) has been followed for 90 days. The DSMC, of course will be able to request unblinding of data coordinated by the CTU. The DSMC will be provided with data on safety parameters bimonthly during trial conduct and can initiate analysis at any time they request.

### **8.5 Early stopping criteria**

After the interim analysis the DSMC may suggest to the steering committee that the trial should be stopped early for benefit due to adjusted, restrictive P-values, according to the Haybittle-Peto rule (a P-value of 0.001 if half of the fixed sample size stipulated number of participants have been analysed).<sup>65</sup> Alternatively the Lan-DeMets group sequential monitoring boundaries with the possibility to analyse whenever the DSMC wishes it will provide the DSMC with adequate stopping rules.<sup>66</sup>

The DSMC may stop or pause the trial if:

- Group difference in the primary outcome measure is found in the interim analysis according to pre-defined rules mentioned above.
- Group difference in serious adverse events is found in the interim analysis.
- Results from other studies show benefit or harm with any of the interventions.

## **8.6 Accountability procedure for missing data/population for analysis**

Trial sites will be asked to complete all CRFs and other forms if missing data is found in the electronic database. Missing data will be reported in the publication. More than 5% missingness will result in multiple imputation with the creation of 5-10 imputed datasets to be analysed separately and then aggregated into one estimate of intervention effect of the primary and secondary outcomes.<sup>67, 68</sup> Analyses will be performed according to the intention to treat principle with patients lost to follow up included in the denominator.

## **8.7 Subgroup analysis and design variables**

Subgroups will be analysed according to pre-defined design variables: over or under 60 years of age, according to if initial rhythm could be defibrillated or not, gender, the presence of shock at admission and time from arrest to ROSC. Difference in intervention effect estimates according to subgroup will be declared exclusively based on a statistically significant test of interaction.

## **9. Direct access to source data/documentation**

The principal investigator and the site investigators will permit monitoring, audits, review of ethical committees and regulatory authorities direct access to source data and documentation.

## **10. Data handling and record keeping**

Individual patient data will be handled as ordinary chart records and will be kept according to the legislation (e.g. data protection agencies) of the countries of each health system.

Anonymous data, coded by the individual patient code kept at each site, will be entered into the electronic database at Expertmaker, Lund. This system fulfils all criteria for handling of patient data according to the Swedish legislation on management of personal data

“Personuppgiftslagen, PUL.” The electronic forms will be exported to the Copenhagen Trial Unit. All original records (incl. consent forms, CRFs, SAE/SUSAR reports and relevant

correspondences) will be retained at trial sites or CTU for 15 years to allow inspection by the GCP Unit or local authorities. The study database will be maintained for 15 years and anonymised if requested by the relevant authorities.

## **11. Quality control and quality assurance**

A monitoring plan will be published before start of the trial.

The trial will be externally monitored by national Good Clinical Practice (GCP)/monitoring offices coordinated by the GCP-unit at the Region Skåne Centre of Competence (Lund Sweden). The frequency of on site monitoring will depend on compliance with the protocol, number of enrolled patients and data handling. There will be at least mandatory monitoring before and after the trial and once during the trial period.

All trial sites will be provided with sufficient information to participate in the trial. This document, CRFs, instructions for registration, checklists for inclusion/exclusion and randomisation, and a protocol for medical treatment will be distributed to all sites. The site investigator will be responsible for that all relevant data is entered into the electronic CRFs. The CRFs will be constructed in order to assure data quality with predefined values and ranges on all data entries.

## **12. Finance and insurance**

The trial will be funded by external foundations for medical research. The trial will not start until there is sufficient funding for the first eighteen months of the trial.

Patients included in the trial will be insured by the health system responsible for each trial site. The site investigator will need to have a written confirmation from the head of the hospital that the included patients will have standard insurance coverage.

### **13. Publication plan and author policy**

The trial will be analysed by an independent statistician and the results interpreted by the steering group. The manuscript will be prepared by the principal investigator in two versions before the allocation code is broken, with the different arms inter-changed (one assuming arm A is intervention, and the other assuming arm B is intervention). All authors must approve both versions before the code is broken. The final manuscript will be submitted to a peer-reviewed international journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement. The author list will start with Niklas Nielsen, the second name will be Jørn Wetterslev and thereafter the steering group members, national investigators and additional names in alphabetical order. The last name will be Hans Friberg. Centres recruiting  $\geq 30$  patients will be entitled to one name and  $\geq 60$  two names in the author list (additional names). After the author list there will be added: “and the TTM-trial group” and a reference to an appendix with all sites, site investigators and number of patients enrolled.

### **14. Enrolment and timeline**

According to data from the Hypothermia Network Registry and a survey of interested hospitals, we will need 30+ active centres enrolling patients to finish inclusion within two to three years.

Timeline:     2010, application for funding and ethical committees, centre recruitment  
                  2011-2013, inclusion of patients  
                  2012, interim analysis  
                  2013, data analysis, manuscript process and publication

## **15. Tasks and responsibilities**

Principle Investigator (PI): Sponsor, Coordination of protocol development, funding, ethical approval, information, recruitment of trial sites, daily management, authorise invoices

Senior Investigator (SI): Funding, information, recruitment of trial sites

Steering Group: Protocol development, funding, information, recruitment of trial sites

National investigators: Ethical approvals, recruitment and management of trial sites in their countries, daily management

Chief trialist: Protocol development, funding, ECRIN approval, daily management

Trial Site Investigators: Responsible for all trial-related procedures at their site including temperature management, education of staff in trial-related procedures, recruitment and follow-up of patients and entry of data. Clinical staff at the trial sites will conduct treatment of trial patients.

Operational management group: Daily management, approve new trial sites, discontinue trial sites, approve changes in trial budget, take responsibility as PI for limited time periods

Independent Data Safety Monitoring Committee: Will evaluate SAEs and SUSARs and perform the interim analyses. Will provide recommendations about stopping, halting or continuing the trial to the Steering Committee of the trial, see Charter for the Independent DSMC, Appendix B.

## **16. Related organisations**

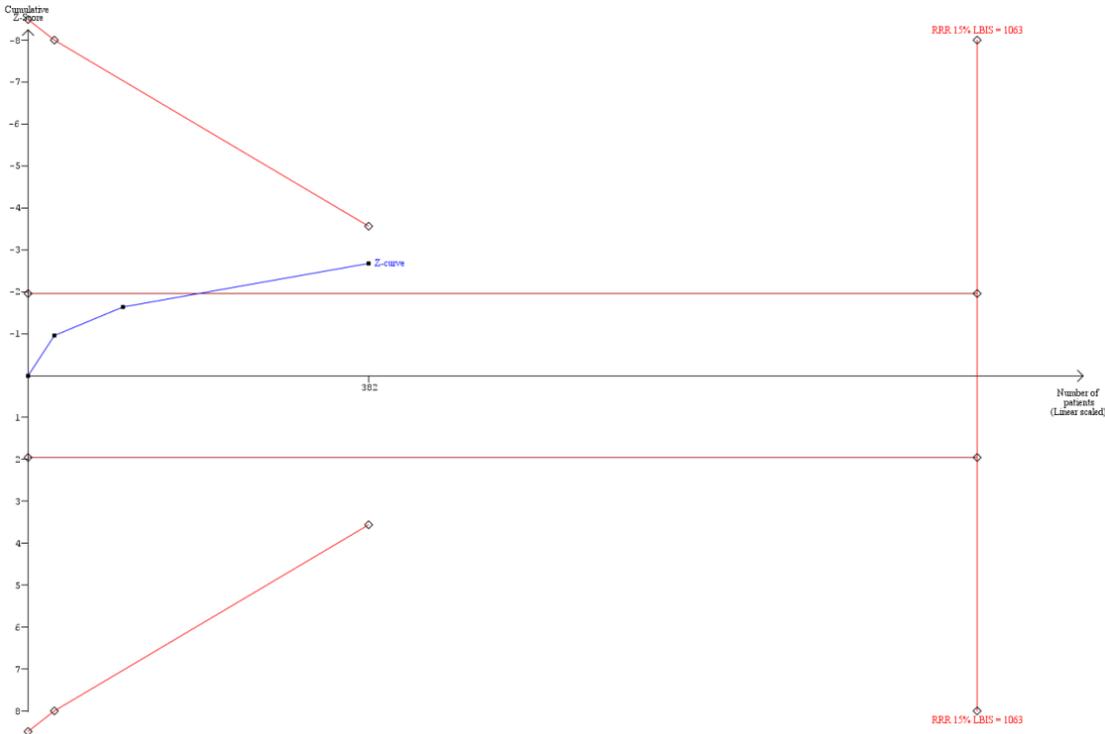
- Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI)
- Scandinavian Critical Care Trials Group (SCCTG)
- Copenhagen Trial Unit (CTU)
- European Clinical Research Infrastructures Network (ECRIN)
- The George Institute of Global Health
- Cardiff and Vale UHB - Research And Development



17. Appendix

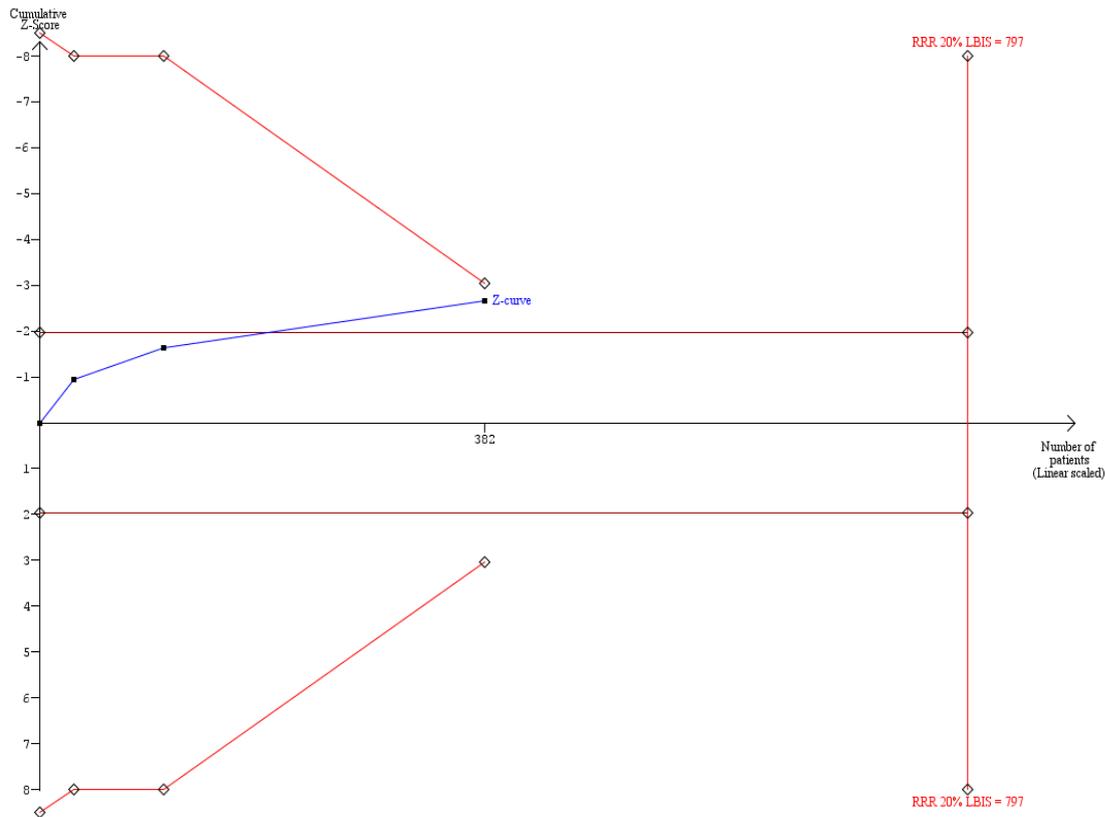
17.1 Appendix A. Trial Sequential Analyses of cumulative meta-analyses of hypothermia vs. normothermia after cardiac arrest

All-cause mortality, trials with lower-risk and higher risk of bias.



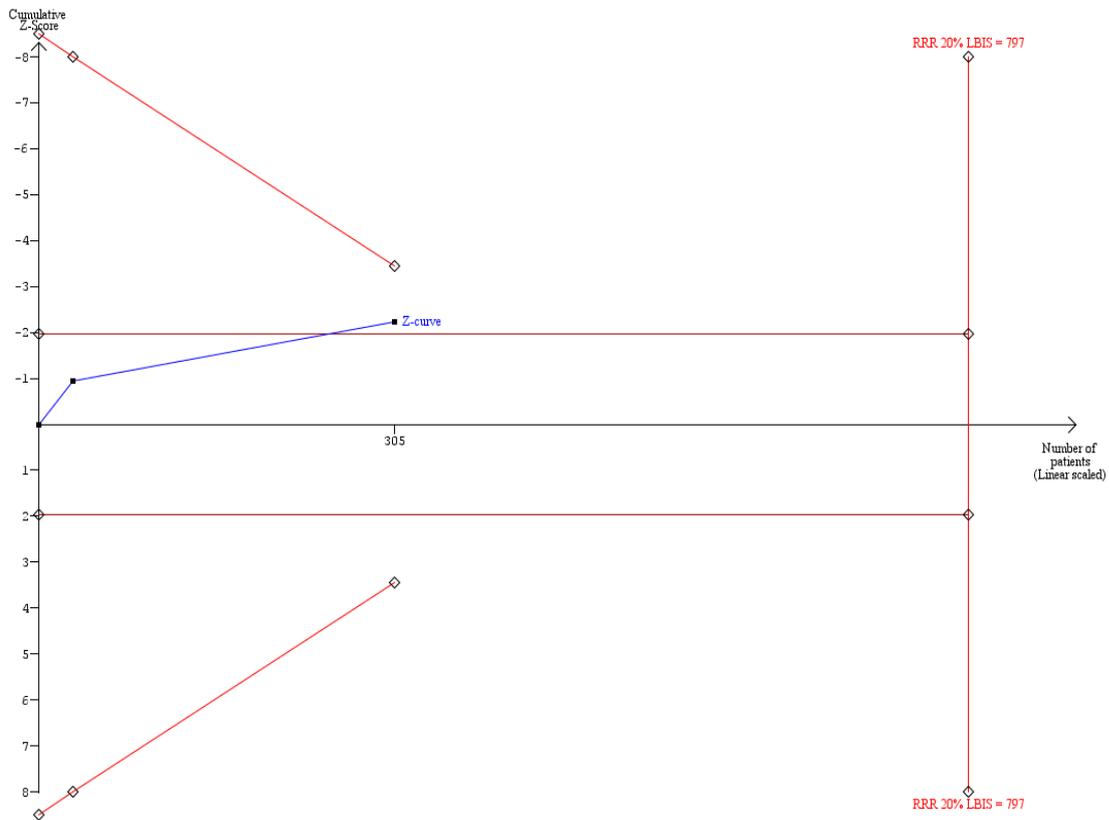
$\alpha = 0.05$  two-sided and  $\beta = 0.20$  (power = 80%) and a priori relative risk reduction of 15% all-cause (APIS) calculated to 1063. The cumulative z-curve constructed according to the fixed effects model as no heterogeneity was present  $I^2 = 0$ . The z-curve (blue) crosses the traditional boundary ( $P = 0.05$ ) but not the trial sequential monitoring boundary indicating lack of firm evidence for a beneficial effect of the intervention when the analysis is adjusted for repetitive testing on accumulating data. There is lack of information to reject an intervention effect of 15% RRR of all-cause mortality as the information size is not yet reached.

## All-cause mortality, trials with lower risk and higher risk of bias



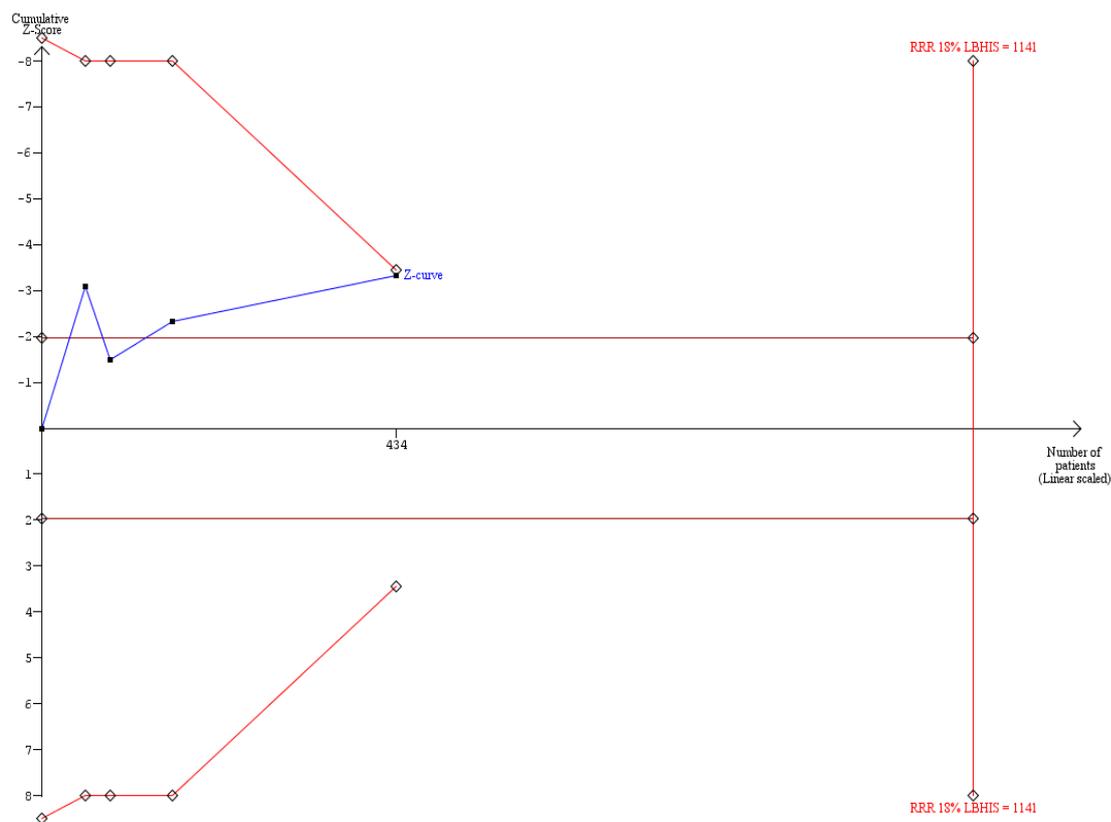
$\alpha = 0.05$  two-sided and  $\beta = 0.10$  (power = 90%) a relative risk reduction of 20% all-cause mortality as suggested by the low bias trials was assumed and the information size (LBIS) calculated to 797. The cumulative z-curve constructed according to the fixed effects model as no heterogeneity was present  $I^2 = 0$ . The z-curve (blue) crosses the traditional boundary ( $P = 0.05$ ) but not the trial sequential monitoring boundary indicating lack of firm evidence for a beneficial effect of the intervention when the analysis is adjusted for repetitive testing on accumulating data. There is lack of information to reject an intervention effect of 20% RRR of all-cause mortality as the information size is not yet reached.

## All-cause mortality, lower-bias trials only



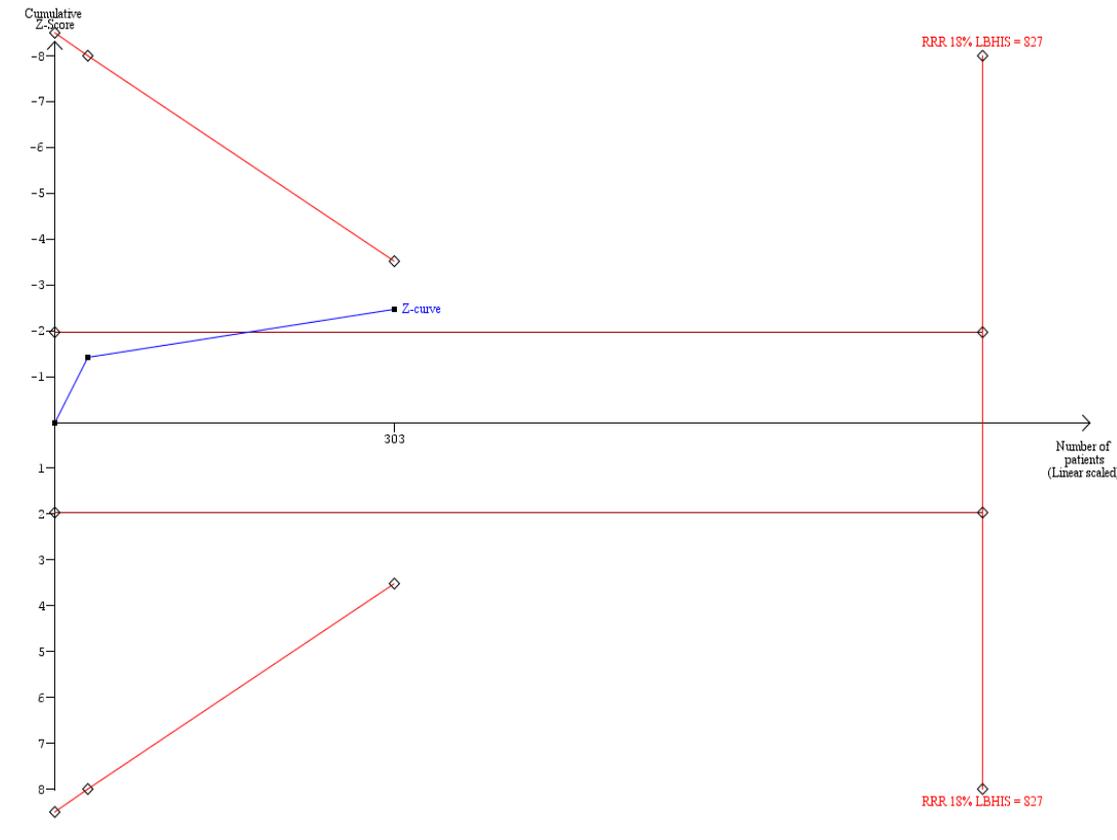
$\alpha = 0.05$  two-sided and  $\beta = 0.10$  (power = 90%) a relative risk reduction of 20% all-cause mortality as suggested by the low bias trials was assumed and the information size (LBIS) calculated to 797. The cumulative z-curve constructed according to the fixed effects model as no heterogeneity was present  $I^2 = 0$ . The z-curve (blue) crosses the traditional boundary ( $P = 0.05$ ) but not the trial sequential monitoring boundary indicating lack of firm evidence for a beneficial effect of the intervention when the analysis is adjusted for repetitive testing on accumulating data. There is lack of information to reject an intervention effect of 20% RRR of all-cause mortality as the information size is not yet reached.

## Poor neurological outcome, lower- and high-bias trials



$\alpha = 0.05$  two-sided and  $\beta = 0.10$  (power = 90%) a relative risk reduction of 18% in poor neurological outcome as suggested by the low bias trials was assumed and the information size adjusted for heterogeneity (LBHIS) calculated to 1141. The cumulative z-curve constructed according to the random-effects model as considerable heterogeneity of 41% was present  $I^2 = 0.41$ . The z-curve (blue) crosses the traditional boundary ( $P = 0.05$ ) but not the trial sequential monitoring boundary indicating lack of firm evidence for a beneficial effect of the intervention when the analysis is adjusted for repetitive testing on accumulating data. There is lack of information to reject an intervention effect of 18% RRR as the information size is not yet reached.

## Poor neurological outcome, lower-bias trials only



$\alpha = 0.05$  two-sided and  $\beta = 0.10$  (power = 90%) a relative risk reduction of 18% in poor neurological outcome as suggested by the low bias trials was assumed and the information size adjusted for heterogeneity (LBHIS) calculated to 827. The cumulative z-curve constructed according to the random-effects model as a heterogeneity of 15% was present  $I^2 = 0.15$ . The z-curve (blue) crosses the traditional boundary ( $P = 0.05$ ) but not the trial sequential monitoring boundary indicating lack of firm evidence for a beneficial effect of the intervention when adjusting for repetitive testing on accumulating data. There is lack of information to reject an intervention effect of 18% RRR as the information size is not yet reached.

## **17.2 Appendix B, Charter for the independent Data Safety Monitoring Committee (DSMC) of the TTM-trial.**

Clinical Trial no. NCT01020916

### **Introduction**

The Charter will define the primary responsibilities of the DSMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMC, and an outline of the content of the Open and Closed Reports that will be provided to the DSMC.

### **Primary responsibilities of the DSMC**

The DSMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMC will provide recommendations about stopping or continuing the trial to the Steering Group (SG) of the TTM-trial. To contribute to enhancing the integrity of the trial, the DSMC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DSMC will be advisory to the SG. The SG will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DSMC is planned by protocol to meet physically in order to evaluate the planned interim analysis of the TTM-trial. The interim analysis will be performed by an independent statistician selected by the member of the DSMC. The DSMC may additionally meet whenever they decide, contact each other by telephone or e-mail in order to discuss the safety for trial participants. The Principal investigator has the responsibility to report monthly to the DSMC the overall number of Serious Adverse Events (SAE) and Serious Unexpected Suspected Adverse Reactions (SUSARS). The DSMC can request at any time during the trial the distribution of events, including outcome measures, SAEs and SUSARs, according to intervention groups. The recommendations of the DSMC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the SG of the TTM-trial. The SG has the responsibility to inform as fast as possible, and no later than 48 hrs, all investigators of the trial and the departments including patients in the trial the recommendation of the DSMC and the SG decision hereof.

### **Members of the DSMC**

The DSMC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomised clinical trials.

### **Conflicts of interest**

DSMC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature.

Any DSMC members who develop significant conflicts of interest during the course of the trial should resign from the DSMC.

DSMC membership is to be for the duration of the clinical trial. If any members leave the DSMC during the course of the trial, the SG will appoint the replacement(s).

### **Formal interim analysis meeting**

One 'Formal Interim Analysis' meeting will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DSMC will meet when 90-day follow-up data of 425 patients have been obtained.

### **Proper communication**

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group (0,1). An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DSMC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DSMC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for Open Sessions and Closed Sessions will be implemented. The intent of this format is to enable the DSMC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DSMC and others who have valuable insights into trial-related issues.

#### **Closed Sessions**

Sessions involving only DSMC membership who generates the Closed Reports (called Closed Sessions) will be held to allow discussion of confidential data from the clinical trial,

including information about the relative efficacy and safety of interventions. In order to ensure that the DSMC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DSMC will be blinded in its assessment of safety and efficacy data. However, the DSMC can request unblinding from the SG.

#### Open Reports

For each DSMC meeting, Open Reports will be provided available to all who attend the DSMC meeting. The Reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The primary trial statistician will prepare these Open Reports.

Closed Reports will include analysis of the primary efficacy outcome measure. In addition, analyses of the secondary outcome measures and serious adverse events will also be reported. These Closed Reports will be prepared by an independent biostatistician, with assistance from the trial biostatisticians, in a manner that allow them to remain blinded.

The Closed Reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DSMC meeting.

The Reports should be provided to DSMC members approximately three days prior to the date of the meeting.

#### Minutes of the DSMC Meetings

The DSMC will prepare minutes of their meetings. The Closed Minutes will describe the proceedings from all sessions of the DSMC meeting, including the listing of recommendations by the Committee. Because it is likely that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DSMC.

## **Recommendations to the Steering Committee**

After the interim analysis meeting, the DSMC will make a recommendation to the SC to continue, hold or terminate the trial.

This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this Charter and the trial protocol.

The SC is jointly responsible with the DSMC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DSMC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, hold or stop the trial based on the DSMC recommendations.

The DSMC will be notified of all changes to the trial protocol or conduct. The DSMC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

## **Statistical monitoring guidelines**

The outcome parameters are defined in the TTM-trial protocol.

For the two intervention groups, the DSMC will evaluate data on:

### The primary outcome measure

All cause mortality at 90 days

### The secondary outcome measures

The composite outcome of all cause mortality and poor neurological outcome (CPC 3 and 4) at hospital discharge and at 90 days.

Serious adverse reactions - SAEs - and suspected unexpected serious adverse reactions - SUSARs

The DSMC will be provided with these data from the Coordinating Centre as:

- a. Number of patients randomised
- b. Number of patients randomised per intervention group (0,1)
- c. Number of patients stratified pr. stratification variable per intervention group (0,1)
- d. Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DSMC will decide if they want further data from the Coordinating Centre and when next to perform analyses of the data.

For analyses, the data will be provided in one file as described below.

Based on the analyses of the primary outcome measure and SAEs, the DSMC will use  $P < 0.001$  (Haybittle-Peto) as the statistical limit to guide its recommendations regarding early termination of the trial.

Based on 28- and 90-day mortality analyses, the DSMC will use  $P < 0.001$  (Haybittle-Peto) and group sequential monitoring boundaries as the statistical limit to guide its recommendations regarding early termination of the trial.

DSMC should also be informed about all SUSARs and SAEs occurring in the two groups of the trial.

The DSMC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

### **Conditions for transfer of data from the Coordinating Centre to the DSMC**

The DSMC shall be provided with the data described below in one file.

The DSMC will be provided with an Excel database containing the data defined as follows:

1. Row 1 contains the names of the variables (to be defined below).
2. Row 2 to N (where N-1 is the number of patients who have entered the trial) each contains the data of one patient.
3. Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database:

- 1: PtID: a number that uniquely identifies the patient.
- 2: Rdcode: The randomisation code (group 0 or 1) – the DSMC is not to be informed on what intervention the groups received.
3. 1.EndInd: Primary outcome measure indicator (1 if patient fulfilled the primary outcome measure at day 90 and 0 if the patient did not).

4: 90MInd: 90 day-mortality indicator (2 if patient is censored, 1 if patient was dead, and 0 if the patient was alive at day 90).

5: 90MBNInd: Mortality and poor neurological outcome at 90 days (2 if patient is censored, 1 if patient fulfils criteria, and 0 if the patient does not).

6: HospdMBNInd: Mortality and poor neurological outcome at hospital discharge (2 if patient is censored, 1 if patient fulfils criteria, and 0 if the patient does not).

7: SAEInd: Serious Adverse Event indicator (1 if patient has had a SAE during ICU stay and 0 if the patient did not).

8: SUSARInd: Suspected Unexpected Serious Adverse Reaction indicator (1 if patient has had a SUSAR during ICU stay and 0 if the patient did not).

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**List of changes between 3.2 and 3.3:**

- Active site list is updated
- Paragraph 4.4 is removed (registration of non-randomised patients)
- Section 6: The paragraph on Secondary outcomes is expanded to two paragraphs (secondary and tertiary outcomes)
- 8.2 The information on the primary outcome is changed: “The primary analysis will be adjusted for the stratification variable: site”