TTM2

Hypothermia or Early Treatment of Fever

Targeted Hypothermia vs. Targeted Normothermia after Out-of-hospital Cardiac Arrest, a Randomised Clinical Trial

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Acronyms

AHA	American Heart Association
BSAS	Bedside shivering assessment scale
CA	Cardiac arrest
CPC	Cerebral Performance Category
DNR	Do not resuscitate
DSMC	Data safety monitoring committee
eCRF	electronic case report form
EQ5D-5L	Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses.
ERC	European Resuscitation Council
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale-extended
HRQoL	health-related quality of life
IHCA	In-hospital cardiac arrest
ILCOR	International Liaison Committee on Resuscitation
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
MoCA	Montreal Cognitive Assessment
mRS	modified Rankin Scale
NSE	Neuronspecific enolase
OHCA	out-of-hospital cardiac arrest
RASS	Richmond Agitation-Sedation Scale
ROSC	return of spontaneous circulation
SAE	Serious adverse events
SBU	Swedish agency for health technology assessment and assessment of social services
SDMT	Symbol Digit Modalities Test
TSQ	Two Simple Questions
WLST	Withdrawal of life sustaining therapies

1 Study Overview

The TTM2 trial is a continuation of the collaboration that resulted in the previous Target Temperature Management after out-of-hospital cardiac arrest trial (hereafter: TTM1). With its planned size TTM2 will supersede the TTM1 trial as the largest trial on temperature management as a post-cardiac arrest intervention.

The TTM1 trial (NCT01020916) [1] was a multicenter, multinational, outcome assessor-blinded, parallel group, randomised clinical trial comparing two strict target temperature regimens of 33°C and 36°C in adult patients, who had sustained return of spontaneous circulation and were unconscious after out-of-hospital cardiac arrest, when admitted to hospital. The trial did not demonstrate any difference in survival until end of trial (Hazard Ratio with a point estimate in favour of 36°C of 1.06 (95% confidence interval 0.89-1.28; P=0.51)) or neurologic function at six months after the arrest, measured with the Cerebral Performance Category (CPC) and the modified Rankin Scale (mRS).

The planned study is a international, multicenter, parallel group, non-commercial, randomised, superiority trial in which a target temperature of 33°C after cardiac arrest will be compared to normothermia with early treatment of fever (≥37.8°C)

Patients eligible for inclusion will be unconscious adult patients with out-of-hospital cardiac arrest (OHCA) of a presumed cardiac cause with stable return of spontaneous circulation. Randomisation will be performed by a physician in the emergency department, in the angiography suite or in the intensive care unit via web-based application using permuted blocks with varying sizes, stratified by site. Due to the nature of the intervention, health care staff will not be blinded to the intervention. However, the health care personnel who will assess outcomes will be blinded to temperature allocation, as will those who perform prognostication.

The intervention period will commence at the time of randomisation. Rapid cooling in the hypothermia group will be achieved by means of cold fluids and state-of-the-art cooling devices (intravascular/body-surface/nasal/oesophageal). A closed loop system will be used to maintain the target temperature. In the normothermia arm the aim will be early treatment of fever (≥37.8°C) using pharmacological measures and physical cooling when needed. For patients who develop a temperature of 37.8°C (trigger), a device will be used and set at 37.5°C. All patients will be sedated, mechanically ventilated and haemodynamically supported throughout the intervention period of 40 hours. After 28 hours the patients in the hypothermia group will be rewarmed during 12 hours.

Patients who remain unconscious will be assessed according to a conservative protocol based on the European Resuscitation Council (ERC)'s recommendations for neurological prognostication after cardiac arrest.

Follow-up will be performed at 6 and 24 months after cardiac arrest. The main results of the trial will be published following the 6-month follow-up, results from the long-term follow-up will be presented separately.

2 Background and Significance

In Europe approximately 300 000 inhabitants suffer an OHCA each year. Of those admitted to hospital with return of spontaneous circulation, the majority are unconscious and will need intensive care treatment and only 30-55% will be discharged alive. In survivors discharged from hospital the frequency of cognitive disability varies between reports. Using crude, but recommended, outcome scales such as the CPC-scale, Glasgow Outcome Scale (GOS), or the mRS, the general neurological function is good in the majority of patients, with only 10% having a severe neurological disability. In studies using more detailed instruments, cognitive impairment is reported to be present in 50% of survivors, and associated with lower quality of life and increased caregiver strain.

Many interventions have been tested in order to lower mortality and improve neurologic function in patients resuscitated after out-of-hospital cardiac arrest. Despite promising results in experimental models, all but one have failed in clinical trials. To date, induced hypothermia is the only intervention that has shown promising results in clinical trials.

2.1 Randomised Trials

In 2002 two small trials (n=77 and 275) reported a substantial improvement in survival and neurological function when unconscious patients with bystander witnessed OHCA of a presumed cardiac origin and with initial shockable rhythms, were cooled to 32 to 34°C for 12 to 24 hours after return of spontaneous circulation. [2, 3] These two trials received worldwide attention and international societies such as the American Heart Association (AHA), ERC, and the International Liaison Committee on Resuscitation (ILCOR) recommended the intervention in this patient group (strong recommendation, high level of evidence) and also for cardiac arrests of other origins, and with other initial rhythms. Cochrane reviews from 2009 and 2012 drew the same conclusion, strongly advocating hypothermia after cardiac arrest.

We performed a systematic review of the available evidence using meta-analysis, trial sequential analysis and the GRADE methodology and could report that earlier trials on hypothermia were at high risk of systematic error (bias), random error (play of chance) and also hampered by obvious design problems (for instance very selective inclusion criteria excluding more than 90 percent of potential patients). Our conclusion was that the overall quality of evidence was on a low level, implying equipoise for additional research on hypothermia. In addition, it was clear that the optimal target temperature range was not defined and unclear whether the suggested benefit in earlier trials was attributable to hypothermia, or merely to avoiding the fever response, that is the natural trajectory for most unconscious cardiac arrest patients.

With these findings in mind we designed and conducted the Targeted Temperature Management, 33°C versus 36°C in Out-of-hospital cardiac arrest trial during 26 months between 2010 and 2013. This trial included 950 patients in 36 hospitals in ten countries and randomised patients to 36 hours of temperature management at either 33°C or 36°C. The trial was more inclusive than earlier trials including 4 out of 5 unconscious patients with OHCA of a cardiac origin admitted to the emergency departments of the participating sites. The number of included patients was twice that of all previously randomised patients combined. The TTM1-trial did not demonstrate any difference in survival until end of trial (Hazard Ratio with a point estimate in favour of 36°C of 1.06 (95% confidence interval 0.89-1.28; P=0.51)) or neurologic function at six months after the arrest, measured with CPC and mRS. Health-related quality-of-life was good among the

survivors and equal in the two intervention groups. [4] Detailed cognitive testing in a large subset of patients detected cognitive impairment in approximately half of the surviving patients, [5] but the levels of anxiety and depression were similar in a control population. [6]

Critique of the trial has included that the hypothermia induction was not sufficiently rapid (although similar to previous trials), that the confidence limits were wide enough to include both clinically meaningful benefit and harm of the intervention, that subgroups within the general study population could benefit from either intervention strategy, and that follow-up with neurocognitive testing should have been delayed further beyond the 6-month visit used in the trial. International guideline groups raised the following questions as a result of the TTM1-trial:

- Is fever control a sufficient measure to attenuate brain damage after cardiac arrest?
- Are there subgroups that would benefit from temperature management at a higher or lower level (for instance patients with longer arrests and more severe brain damage, or patients in circulatory shock)?
- Could faster and earlier induction of hypothermia improve outcomes in the 33°C-group?
- Were the results of the TTM1-trial not precise enough? Which would imply the need for larger sample sizes or meta-analytical approaches to better estimate effects.
- Could a longer follow-up perspective help in guiding which intervention is superior?

2.2 Hypothermia in other areas

In systematic reviews of multiple trials, hypothermia to 33°C was found effective in improving functional outcome in neonates with hypoxic ischaemic encephalopathy, a disease with many similarities with adult cardiac arrest. [7, 8] In paediatric cardiac arrest the picture is less clear, with one trial showing no statistically significant difference, but with point estimates with a strong numerical tendency in favour of the 33°C-arm, and the lack of significance may in part have been due to sample size problems. [9] In contrast to this, a trial of hypothermia for adult traumatic brain injury showed consistently worse outcomes in the cooled group, and the trial was stopped early due to harm. [10]

2.3 Rationale for a new trial

The evidence for hypothermia in a broad context is conflicting. Clinical trials in various areas of brain damage indicate both benefit and harm. Theoretical rationale exists and currently hypothermia is the only intervention strategy to treat acute ischaemic brain injury in clinical use. Specifically, in adult cardiac arrest low quality evidence indicate benefit of 33°C and moderate quality evidence indicate no difference between 33°C and 36°C. The recent TTM1-trial has had a significant influence on the new ILCOR, AHA and ERC statements and guidelines for 2015, [11, 12] which have adopted the view that both lower and milder forms of temperature management provide similar clinical results, and the recommended temperature range has been changed to include 36°C. Most important, however, is that the overall evidence level for temperature management after OHCA has been changed to *low*, in line with our conclusion from the meta-analyses performed in 2010. In an international perspective, many hospitals and regions have already changed strategy in favour of the 36°C-arm, reasoning that a less invasive and easier administrated temperature strategy yielding the same clinical results is preferable. Many

hospitals however still remain at 33°C based on earlier evidence while others, motivated by a lack of robust evidence, do not use temperature management at all.

Based on the above and the knowledge gaps indicated in international guidelines and reported by Swedish agency for health technology assessment and assessment of social services (SBU), it is reasonable to again test whether rapidly administered hypothermia to a low target level (32-33°C) is beneficial, and specifically to *a priori* define subgroups where the intervention effect could be studied. At the same time, it is important to clarify if early treatment of fever (easier, less costly and less invasive than the 36°C-arm in the TTM1-trial) is sufficient to achieve a good functional outcome. It is also important to, for the first time, investigate the evolution of neurological recovery over an extended period of time. We therefore propose the TTM2-trial.

2.4 Rationale for early treatment of fever

Fever is a risk factor for death after Cardiac arrest (CA) although it still remains an open question if it is a *causative and modifiable* risk factor. Zeiner and colleagues showed an increase in the odds of a poor neurological outcome for each degree higher than 37°C. [13] However, a body temperature above 37°C can occur due to individual or diurnal variation. When temperature is measured in large population it appears that 37°C has no special significance to human thermometry. [14, 15] It therefore seems reasonable to apply a less strict definition of fever than >37.0°C. At the other end of the spectrum, it could be argued that it would be problematic to allow temperatures up to 38.3°C (A level usually employed in the definition of fever of unknown origin). [16]

This study will employ normothermia-targeted temperature management in the control arm, with 37.8°C as a trigger for active temperature management with a feedback device. Although any temperature cut-off is to some extent arbitrary, the choice of these values are motivated by the following.

- Diagrammatic data from the HACA-trial [3] suggests a median temperature between 37.5°C and 37.8°C among patients in the control arm of the study. If a similar distribution is assumed in the current trial a substantial amount of patients will *not* require a device, thus making temperature management considerably less labour and resource intense.
- 37.7°C has been proposed as the upper limit of normal body temperature in healthy adults. [14] Employing active fever control for any patient who exceeds this temperature therefore constitutes an aggressive approach to fever control.
- Temperature fluctuations are unavoidable. In the TTM1-trial, the measured temperature among patients allocated to TTM at 36°had a standard deviation of approximately 0.5°C. Assuming a similar variation around 37.5°C (for patients in whom active temperature management is used), very few patients would become unequivocally febrile with temperatures above 38.3°C.

The functional definition of fever in this trial will therefore be temperatures greater than, or equal to 37.8°C. Normothermia will be defined as 36.5-37.7°C

3 Study Hypotheses and Endpoints

We designed the study to test the hypothesis that post-ischaemic hypothermia, when compared to normothermia and early treatment of fever, decreases mortality and improves neurologic function in unconscious adults after out-of-hospital cardiac arrest. This hypothesis will be assessed by studying the primary and secondary endpoints at 180 days after cardiac arrest.

3.1 Primary Endpoint

The primary objective of this study is to determine if hypothermia (33°C) increases 180 day survival when compared to normothermia and early treatment of fever, in patients who are unconscious after OHCA.

3.2 Secondary Endpoints

The secondary aims of the TTM2 trial are:

- To evaluate if there is any difference in functional outcomes, using the Glasgow Outcome Scale-extended (GOS-E) between patients managed at 33°C compared to normothermia and early treatment of fever. GOS-E will be assessed at 180 days and at 24 months.
- To evaluate potential differences in health-related quality of life (HRQoL) at follow up using EQ5D-5L at 180 days and at 24 months.
- Time-to-event (survival). All patients will be followed until the last included patient has been followed-up at 180 days. If death has not occurred patients will be censored at this point.

3.3 Tertiary explorative endpoints

- To evaluate functional outcomes using the mRS at 30 days and 180 days after CA
- To test leg strength and endurance, using the The 30-Second Chair Stand Test. The test will be performed at 180 days and at 24 months.
- Detailed neuro-cognitive function assessed by the Montreal Cognitive Assessment (MoCA) and the Symbol Digit Modalities Test (SDMT). Neuro-cognitive function will be assessed at 180 days and at 24 months.
- Self- and observer reported cognitive disability using Two Simple Questions (TSQ) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). These tests will be performed at 180 days and at 24 months. A relative or close friend will be approached for a baseline assessment of cognitive decline using the IQCODE during the ICU-stay
- Assessment at 24 months (Survival, GOS-E, EQ5D-5L, MoCA, SDMT, TSQ, IQCODE and The 30-Second Chair Stand Test)

3.4 Rationale for chosen endpoints

To minimise biased assessment and to avoid competing risks, survival was chosen as the primary outcome. Although the intervention is primarily thought to affect the development of brain injury, survival is a global assessment of the intervention's effect on all organ systems. The estimated 45% mortality of the target population yields a high power to detect differences in a reasonably sized study.

We recognise the risk that clinically relevant effects on the development of brain injury may be missed using survival as the only outcome as neurological outcome for OHCA-survivors range from a vegetative state to complete recovery.

To complement and support the primary outcome we will therefore use the GOS-E scale to measure overall recovery. GOS-E is an 8-point ordinal scale that has been validated for brain injury and reports effects on major life areas, ranging from levels of basic abilities (consciousness and dependence in everyday activities) to upper levels of a good recovery (return to a normal life, including work, and leisure activities). A standardised questionnaire and good psychometric properties secure reliable and valid outcome reports between multiple assessors and sites. [17] The commonly used CPC-scale can be extracted from the GOS-E to facilitate comparisons between trials (including the TTM1-trial) and meta-analyses. To include patient reported outcome measures, HRQoL was recommended by guidelines for outcome reporting after cardiac arrest [18] and will likely be part of the core outcome set (COS) for cardiac arrest trials, which is being developed by an ILCOR consensus group including patient and partner representatives.

The EQ5D-5L was chosen as the TTM2-trial HRQoL-instrument since it is easy to use, validated, performs well when obtained by proxy and may be used to calculate quality-adjusted life-years. [19]

In the exploratory analyses we will use two tests to address the survivors' neuro-cognitive functions in the domains mostly affected after CA: memory, executive functions and attention/mental processing speed. [18] The MoCA is a global cognitive screening test administered in approximately 10 minutes, which assesses multiple aspects of executive functions, short-term memory and delayed recall. [20] The SDMT is one of the most sensitive cognitive assessments to indicate brain injury and specifically assess attention/mental processing speed. [21] In a sub-study of the TTM1 trial the SDMT was the best discriminator of cognitive function between OHCA-patients and controls. [5] As in the TTM1-trial, we will use the 26-item IQCODE to obtain a relatives' perspective on changes in the patient's cognitive performance in everyday life [22] and the TSQ to obtain the patient reported cognitive outcome. [23] We have modified the IQCODE to the CA-situation. [24] The preliminary result of our validation study is that the psychometric properties are retained from the original test. In an attempt to measure a composite outcome of lower limb strength, proprioception and balance, the 30-second chair stand test will also be performed. [25]

4 Eligibility

The study population is the adult population, 18 years of age or older who experience a cardiac arrest of a cardiac or unknown cause with return of spontaneous circulation (ROSC).

Patients will be eligible for enrolment if they meet all of the following inclusion criteria and none of the exclusion criteria.

4.1 Inclusion criteria

- OHCA of a presumed cardiac or unknown cause
- Sustained ROSC - defined as 20 minutes with signs of circulation without the need for chest compressions [26]
- Unconsciousness (FOUR-score motor response of <4, not able to obey verbal commands) after sustained ROSC.
- Eligible for intensive care without restrictions or limitations

4.2 Exclusion criteria

- Known limitations in care or a Do not resuscitate (DNR)-order
- Known disease making 180 day survival unlikely
- Temperature on admisison <30°C.
- On ECMO prior to ROSC
- Obvious or suspected pregnancy
- Intracranial bleeding

4.3 Note on inclusion and exclusion criteria

In prior trials on hypothermia for cardiac arrest, inclusion criteria have usually included a cardiac or unknown cause of arrest. Since the update of the Utstein criteria [26] the term "medical cause of arrest" has been introduced. It is backward compatible with the earlier definition (presumed cardiac or unknown, other medical aetiologies). A medical cause of arrest can include asthma/COPD, anaphylaxis or GI-bleeding. One likely result of broadening the inclusion criteria would be an increased mortality due to other reasons than neurological damage, which would decrease the power to detect a significant effect of the intervention in this regard. The inclusion criteria of this trial have therefore not been edited to reflect this change in terminology.

There are three main reasons for including both patients with shockable and non-shockable rhythms. The first is that any neuroprotective effect of a lower target temperature reasonably would apply to both patient groups as the mechanism of cerebral injury is the same. Second, it is reasonable to presume that any evidence for or against an intervention for patients with shockable rhythms will also be used for patients with non-shockable rhythm, as evidenced by the widespread use of hypothermia in both groups during the last decade. Third, including patients

with non-shockable rhythms would increase the proportion of patients with a poor outcome, leading to an increased power to detect an *a priori* set relative risk reduction of 20%.

Patients with refractory shock (systolic blood pressure <80mmHg despite receiving volume, inotropic/vasopressor support and/or an intra-aortic ballon pump (IABP)) will not be excluded from the trial. Results from the TTM1-trial showed that only 2% of patients assessed for eligibility in the trial were excluded due to refractory shock. The inclusion of these patients are therefore unlikely to effect the baseline risk of death in a significant way. Additionally, should the trial show positive results for hypothermia, the intervention will likely be used on patients in shock. We therefore deem the inclusion of these patients as a pragmatic approach.

Patients who are dependent on others for activities of daily living will not be excluded from the trial. Our experience from the TTM1-trial has been that a rapid identification of the patient's pre-morbid functional status is difficult to ascertain. To avoid any potential bias in recruitment, these patients will not be excluded. As the primary outcome will be death, and the main analysis of functional outcomes will be performed according with an ordinal shift analysis this will not impact the main results. Patients who are later identified to have had a pre-morbid status corresponding to CPC3/GOS-E 3-4 may not be excluded from any analysis where patients are dichotomised into good and poor neurological outcomes.

Rather than gauging the patients' pre-morbid status before randomisation we think it more important to use factors that are known, and easier to establish from medical records at the moment of randomisation (limitations in care and 180 day-survival unlikely). The potential inclusion of a patient with a DNR is likely to have a larger effect on the results than the inclusion of a patient with a pre-morbid CPC of 3.

4.4 Exit from the study

A patient is free to withdraw his/her informed consent from the trial at any time after regaining consciousness. A patient will exit the trial if this patient withdraws consent. The reason for the exit 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, 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 permission is obtained, the patient will be included in the final analyses. If the patient declines, all data from that patient will be destroyed.

If the study intervention is discontinued by the treating physician because of adverse events, or any other reason, this does not constitute subject withdrawal from the study and the patient will not exit the trial. All cases randomised in this study will be analysed on an intention-to-treat basis.

5 Study design

The TTM2-trial is a multicenter, international, randomised trial with a 1:1 concealed allocation of OHCA patients to targeted temperature management with hypothermia at 33°C or normothermia and early treatment of fever equal to, or greater than 37.8°C. The trial is investigator-initiated and non-commercial. Evaluation of functional outcomes will be performed by a blinded assessor.

5.1 Screening and Randomisation (Phase 1)

Screening can be performed either in the emergency room, angiography suite, or in the intensive care unit. Clinical investigators at each participating site will be responsible for screening of all patients who are resuscitated from an OHCA. A screening log will be compiled and include all OHCA-patients, whether they are eligible for inclusion, or not. Informed consent will be obtained according to national ethical approval.

Trial sites will have access to an internet based randomisation application 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 performed with permuted blocks, stratified for trial site. *Phase 1* will be identical for both the intervention and control group.

5.2 Overview of the ICU period (Phase 2)

The intervention period will commence immediately after randomisation. Patients allocated to TTM at 33°C, will be rapidly cooled with a device to 32.0-32.5°C. Upon reaching this first temperature goal a maintenance phase will commence, which will end 28 hours after randomisation. During the maintenance phase the target temperature will be 33°C. This will be followed by rewarming at $\frac{1}{3}$°C/ hour. In the normothermia group the aim will be a temperature below 37.5°C. If conservative and pharmacological measures are insufficient and the temperature reaches 37.8°C, cooling with a device will be initiated with a target temperature of 37.5°C. All patients will be sedated and mechanically ventilated.

5.3 After the intervention period (Phase 3)

Extubation should be attempted at the earliest possible time, based on standard procedures for discontinuation of mechanical ventilation. For patients who remain in the ICU and are comatose or sedated at 40 hours after randomisation (end of the intervention) both allocation groups will have temperature maintained in the normal range (36.5-37.5°C) until 72 hours after randomisation. Neurological evaluation will be performed by a blinded physician after a minimum of 96h have passed since randomisation and any use of a temperature management device will be at the discretion of the treating physician.

5.4 General ICU-care

General ICU-care will be the same in both allocation groups. Fluid therapy will be guided by standard procedures for haemodynamic support (fluid responsiveness, urinary output, haemodynamic and laboratory values, echocardiography etc). There will be treatment recommendations for sedation and management of shivering (outlined below). Management of haemodynamics, respiration, metabolic disturbances and seizures will be according to local protocols, at the discretion of the treating physician. Cardiac interventions will also be guided by local protocols, however participating centers will need to have access to around-the-clock invasive management, either on-site or at a nearby hospital also part of the trial. Cardiac catheterisation should not be delayed by the intervention, but efforts should be made to ensure temperature management during the procedure.

5.4.1 Sedation

Sedation will be mandatory for 40 hours after randomisation. There will not be a defined protocol for sedation analgesia but short-acting drugs or volatile anaesthesia will be recommended. The sedative should be titrated to achieve deep sedation, Richmond Agitation-Sedation Scale (RASS) of minus 4-5 - any movement (but no eye-contact) to voice/No response to voice or physician stimulation. [27]

Beyond adequate sedation during TTM, prolonged sedation is not recommended in international guidelines. Requiring 40 hours of sedation in both allocation arms therefore constitutes a departure from what is normally considered standard care. However, since patients included in the TTM2-trial would have received TTM and sedation, whether they were included in the trial or not, there is no difference in their treatment in regards to sedation. This approach is to facilitate a true comparison of two targeted temperatures, hypothermia and normothermia. Without sedation requirements there would be a substantial difference in the total dose of sedative agents between the hypothermia and normothermia treatment arms. Though the amount of sedatives administered in the hypothermia arm may still exceed the dose in the normothermia arm, a required sedation time is likely to lessen the difference.

5.4.2 Shivering

Shivering will be assessed according to the Bedside shivering assessment scale (BSAS). [28] The treatment goal for shivering will be to maintain a BSAS score of 0 or 1. To ensure adequate control of shivering the following protocol will be recommended. The recommended measures to reduce shivering should be continued through the entire intervention period in **both** allocation groups.

- Baseline care for all patients: Acetaminophen/Paracetamol administered either intravenously, parenterally or rectally, according to standard dosing guidelines. Acetaminophen/Paracetamol may be withheld at the discretion of the treating physician if liver dysfunction contraindicates the use. Buspirone, magnesium, clonidine, meperidine and skin counterwarming will be included in baseline care if these interventions are part of the local protocol for management of shivering. They will not be required for baseline care.
- Step 1: Increased sedation with propofol/dexmedetomidine and/or opiate. If the patient is haemodynamically unstable, midazolam may be substituted for propofol.

- Step 2: Administration of a neuromuscular blocking agent

5.4.3 The Bedside Shivering Assessment Scale (BSAS)

0	**None**	No shivering
1	**Mild**	Shivering localized to neck/thorax, may be seen only as artifact on ECG or felt by palpation
2	**Moderate**	Intermittent involvement of the upper extremities ±thorax
3	**Severe**	Generalized shivering or sustained upper/lower extremity shivering

5.5 Prognostication and withdrawal of life sustaining therapies

Prognostication will be performed on *all* patients still in the ICU at 96 hours after randomisation. The prognostication will be based on the ERC and European society for Intensive Care Medicine [11, 29] recommendations and performed at approximately 96h after CA, but may be delayed due to practical reasons (such as weekend or national holiday). Prognostication and the potential decision to withdraw active intensive care are closely related but will be considered separate entities. The results of a blinded prognostication will be categorised *Poor prognosis likely (YES/NO)*. Any decision to withdraw active life support will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. In making this decision the treating physician may use the information from the prognostication. The blinded external physician will not make any recommendation on WLST. Efforts will be made to ensure that prognostication is sufficiently delayed to ensure that any lingering effects of sedative agents affects the assessment.

Prognostication will be based on two mandatory, and three optional modalities.

5.5.1 Clinical examination

A clinical examination including assessment of brainstem reflexes and described using the FOUR-score will be performed daily on all patients. Absent or extensor motor response to pain (FOUR-score motor response 0-1) at 96h or later, is a prerequisite to consider the neurologic prognosis poor. The bilateral absence of pupillary and corneal reflexes at 96h after CA or later, is a finding indicative of a poor prognosis.

The clinical examination should also include a an assessment of status myoclonus (continuous and generalised myoclonus persisting for at least 30 min). Early status myoclonus (within 48 hours) is indicative of a poor prognosis.

5.5.2 EEG

An EEG performed between 48h and 96h after CA will be performed on all patients who survive to this point - regardless if they are awake or not. An EEG with a highly malignant pattern, and without reactivity to sound and pain is indicative of a poor prognosis.

5.5.3 Brain CT

If an early (within 24h) brain-CT shows signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement, this is indicative of a poor prognosis. If an additional CT is performed after 24h this may also be taken into account.

5.5.4 Brain MRI

A brain MRI at 3-5 days may be incorporated into prognostication if it has been performed. However, a brain MRI will not be mandatory. Signs of global, diffuse, or bilateral multifocal ischemic lesions is indicative of a poor prognosis.

5.5.5 Neuron specific enolase

High levels of Neuronspecific enolase (NSE) are indicative of a poor prognosis. NSE-sampling will not be mandatory, but may be used by sites with experience. If serial samples are available, and these are consistently higher than locally established levels associated with a poor outcome, this may be seen as indicative of a poor outcome. Samples with haemolysis should be disregarded.

5.5.6 SSEP

Absent SSEP N20-responses bilaterally may be seen as indicative of a poor prognosis, if SSEP is performed more than 48h after arrest.

5.5.7 Withdrawal of life sustaining therapies (WLST)

All patients in the trial will be actively treated until 96 hours after CA. There will be two exemptions from this rule.

- Patients in whom further treatment is considered unethical due to irreversible organ failure, a disseminated malignancy, or other reasons
- Patients in whom brain death is established, however this will be defined as death rather than WLST

The assumption of a poor neurological prognosis alone will not be considered sufficient to employ withdrawal of active intensive care prior to 96 hours after arrest. After prognostication has been performed, withdrawal of life sustaining therapies due to a presumed poor prognosis will be allowed if the following criteria are fulfilled and all effects of sedation on consciousness are ruled out.

- A FOUR-score motor response of 0 or 1

  AND at least two of the following:

- Bilaterally absent pupillary and corneal reflexes
- Bilaterally absent SSEP N20-responses

- Diffuse anoxic brain injury on CT or MRI
- Status myoclonus <48h
- High levels of serum NSE
- An EEG with a highly malignant pattern and without any observed reactivity to sound or pain. Patterns that are considered highly malignant are: 1. Suppressed background (amplitude <10mV, 100% of the recording) without discharges.
  2. Suppressed background with superimposed continuous periodic discharges.
  3. Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges.
  4. Burst-suppression with superimposed discharges. [30, 31]

Patients who have an unclear prognosis at 96h after CA should be reexamined daily and Withdrawal of life sustaining therapies (WLST) may be considered if neurological function does not improve and metabolic and pharmacological reasons for prolonged coma are ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing care will be recorded. However supporting care may contninue regardless of the neurological prognosis, at the discretion of the treating physician.

5.5.8 Brain death

Patients in whom brain death due to cerebral herniation is established will be registered as dead when a conclusive assessment has been made. If death is due to brain death this will be registered.

5.6 Follow up

A first formal follow-up will take place at 1 month after cardiac arrest. For some patients this follow-up will take place face-to-face in hospital. For those patients who have been discharged, follow-up will be performed by telephone. Patients will be assessed according to the mRS and GOS-scale.

At six and twenty-four months, patients will be invited to a clinic visit, if possible with a relative or close friend. At these visits specially trained, blinded assessors will perform structured interviews according to the secondary and tertiary outcomes. The assessment will focus on cognitive function, quality-of-life, cardiovascular risk factors, ability to work and participation in society. At the twenty-four month visit patients will be approached for consent regarding a potential follow-up at 60 months.

The outcome-assessor may be an occupational therapist, physician, research nurse, psychologist or similar, who is proficient in the English language. Outcome-assessors will be provided with a written study manual with detailed guidelines for performing the questionnaires and assessments. Training sessions will be provided by the study coordinating team. At the end of each training session participants will perform GOS-E scoring on a number of practice cases. Outcome-assessors will also be encouraged to perform all follow-up procedures on a number of pilot persons.

5.7 Blinding

The clinical team responsible for the patient (physicians, nurses and others) and involved with direct patient care will not be blinded to allocation group due to the inherent difficulty in blinding the intervention and as temperature is a vital sign required for clinical care. Measures will be taken to ensure that the information about allocation will not disseminate beyond the immediate group of caregivers responsible for patient care. A blinded physician will evaluate the patient at 96 hours after randomisation and make a statement on neurological prognosis. The intensive care physician will not be allowed to share any information regarding allocation. Patients, their legal representatives, and family will only be informed that the patient has received targeted temperature management. Health personell responsible for outcome assessment at follow-up will be blinded to the allocation of the intervention. If blinding was successful will be tested by asking the outcome-assesor at the six-month follow up about the perceived allocation of the patient. The steering group, author group, trial statistician and the study coordinating team will be blinded to the intervention during the entire trial period and when handling the trial database.

6 Intervention period

6.1 Hypothermia

Phase 2 of the trial starts immediately at randomisation. Temperature will be recorded hourly via a bladder thermometer until 48h after randomisation. If the patient is oliguric, or if a bladder recording is not available the core temperature will be assessed by an oesophageal or intravascular probe. The total length of phase 2 will be 40 hours and will be divided into two blocks.

6.1.1 Block A

Block A constitutes the cooling phase and maintenance phase. After randomisation patients will be cooled as quickly as possible, with an initial target temperature of 32°C. An initial target of 32°C will mean that the device used to induce hypothermia will be set at 32°C. Cooling can be induced by the following means.

- Intravenous cold (4°C) fluids. Normal saline, Hartman's solution or other similar crystalloids are recommended. The maximal volume for the initial cooling will be 30ml/kg^{-1}.
- Approved endovascular cooling devices with closed loop systems
- Approved available surface cooling devices with closed loop systems
- Approved devices for intranasal or oesophageal cooling
- Ice-packs or cooling pads
- Pharmacological treatment with Acetaminophen/Paracetamol (part of anti-shivering protocol)
- Complete expose of the patient
- Lowering of ambient temperature
- Any combination of the above that includes a device

The recommended method of cooling will by a approved available feedback controlled device. To allow for a pragmatic trial, that does not limit the induction of hypothermia to any type of device and at the same time allow rapid cooling, initial cooling with cold fluids will be allowed. If a patient has a temperature between 30°C and 33°C, the patient will be actively rewarmed to 33°C. [11] Use of neuromuscular blocking agents will be recommended to facilitate induction of hypothermia. Feasibility studies of novel cooling devices will not be allowed in the TTM2-trial.

The target temperature should be achieved as soon as possible. Local protocols should be developed to ensure that it is feasible to reach the targeted temperature within 90 minutes or shorter in the majority of patients.

When patients in the hypothermia arm reach below 33°C the target temperature will be adjusted to 33°C.

A target temperature of 33°C will be maintained until 28h after randomisation.

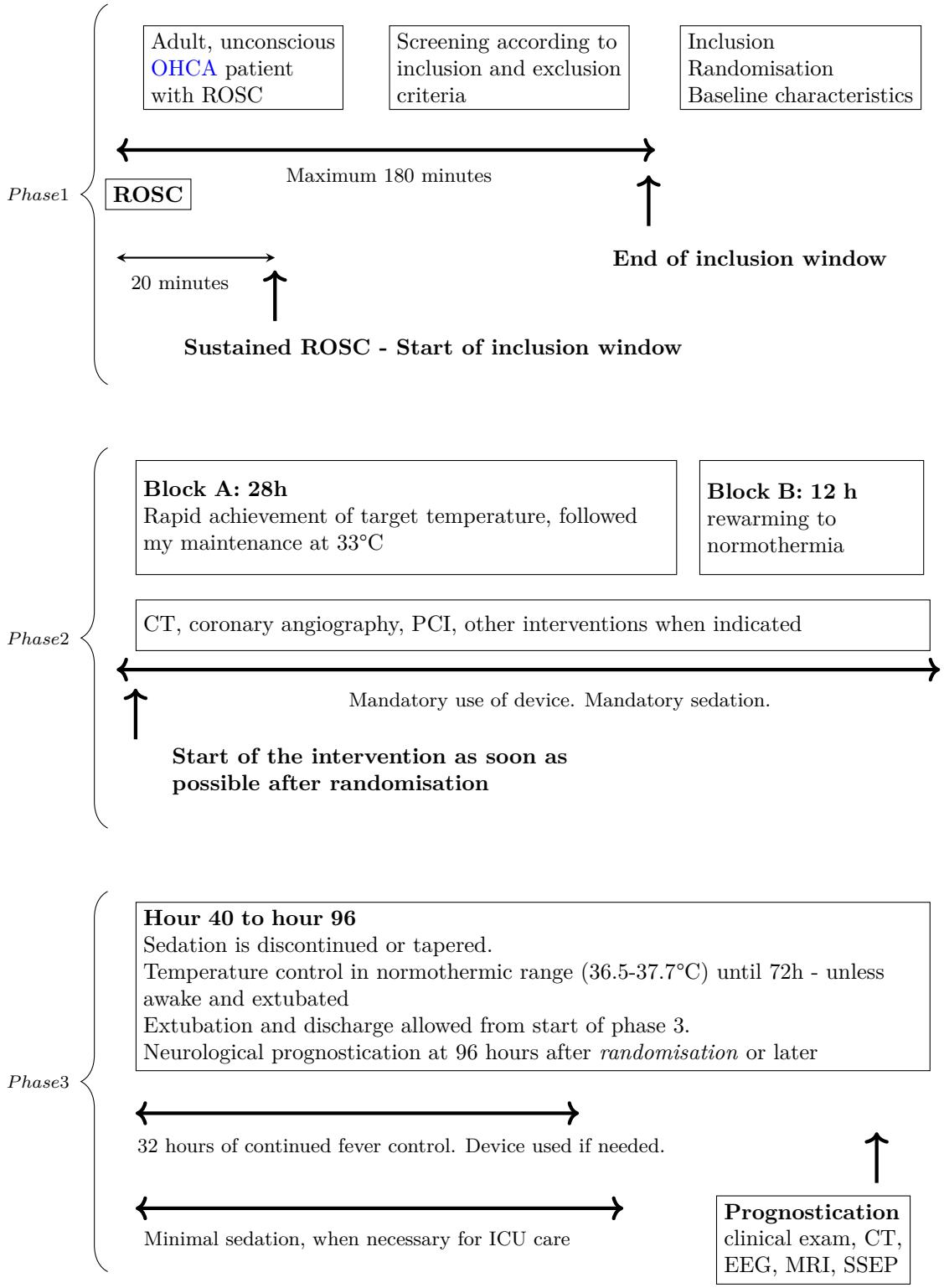

Figure 1: Schematic of trial intervention - Hypothermia

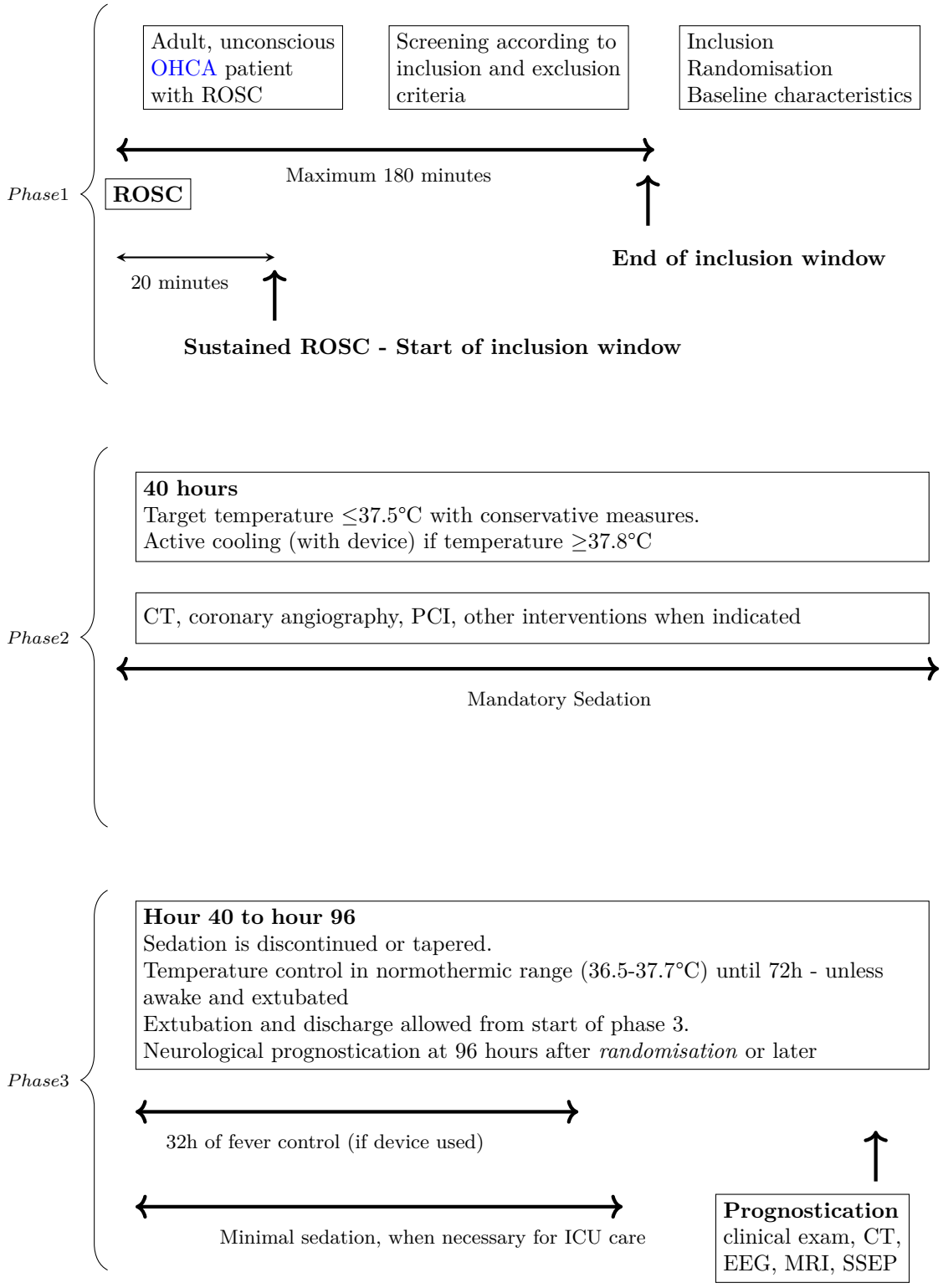

Figure 2: Schematic of control group - Normothermia and early treatment of fever

6.1.2 Block B

Block B is the period (12h) allocated to restoration of normothermia. Patients will be rewarmed at $\frac{1}{3}$°C/ hour (1°C in three hours) allowing 12 hours for rewarming.

6.1.3 Early termination of the intervention

The intervention may be discontinued if hypothermia is the suspected cause of uncontrolled bleeding, life threatening arrhythmia or refractory haemodynamic instability, at the discretion of the treating physician. The target temperature will then be adjusted to ≤37.5°C

6.1.4 After rewarming

After 40 hours, those patients who remain comatose should be kept at a normothermic level (36.5 - 37.7°C) until 72h after randomisation and active warming should be avoided.

6.2 Normothermia and early treatment of fever

Normothermia, an active comparator will mirror the phases of the hypothermia intervention to ensure comparability between the allocation arms. However, the temperature management strategy will be different.

Temperature will be recorded via a bladder thermometer. If the patient is oliguric, or if a bladder recording is not available the core temperature will be assessed by an oesophageal or intravascular probe. Patients who have an initial temperature between 30-33°C will be actively rewarmed to 33°C, at which point active rewarming should be suspended. Patients with an initial body temperature above 33°C will not be actively rewarmed to normothermia (0.5°C/hour). To ensure that temperature does not reach 37.8°C the following conservative interventions will be allowed, at the discretion of the treating physician.

- Pharmacological treatment with Acetaminophen/Paracetamol (part of anti-shivering protocol)
- Complete expose of the patient
- Lowering of ambient temperature

If conservative measures are insufficient, a device for temperature management will be used. The definition of insufficient fever control with conservative measures is:

A single recorded measurement of core body temperature (bladder) ≥37.8°C, regardless whether the origin is deemed to be of infectious origin or a response to neurological injury

If the criterion for insufficient fever control is fulfilled the same methods that will be used in the intervention arm will be used to achieve a target temperature of 37.5°C.

- Approved endovascular cooling devices with closed loop systems
- Approved available surface cooling devices with closed loop systems

- Intravenous cold (4°C) fluids for initial induction of hypothermia, if a device is not in situ. Normal saline, Hartman's solution or other similar crystalloids are recommended. The maximal volume will be 30ml/kg^{-1} or 2 liters. Fluids should be given whilst the device is being applied/inserted.

The treating physician may prescribe the application of a device (insert an endovascular catheter of apply a surface device) either prophylactically in all patients randomised to normothermia or if a rise in temperature is encountered. However the device will not be switched on until a core body temperature of $\geq$37.8°C is measured. Active fever control will be initiated as soon as a core body temperature reaches 37.8°C during the first 40 hours after randomisation. After 40 hours, those patients who remain comatose should be kept at a normothermic level (36.5 - 37.7°C) until 72h after randomisation and active warming should be avoided.

7 Data collection

Clinical, laboratory and background data will be collected at the time of enrolment, during the ICU-stay, at ICU-discharge, at hospital-discharge, and at follow-up. This section provides a summary of the data that will be collected.

Data will be obtained from hospital records, relatives ,and ambulance services and will be entered into a web-based electronic case record form (eCRF) by site personell. The site investigator must sign all eCRFs before study completion to verify that the recorded data is correct and complete. The software for the web-based form will be provided by Lytics, Lund, Sweden. Data from the web-based forms will be migrated to a trial database, which will be handled by the coordinating team.

The sponsor supplies a standard description of all units of measurement in the eCRF. If a trial site uses different units of measurement and this might be a potential source of error, the site investigator should contact the coordinating team to have the data capture module modified. 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)

7.1 Baseline data

This data will be obtained from emergency medical services/ambulance personell or hospital records.

7.1.1 Pre-randomisation characteristics

- Inclusion and exclusion criteria
- National identification number
- Age
- Sex
- Type of temperature management system planned (intravascular or surface cooling)

7.1.2 Pre-hospital data

- Scene of arrest (home, work, public place, nursing facility, other)
- Bystander CPR (Y/N)
- Witnessed arrest (Y/N)
- First monitored rhythm at arrival of EMS
  (asystole, PEA, VF, non-perfusing VT, ROSC after bystander defibrillation, unknown (shockable or unshockable))
- Time from emergency call to arrival of EMS
- Estimated time from arrest to basic life support

- Estimated time from arrest to advanced life support
- Estimated time of ROSC
- Use of active compression-decompression device
  (No, Yes(LUCAS, Autopulse, manual))
- Number of defibrillations (if applicable
- Time from arrest to first defibrillation
- Pre-hospital airway (no, intubated, laryngeal mask)
- Amount of Adrenaline (mg)

7.1.3 Background data

- Height
- Weight
- Pre-arrest CPC/GOS
- Previous cardiac disease and cardiac interventions
- Previous percutaneous coronary intervention? [yes/no]
- Previous coronary artery bypass grafting? [yes/no]
- Previous known coronary artery disease? [yes/no]
- Previous implantable cardioverter defibrillator (ICD)? [yes/no]
- Previous atrial fibrillation of flutter? [yes/no]
- Previous hypertension with pharmacologic treatment? [yes/no]
- Charlson comorbidity index

7.2 Data on hospital admission

- First recorded tympanic temperature (bilateral, highest value)
- FOUR-score, eye response, motor response, brainstem score, respiratory score
- STEMI - New ST-segment elevation $\geq$1 mm in $\geq$2 contiguous ECG leads
- ECG suspicious for acute ischaemia (No, ST-segment depressions (Y/N), T-wave inversions(Y/N), Acute LBBB(Y/N)
- Hypotension on admission, BP<90mmHg for at least 30 minutes or the need for supportive measure to maintain a systolic $\geq$90mmHg and end-organ hypoperfusion (cool extremities, or urine output of less than 30ml/hr, and a HR >60 beats per minute
- Severe shock after admission, A severely shocked state is defined as a systolic blood pressure <80, despite exhaustive supportive measures (Fluid loading, vasopressor/inotropic support, intra-aortic balloon pump or percutaneous ventricular assist device).

7.3 In the ICU

7.3.1 Data during the intervention

- Hourly temperature (bladder)
- Mean arterial pressure, heart frequency
- Use of invasive haemodynamic monitoring (No, Thermodilution catheter, Pulmonary artery catheter)
- Use of prophylactic antibiotics

7.3.2 Daily during day 1-7 of ICU stay:

- FOUR-score, eye response, motor response, brainstem score, respiratory score
- Highest body temperature and accumulated duration of body temperature >37.8°C
- Bradycardia with need for pacing
- Dose of vasopressor/inotropic medication - Using the extended cardiovascular SOFA-score [32]
- Need for mechanical circulatory assistance
- Pneumonia - CPIS score >5
- Net fluid balance
- Mechanical ventilation
- Serious adverse events (SAEs)
- If trial intervention has been discontinued, time of discontinuation and specified reason
- If active intensive care is withdrawn, specify reason
- Do not resuscitate order Y/N
- If dead, specify presumed cause of death, cardiac, cerebral, other

7.3.3 Daily from day 8 to ICU discharge

- FOUR-score, eye response, motor response, brainstem score, respiratory score
- If trial intervention has been discontinued, time of discontinuation and specified reason
- If active intensive care is withdrawn, specify reason
- Do not resuscitate order Y/N
- If dead, specify presumed cause of death, cardiac cerebral, other

7.3.4 At prognostication

- Results and time of SSEP, MRI, CT, NSE and EEG
- Results of the clinical neurological examination
- Presence, timing and duration of any status myoclonus prior to prognostication
- The stated prognosis from the blinded examiner, dichotomised as poor prognosis *likely* (YES/NO)

7.3.5 At ICU discharge

- Time and results of coronary angiography
- Time of thrombolysis/PCI/open-heart surgery, if performed
- Time when obeying verbal commands (awake - FOUR-score M4)
- Discharge facility (coronary care unit/general ward/other ICU/dead)

7.4 At hospital discharge

- Discharged to: nursing home/rehabilitation unit/other hospital/home/dead
  If dead, presumed cause of death: cardiac/cerebral/multiorgan failure/other
- Likely cause of cardiac arrest

7.5 30 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
- GOS and mRS assessment

7.6 180 days after randomisation

- Survival status obtained from hospital or civil registries
- GOS-E and mRS assessment
- Cognitive function tested with MoCA, IQCODE, SDMT, 30-second chair stand test, and health-related quality of life tested with: EQ5D-5L
- Cardiovascular risk factors (Physical activity, HbA1c, cholesterol, blood pressure)

7.7 24 months after randomisation

- Repeat evaluation of GOS-E, mRS, EQ5D-5L, cognitive tests and participation in society.

7.8 Planned investigations

Most investigations and interventions are performed at the discretion of the treating physician. However a EEG at 48-96h after randomisation is strongly recommended by the protocol. Reasons for omission will be collected.

7.9 Laboratory testing

Laboratory testing will be performed as soon as possible after ROSC and continuously during the ICU-period. All blood gases will be analysed using the alpha-stat method.

- Earliest available blood gas after ROSC: FiO_2, pCO_2, BE, pH, lactate, glucose.
- Blood gas every six hours during the intervention (FiO_2, pCO_2, BE, pH, lactate, glucose and insulin dose)
- On admission to ICU (Lowest Thrombocytes, Lowest PaO_2, highest creatinine, highest bilirubin, HbA1c)
- Daily in the ICU (highest creatinine)

7.10 Biobank

Additional blood samples will be taken at admission, 24, 48, and 72 hours after cardiac arrest according to a separate protocol and stored in a biobank. Analysis of biomarkers will commence after the last patient has been followed up.

8 Ethics and informed consent

An ethics application (2015/228) is approved by the Regional Ethics Committee at Lund University. Ethics applications will be submitted to all relevant ethics boards in every country participating. The ethics applications will seek approval for a delayed written consent process, since temperature management must be regarded as an emergency procedure and must be started as soon as the patients are admitted to the Emergency Departments. We judge that this strategy is justifiable according to the Declaration of Helsinki article 30 available from the World Medical Association. Patients regaining consciousness will be asked for written consent as soon as they are able to make an informed decision. The consenter will be provided with written and oral information on this trial to make an informed decision about participation in the trial. The consent form must be signed by the participant or legally acceptable surrogate and by the investigator seeking the consent. Relatives will be approached for written consent for their participation during follow-up visits.

9 Data management

9.1 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 each participating country. Pseudonymised data will be entered into the electronic database (eCRF) produced by Lytics-Health, Malmö, Sweden. The electronic data capture module fulfils all criteria for handling of patient data according to the Swedish legislation on management of personal data "Personuppgiftslagen", (PUL) and is FDA (Food and Drug Administration) and HIPAA (Health Insurance Portability and Accountability ACT) compliant. The electronic forms will be exported to Clinical Studies Sweden - Forum South. All original records (incl. consent forms, CRFs, SAE reports and relevant correspondence) will be retained at trial sites or the Center for Cardiac Arrest at Lund University for 15 years to allow inspection by relevant authorities. The study database will be maintained for 15 years and anonymised if requested for revision.

9.2 Quality control and quality assurance

The trial will be externally monitored by national monitoringoffices coordinated by the clinical trial manager and Clinical Studies Sweden, Forum South. The frequency of on site monitoring will depend on compliance with the protocol, number of enrolled patients and data handling. At a minimum, there will be a pre-study visit, mandatory monitoring after the trial and once during the trial period. Source data verification will be performed according to a monitoring plan which will be available only to the trial monitors before the start of the trial.

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. Data management activities will be performed and organised by the study coordinating team.
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10 Adverse events

Detection, documentation and reporting of the following events will be the responsibility of the local investigator.

10.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject. Untoward medial occurrences are expected in all patients who are resuscitated from cardiac arrest and treated in intensive care. This critically ill group of patients will per definition experience be monitored and treated for untoward medical occurrences, and this is considered standard care. Therefore **no** adverse events will be reported.

A serious adverse event SAE is defined as any adverse event that:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of current hospitalisation
- Results in persistent or significant disability or incapacity

Death is an expected outcome among survivors of cardiac arrest. Approximately 45% of patients will not survive to six months, therefore death will not be considered a serious adverse event. Standard care of cardiac arrest patients includes a host of complications that fit the definition of an SAE. For example, more than 90% of all patients in the TTM1-trial experienced a serious adverse event. Only a small number of those events could be considered to be caused by the intervention. Additionally, when TTM at 33°C and 36°C was compared in the TTM1-trial, only hypokalaemia (which occurred in the majority of patients) differed between temperature groups.

The complications attributable to hypothermia in prior research primarily include electrolyte disorders, infection, arrhythmias, bleeding, haemodyanamic instability and skin complications related to the use of surface devices for temperature control. Despite this, none of the randomised trials on temperature control for cardiac arrest have shown any difference in the incidence of these complications (hypokalaemia in the TTM1-trial being the exception). To strike a balance between over-reporting, and maximise the probability of finding any true differences only the following complications will be considered serious adverse events:

- Sepsis and septic shock, according to the 3rd international consensus definitions for sepsis and septic shock
- Moderate or severe bleeding, according to the GUSTO criteria
- Device related skin complications
- Haemodynamic instability necessitating rewarming
- Arrhythmias necessitating rewarming
- Bradycardia necessitating pacing
- Other unexpected serious adverse events

Events collected in the "other unexpected SAEs" category will be at the discretion of the local investigator. The circumstances of the SAE should be specified. Expected events in this study include, but or not limited to: mortality (unless believed to be related to cooling), haemodynamic instability, cardiac arrhythmias, electrolyte abnormalities, acidosis, infections, or bacteraemia, fever, bleeding, seizures, cerebral oedema and other brain injury, worsening neurological function, renal dysfunction, liver dysfunction, reintubation, hypoxia, ARDS, pulmonary oedema and complications related to the condition that led to cardiac arrest.

10.2 Reporting of serious adverse events

SAEs will be recorded daily in a pre-specified form in the eCRF. At each assessment all Serious adverse events (SAE)s either observed by the investigator or other caregivers must be recorded by the investigator and evaluated. The SAE should be reported within 24 from awareness of the event. The local investigator is required to follow each participant with an SAE until resolution of symptoms. The frequency of adverse events will be reported to the DSMC.

11 Statistical plan and data analysis

A statistical analysis plan will be published before the first scheduled interim analysis.

11.1 Sample size

Based on the results of the TTM1-trial and information in the International cardiac arrest registry, (INTCAR) we estimate a total mortality of 45%. The power calculation is based on a 50% mortality in the normothermia arm and a 40% mortality in the hypothermia arm, at 180 days.

To demonstrate a relative risk of 0.8 with 90% power, using an unadjusted chi-square test, 518 patients are required in each group. The sample size calculation corresponds to a relative risk reduction (RRR) of 20%, an absolut risk reduction (ARR) of 10% and a number needed to treat (NNT) of 10. The estimated relative risk is based on results from earlier trials on hypothermia for CA. [2, 3] To allow for a possible loss to follow-up we will recruit 1200 patients.

Statistical tests will be performed on an intention-to-treat basis with two-sided tests at the 0.05 significance level.

11.1.1 Expanded trial scenario

Should an increased sample size be possible, we will aim to demonstrate a relative risk of 0.85, which would require 953 patients in each group. This scenario corresponds to a relative risk reduction (RRR) of 15%, an absolut risk reduction (ARR) of 8.5% and a number needed to treat (NNT) of 11.8.

11.2 Primary outcome

The primary outcome (survival status at 180 days) will be analysed by an unadjusted chi-square test. A sensitivity analysis will be performed by an adjusted analysis. Adjustments will be made in a logistic regression model for site and for known predictors of outcome (site, age, sex, bystander CPR, initial rhythm, time to ROSC and circulatory status on admission).

11.3 Secondary endpoint

The secondary endpoint GOS-E at 180 days will take the ordinal nature of the GOS-E into account. It is currently unclear which methodology should be employed in a cardiac arrest population. Prior methodologies in stroke and TBI have advocated the pooling of lower categories and then performing an ordinal shift analysis. The preferred method will be presented in the statistical analysis plan, after simulations (based on the outcomes in the TTM1-trial) have been performed.

The secondary endpoint survival time will be presented in a Kaplan-Meier plot and analysed. The primary analysis will be a log-rank test. A sensitivity analysis will be performed using cox regression with adjustment for site and known predictors of outcome.

The secondary endpoint HRQoL will be presented by comparing the EQ5D-5L index values, and EQ5D-5L VAS-Assessment with a t-test. A sensitivity analysis will be performed using linear regression with adjustment for site and known predictors of outcome.

11.4 Missing data

Missing data will be reported in the publication. If further analyses reveals substantial missingness, multiple imputation with several imputed datasets will be analysed separately and aggregated into one estimate of intervention effect on the primary and secondary outcomes, in the multivariate analyses. A complete-case analysis will also be performed if imputation is required.

11.5 Subgroup analysis

Subgroups will be analysed according to pre-defined variables

- Age
- Sex
- Bystander CPR
- Initial rhythm
- Time to ROSC
- Circulatory status on admission
- Severity classification, Pittsburgh cardiac arrest category [33]

11.6 Data safety monitoring committee

There will be an independent Data safety monitoring committee (DSMC) arranging an independent statistician to conduct two primarily blinded interim analyses after one third and two thirds of the trial participants have been recruited and followed up at 180 days. The DSMC will be able to request unblinding of data if they find it necessary. The DSMC will be provided with data on survival and safety parameters continuously during the conduct of the trial, and can initiate analysis at any time they request. The Haybittle-Peto boundary will provide the DSMC with stopping rules. Lan-Demets group sequential monitoring boundaries will be used if more interim analyses are needed. 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 stopping rules mentioned above (p-value, 0.001
- Group difference in serious adverse events is found in the interim analysis
- Results from other studies show benefit or harm with one of the allocation arms

A charter for the DSMC will be published before the start of the trial.

12 Publication of Data

The trial will be analysed by an independent statistician and the results interpreted by the steering group. The analysis will be performed six months after inclusion of the last patient. The analysis process will be performed with the allocation code unbroken and with the trial arms only known as A and B.. Two different abstracts will be prepared before the allocation code is broken, with the different arms inter-changed (one assuming arm A is hypothermia, and the other assuming arm B is hypothermia). 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 include the steering group members, national investigators and additional names in alphabetical order. Centres recruiting >30 patients will be entitled to one name and >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. The main publication will report the primary and secondary outcomes. In doing so, survival, neurological outcome and HRQoL will be reported. Tertiary outcomes will, due to complexity of reporting be submitted to a peer-reviewed journal as a separate manuscript, as will the results from the 24 month follow-up. A detailed authorship plan will be decided upon after the first interim analysis.

13 Financing and insurance

The trial will be funded by external foundation for medical research. Patient recruitment will not commence until there is sufficient funding to allow for inclusion and 180-day follow-up of the proposed sample size.
The trial is funded by:
The Swedish Research Council(Vetenskapsrådet) - Grant Nr: 2016-00428
The Swedish Heart-Lung Foundation
Stig and Ragna Gorthon Foundation
Knutsson Foundation

14 Timeline

2016	Trial design, ethics application, site recruitment, application for funding
2017	First patient recruitment, run-in period, site initiations
2017-2019	Patient recruitment and interim analysis
2019/2020	Presentation of results, Long-term follow-up performed
2022	Presentation of long-term outcomes

15 Study Participants

15.1 Steering Group (Preliminary list)

Niklas Nielsen MD, PhD	Intensive Care, Helsingborg Hospital, Helsingborg, Sweden (PI)
Jan Bělohlávek MD, PhD	General University Hospital, Prague, Czech Republic (NI)
Clifton Callaway MD, PhD	Emergency medicine, University of Pittsburgh, Pittsburgh, USA (NI)
Alain Cariou MD, PhD	Intensive Care, Descartes University, Paris, France (NI)
Tobias Cronberg MD, PhD	Neurology, Lund University Hospital, Lund, Sweden (SI)
Josef Dankiewicz MD, PhD	Intensive Care, Lund University Hospital, Lund, Sweden (CI)
David Erlinge MD, PhD	Cardiology, Lund University Hospital, Lund, Sweden
Hans Friberg MD, PhD	Intensive Care, Lund University Hospital, Lund, Sweden (SI)
Jan Hovdenes MD, PhD	Intensive care, Rikshospitalet, Oslo University Hospital, Oslo, Norway (NI)
Michael Joannidis MD, PhD	Intensive Care, Medical University Innsbruck, Austria (NI)
Helena Levin MSc	Center for Cardiac Arrest, Lund, Sweden (Clinical trial manager)
Gisela Lilja OT, PhD	Neurology, Lund, Sweden (follow-up coordinator)
Per Nordberg MD, PhD	Södersjukhuset, Stockholm, Sweden
Mauro Oddo MD, PhD	Intensive Care, Université de Lausanne, Lausanne, Switzerland (NI)
Paolo Pelosi, MD, FERS	Anaesthesia and Intensive Care - IRCCS AOU San Martino IST University of Genova, Genova, Italy (NI)
Christian Rylander MD, PhD	Sahlgrenska University Hospital, Gothenburg, Sweden (NI)
Pascal Stammet MD, PhD	Centre Hospitalier de Luxembourg, Luxembourg (NI)
Christian Storm MD, PhD	Chartité University Hospitals, Berlin, Germany (NI)
Fabio Taccone MD, PhD	Brussles, Belgium (NI)
Susann Ullén PhD	Clinical trials Sweden - Forum South, Lund, Sweden (Chief Statistician)
Matthew P. Wise MD, Dr Phil	University Hospital of Wales, Cardiff, UK (NI)
Anders Åneman MD, PhD	Intensive Care, Sydney, Australia (NI)

PI - Principal Investigator
SI - Senior Investigator
NI - National Investigator
CI - Coordinating investigator

15.2 Investigators - TBD

15.3 Investigator responsibilities

The trial site investigator is responsible for:

- Screening and listing eligible patients
- Performing randomisation
- Achieving temperature control according to allocation group
- Ensuring that achievement of hypothermia is feasible within 2 hours of randomisation
- Maintaining temperature control according to allocation group
- Collection and reporting of data according to the trial protocol and electronic case report form (eCRF)
- Obtaining written informed consent from patients whom regain consciousness
- Performing and reporting follow-up according to the trial protocol and the eCRF

The national investigator is responsible for:

- Coordination of national sites
- Representing national sites in the steering group
- Reviewing reasons for potential incomplete screening and randomisation at national sites
- Ethical Review Board - application and approval
- Dissemination of protocols and updates to sites
- Proposing suitable candidates for vacant site investigator positions

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A The FOUR SCORE

Eye response	
Eyelids open and tracking, or blinking on command	4
Eyelids open but not tracking	3
Eyelids closed but open to loud voice	2
Eyelids closed but open to pain	1
Eyelids closed with pain	0
Motor response	
Makes sign (thumbs-up, fist, other)	4
Localising to pain	3
Flexion response to pain	2
Extension response to pain	1
No response to pain	0
Generalised myoclonic status	0
Brainstem response	
Pupil reflexes present, corneal reflexes present and cough present	4
One pupil wide and fixed, corneal reflexes present and cough present	3
Pupil reflexes absent, corneal reflexes present	2
Pupil reflexes present, corneal reflexes absent	2
Pupil reflexes absent, corneal reflexes absent, cough present	1
Pupil reflexes absent, corneal reflexes absent, cough absent	0
Breathing	
Not intubated with regular breathing	4
Not intubated with Cheyne- Stokes type of breathing	3
Not intubated with irregular breathing	2
Not intubated with apnea	0
Intubated with breathing above ventilator rate	1
Intubated with breathing at ventilator rate	0

In contrast to previous trials on cardiac arrest, the TTM2-trial will not use the Glasgow Coma Score in any reporting. There are several reasons for this:

- The FOUR-score offers a less equivocal inclusion criteria as a "fist" or "thumbs-up" response is required for a motor score of 4. This also applies to the definition of awakening which is made clearer by requiring a limb movement rather than only eye movements
- The FOUR-score can be rated in the intubated patient and (as part of the Pittsburgh cardiac arrest category [33, 34]

Links:
Figure of FOUR-score from Iyer et.al [34]
FOUR-score calculator