SED-CARE

TEMP-CARE

MAP-CARE

Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation – the STEPCARE trial

Version 1.1
February 17, 2023

Short title:
STEPCARE

Clinical trials identifier: NCT05564754

Sponsor: Region Skåne – Skånes Sjukhus Nordväst - Helsingborgs Hospital

S Vallgatan 5, 251 87 Helsingborg, Sweden

Study Chair: Niklas Nielsen, MD, PhD, DEAA, EDIC
Department of Anesthesiology and Intensive Care, Helsingborg Hospital
Lund University, Faculty of Medicine

PROTOCOL TITLE:
Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation:
A Factorial Randomized Trial with Three Interventions

Study Chair: Niklas Nielsen, MD, PhD
Region Skåne, Lund University

Protocol Version: 1.1
Version Date: February 17, 2023

I confirm that I have read this protocol and that I understand it. I will conduct the study according to the protocol and according to the ethical principles that have their origin in the World Medical Association's Declaration of Helsinki.

Principal Investigator Name:

Niklas Nielsen

Principal Investigator Signature:

Date: February 17 2023

Contents

1 Overview

The STEPCARE (Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation) trial is a continuation of the collaboration that resulted in the previous Target Temperature Management after out-of-hospital cardiac arrest trial, Targeted Hypothermia versus Targeted Normothermia after Out-of-hospital Cardiac Arrest trial[1,2] (hereafter: TTM1 and TTM2), and the COMACARE (Carbon dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and Resuscitation) trial.[3] With its planned size STEPCARE will be the largest trial on intensive care unit (ICU) management after cardiac arrest ever conducted.

Basic management for patients who have suffered a cardiac arrest and are admitted to an ICU includes setting goals for physiological parameters such as sedation, temperature, and blood pressure. However, optimal targets are unknown.

In an international collaboration, STEPCARE will aim to improve the evidence for these aspects of care, and ultimately improve outcomes for patients who suffer a cardiac arrest.

The STEPCARE trial is an international, multicenter, parallel group, non-commercial, randomized, factorial, superiority trial in which sedation, temperature and blood pressure strategies will be studied.

Patients eligible for inclusion will be unconscious adult patients resuscitated from out-of-hospital cardiac arrest with stable return of spontaneous circulation. Randomization will be performed by a healthcare professional in the emergency department, in the angiography suite or in the ICU via web-based application using permuted blocks with varying sizes, stratified by site. Due to the nature of the interventions, clinicians responsible for the treatment of trial patients cannot be blinded to the interventions. However, outcome assessors, prognosticators, statisticians, management group, steering group and authors will be blinded to group allocation.

All patients will be randomized to three allocation groups, and each strategy will be studied separately regarding safety and reporting of results.

The three comparisons are:

1. Continuous sedation for 36 hours or minimal sedation (SED-CARE)
2. Fever management with or without a feedback-controlled device (TEMP-CARE)
3. A mean arterial pressure target of >85 mmHg or >65 mmHg. (MAP-CARE)

Participants who remain unconscious will be assessed according to a conservative protocol based on the European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) recommendations for neurological prognostication after cardiac arrest.[4]
Follow-up will be performed at 30 days and 6 months after cardiac arrest. The main results of the trial will be published following the 6-month follow-up in three separate articles. This trial protocol will describe all three interventions but separate protocol papers, one per intervention, will be published.

2 Background and Significance

In Europe approximately 300 000 people suffer an out-of-hospital cardiac arrest each year. Of those admitted to hospital with return of spontaneous circulation, the majority are initially unconscious and will need intensive care treatment. Of those admitted to intensive care only 30-55% will be discharged from hospital alive. In survivors discharged from hospital, levels of cognitive disability vary between reports. Using basic, but recommended, outcome scales such as the Cerebral Performance Category (CPC)-scale, Glasgow Outcome Scale (GOS), or the modified Rankin Scale (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 evaluation instruments, some level of cognitive impairment is reported in 50% of survivors and these impairments are associated with lower quality of life and increased caregiver strain.[5]

Even a modest improvement in the proportion of patients with a good neurological outcome after out-of-hospital cardiac arrest would have a profound impact on many thousands of lives. Many interventions have been tested to lower mortality and improve neurologic function in patients resuscitated after out-of-hospital cardiac arrest. Despite promising results in experimental models, all have ultimately failed in clinical trials.

2.1 Sedation Target: SED-CARE

2.1.1 Randomized trials on sedation in the ICU

Minimizing sedation through daily interruptions of sedative infusions or using a protocol targeting light sedation, resulted in fewer days of mechanical ventilation and fewer days in the ICU.[6,7] A strategy of non-sedation has been compared with light sedation (targeting a RASS of -2 to -3) in general ICU patients with two trials finding conflicting results. While a 140-patient single center study showed more ventilator-free days in the non-sedation group,[8] this was not replicated in the subsequent 710-patient multicenter study by the same study group.[9] A possible explanation for these divergent results is the increasing trend to implement light sedation in standard care, leading to less separation between trial groups in the second study. With other randomized trials consistently showing a benefit of lighter (compared to deeper) sedation, standard practice is therefore to minimize both the duration and depth of sedation in all but a minority of ICU patients who may have specific indications for sedatives; most commonly those with acute neurological emergencies e.g., refractory raised intracranial pressure, a therapy-refractory status epilepticus, or patients with severe respiratory failure.

2.1.2 Sedation after cardiac arrest

In contrast to the current recommendation to use light sedation for almost all mechanically ventilated patients, deep sedation was introduced for cardiac arrest patients as an essential part of the targeted temperature management (TTM) regimen to counteract undesirable physiological effects and discomfort from induced sub-normal temperatures and to facilitate the cooling process. Based on physiological reasoning and animal data, sedation has also been proposed as a potentially brain protective and seizure prophylactic intervention in itself.[10–12] The only randomized data on sedation after cardiac arrest is a trial from 1986 where a single dose of sodium thiopental was administered.[13] This trial did not demonstrate any significant difference in outcome between the patient groups, but one may argue that the dose and duration of sedation were inadequate. All cardiac arrest trials since have targeted deep sedation. Notably, in a 4267-patient, 40-hospital registry study, higher doses of sedatives were associated with worse patient outcomes, but that study may have been confounded by indication.[14]

2.1.3 Effects of sedation

For mechanically ventilated patients, sedation can increase comfort, improve ventilator synchrony, and avoid adverse effects of agitation. Sedation may also have beneficial effects on the function of the glymphatic system through inducing non-REM-sleep.[15–17] The glymphatic system is believed to eliminate toxic breakdown products from the brain such as □-amyloid and tau-protein from damaged neurons, thereby preventing aggregation which is a central neurodegenerative mechanism in Alzheimer's disease. Approximately one third of cardiac arrest patients have epileptic seizures and sedative drugs are potent antiepileptic agents commonly used for treating refractory status epilepticus. Seizures may cause metabolic stress which could further aggravate the hypoxic injury. Propofol, the most commonly used sedative drug in cardiac arrest protocols effectively suppresses clinical seizures but in one small study mortality was not affected.[20] A recent randomized trial also failed to show a survival benefit of suppressing rhythmic and periodic EEG activity with antiseizure medication, including a sedative agent (usually propofol or midazolam).[21]

However, while sedation may be beneficial it may also increase the risk of adverse effects like pneumonia, circulatory compromise, delirium, delayed awakening and mobilization, and prolonged ICU stay, which all may negatively affect outcome.[12] In addition, sedation interferes with neurological prognostication as it confounds clinical neurologic examination and may alter EEG-patterns.[18,19] In cardiac arrest patients with hypoxic-ischemic encephalopathy and potentially impaired autoregulation of cerebral blood flow it is unclear whether the potential benefits of sedation outweigh the detrimental effects.

In the context of these conflicting arguments for and against deep sedation in the first days following cardiac arrest, there is substantial uncertainty as to optimal clinical practice.

2.2 Temperature target: TEMP-CARE

Active temperature management was established as an intervention to reduce brain injury after cardiac arrest, based on animal data, clinical observations and the results of phase-2 trials from 2002.[22,23] Active temperature management is delivered in the ICU to patients using feedback-controlled cooling devices either with heat exchange pads attached to the body surface or with heat exchange catheters introduced in a central vein. International guidelines recommend active prevention of fever, despite limited supporting evidence.[24,25] Globally, there is a wide variability in the use and practice of active temperature management reflecting uncertainties of its effects. In a 950-patient trial (TTM1) we showed similar survival, functional status, HRQoL and cognitive impairment for TTM with cooling devices targeting 33°C or 36°C, but the confidence limits were wide and encompassed both patient important benefit and harm of the interventions.[1]

In the TTM2-trial we randomized 1900 patients to TTM at 33°C or to a TTM-strategy to maintain normothermia with active treatment of fever (defined as a core body temperature ≥37.8°C).[2] The TTM2-trial employed cooling devices in both trial groups (for reaching 33°C as well as avoiding fever) and was therefore similar in design to the TTM1-trial, but with wider temperature separation and a higher statistical power. All trial participants were physically cooled in the 33°C group while approximately 50% received physical cooling in the normothermia group. As the results were neutral and almost identical to TTM1, TTM2 strongly reinforced the TTM1-results, confirming that cooling to subnormal temperatures does not provide benefit compared with targeting normothermia and avoiding fever. This was also supported by an individual patient data meta-analysis of TTM1 and TTM2.[26] Recently a study on the use of TTM targeting 33°C after in-hospital cardiac arrest was published. A trial conducted in German hospitals found that in 249 patient the use of TTM targeting 33°C for 24 hours did not decrease mortality or improve functional outcome.[27]
Following the publication of the TTM2-trial one meta-analysis concluded that routine use of moderate or deep hypothermia may be associated with harm.[28] Another meta-analysis by the ILCOR Advanced Life Support Task Force stated that TTM at 32-34°C did not result in improved outcomes.[29] Following this ILCOR meta-analysis guidelines were updated to recommend active fever prevention rather than cooling to sub-normal temperatures.[25]

Fever after cardiac arrest has been suggested as a risk factor for death, but guideline recommendations to treat fever are based on non-randomized studies, and it is not known whether there is a causal and modifiable relationship. It remains to be determined if fever is harmful for a neurologically impaired patient or if it is merely an epiphenomenon, and if active fever prevention is beneficial or harmful.[30,31]

Unpublished data from the FINNRESUSCI study (Skrifvars, personal communication) showed in a cohort of 195 OHCA not treated with any TTM, that fever above 37.8°C occurred in around 45% of patients. A multivarable analysis of factors associated with long term outcome did not find any association between fever and long-term outcome. In addition, the study showed that fever higher than 39°C occurred in less than 5% of patients at similar rates in those with a good or poor long term functional outcome. Similar prevalence figures for high fever have been reported in patients treated in the ICU following different types of neurointensive care diagnoses such as subarachnoidal hemorrhage and traumatic brain injury.[32]

In a systematic review by our group, a meta-analysis did not find any evidence suggesting a beneficial effect of fever therapy on all-cause mortality, RR 0.98; 95 % CI 0.94 – 1.03; I2 = 6.37 %; p = 0.38, (based on 16 trials, evidence of moderate certainty).[33] A trial conducted at two hospitals in Denmark compared fever management after completion of TTM, from 36 to 72 hours from the cardiac arrest. The study randomized patients resuscitated from a cardiac cause of arrest and the rate of favorable outcome was high (70%). They compared management with a device or management without a device. The study showed no difference in outcome between the two groups.[34]

While TTM with devices targeting normothermia may prevent a potentially harmful fever, it may also cause adverse effects[35] such as shivering, requirement for a deeper level of sedation and prolong ICU stay, which in turn might negatively affect patient outcomes and increase resource consumption. The recent study on fever management with or without a device, suggested that post TTM fever need not be managed with a device, but the population was selected and the confidence limits wide. Therefore, the primary outstanding question regarding TTM after out-of-hospital cardiac arrest is whether any fever management with temperature management devices is beneficial.[8]

2.3 Mean arterial pressure target: MAP-CARE

Blood pressure is one of the main determinants of perfusion to the brain, heart and kidneys. Current guidelines recommend targeting a mean arterial blood pressure higher than 65 mmHg[4]. This is based on observational data alone. Smaller pilot trials have suggested feasibility and safety of a target of 85-100 mmHg in cardiac arrest patients, and preliminary data suggest organ protective effects from a higher blood pressure.[3,37].

2.3.1 Randomized Trials

Two pilot trials published in 2018 and 2019 have investigated targeting a higher pressure in patients after OHCA.[3,38] These trials had surrogate endpoints such as brain injury biomarkers or the extent of hypoxic injury assessed with magnetic resonance imaging (MRI). The COMACARE trial published in 2018 randomized 120 patients with OHCA and ventricular fibrillation as the initial rhythm, to a MAP target of either 65-75 mmHg or 80-100 mmHg. The study did not find any difference in levels of the biomarker neuron specific enolase (NSE) which reflects the extent of injury to the gray matter of the brain. However, in a further analysis using the novel and very sensitive axonal injury biomarker neurofilament light (NFL), NFL levels were significantly lower at 48 and 72 hours from the cardiac arrest in the higher MAP group.[39]

The NEUROPROTECT study including 112 OHCA patients of all cardiac arrest rhythms investigated hemodynamic optimization after cardiac arrest ,the main aspect being a MAP target of 85-100 mmHg compared to 65-70 mmHg.[38] In addition the study aimed to optimize mixed venous oxygen saturation with the use of inotropes, intravenous fluids as well as packed red blood cell transfusions. The study did not show any difference in brain injury based on findings on magnetic resonance imaging (MRI) during follow-up.

A pooled analysis of the 120 patients with acute myocardial infarction and need for vasopressor medication included in the COMACARE and NEUROPROTECT trials revealed that patients treated with higher MAP target had lower levels of high sensitivity troponin (hsTNT) over time suggesting less myocardial injury[37]. In addition, the higher MAP target was associated with a favorable hemodynamic profile with higher diastolic blood pressure, relatively low heart rate and fewer arrhythmias.

The BOX-trial compared a target MAP of 63 mmHg to 77 mmHg in comatose OHCA patients for the time patients had invasive arterial pressure monitoring using a blinded approach to blood pressure management.[40] It was powered to detect an absolute risk difference of 10% and a relative risk reduction of 26%. The trial included 789 patients with cardiac arrest of a presumed cardiac cause and showed no differences in the composite primary endpoint of death or a poor neurological function at discharge from hospital. There was no difference in levels of neuron-specific enolase (NSE) or scores on the modified Rankin Scale at 3 months.

2.3.3 Physiologic rationale for a trial on mean arterial pressure after cardiac arrest

Multiple publications have indicated the pathophysiological importance of inadequate cerebral perfusion and increasing brain injury in patients after cardiac arrest.[41,42] Studies focusing on the pathophysiology have reported a decrease in cerebral blood flow and cerebral vasoconstriction occurring in the early phase after the arrest. It follows that targeting a higher MAP may lower the risk of inadequate cerebral blood flow related to low MAP. Whether this translates into improved outcome in patients with and without chronic hypertension is unknown.

In myocardial infarction reduced cardiac output results in a cascade of neurohormonal activation and vasoconstriction which is the target of subsequent therapy for heart failure. Although increasing blood pressure in the acute phase of myocardial infarction complicated by cardiac arrest is at odds with the concept of acute unloading to limit infarct size, results from the COMACARE trial showed lower levels of troponin among patients who were assigned to a higher MAP-target. Taken together with the neutral results of the BOX-trial, in which almost half of the participants had an ST-elevation myocardial infarction, this supports the safety of a higher MAP-target among patients with cardiac arrest and acute coronary ischemia.

The large sample size of the STEPCARE trial will allow for hypothesis-generating subgroup analyses based on pre-randomization parameters such as previous coronary vascular disease and heart failure.

2.3.4 Rationale for this trial on mean arterial pressure targets after cardiac arrest

The evidence which forms the basis for Current Guidelines on post-cardiac arrest management is limited.[4] MAP is one easily modifiable physiological variable in all critically ill patients. The majority of OHCA patients need treatment for low blood pressure during the first 48 hours after a cardiac arrest.[43] Pilot data suggest that by using slightly higher doses of vasopressor the higher MAP target is achievable in most OHCA patients.[3,37,38,44] The intervention is cheap and applicable in ICUs all over the world. While the BOX-trial has provided evidence that any effect of a modestly increased MAP target is likely small, it remains to be determined if larger increases in the MAP-target are beneficial. The BOX-trial also leaves an evidence gap among patients who have a non-cardiac cause of arrest. Only a large trial will help in informing clinicians on whether a higher MAP target improves outcome in OHCA patients.

3 Trial hypotheses and outcomes

We will investigate the following main hypotheses:

In adults who are comatose following resuscitation from out-of-hospital cardiac arrest, continuous sedation for 36 hours leads to lower six-month mortality than minimal sedation.

In adults who are comatose following resuscitation from out-of-hospital cardiac arrest, fever management with a device leads to a lower mortality than fever management without a feedback-controlled device.

In adults who are comatose following resuscitation from out-of-hospital cardiac arrest, targeting a mean arterial pressure of >85 mmHg leads to a lower mortality than targeting a mean arterial pressure of >65 mmHg.

3.1 Primary outcome

- All-cause mortality assessed at 6 months after randomization

3.2 Secondary outcomes

- Proportion of participants with a poor functional outcome measured in either one of two ways (hierarchical order):
  1. Using the clinician reported modified Rankin Scale (mRS)-scale (mRS 4-6) at 6 months after randomization
  2. If a score cannot be assigned using the standardized assessment patients with be categorized based on whether they are found to be dependent on others for basic activities of daily life (moving indoors, eating, dressing, personal hygiene)

- Patient reported Health-Related Quality of Life (HRQoL) using EQ5D-5L including EQ-VAS at 6 months after randomization

- Proportion of patients who had a pre-defined safety event or death in the ICU. (For each trial)

  - SED-CARE: sepsis or septic shock (Sepsis III criteria), arrhythmia requiring defibrillation, cardioversion or chest compressions, venous thromboembolism, reintubation, non-planned extubation

  - TEMP-CARE: sepsis or septic shock (Sepsis III criteria), arrhythmia requiring defibrillation, cardioversion or chest compressions, venous thromboembolism, moderate or severe bleeding (GUSTO criteria)

  - MAP-CARE: arrhythmia requiring defibrillation, cardioversion or chest compressions, moderate or severe bleeding (GUSTO criteria), acute kidney injury with renal replacement therapy, limb ischemia requiring radiological or surgical intervention, or gut ischemia demonstrated at laparotomy/laparoscopy or clinically suspected based on abdominal CT-scan or in the context of palliative management.

3.3 Exploratory outcomes

- Ventilator free days within the first 30 days
- Hospital/institution free days alive within the first 30 days

3.4 Exploratory analyses

- Time-to-event (survival). All participants will be followed until 6 months. If death has not occurred, participants will be censored at this point
- Ordinal analysis of mRS-categories for participants who are evaluated using a structured assessment
- Win ratio (Dead vs alive, all steps on the mRS-scale, safety event, HRQoL)

3.4 Additional exploratory analyses

- All data points collected in the electronic Case Record Form may be subject to separate analyses and with separate outcomes. These analyses will be presented in separate publications

3.5 Rationale for chosen outcomes

To minimize biased assessment and to avoid competing risks, survival was chosen as the primary outcome. Although the interventions are primarily thought to affect the development of brain injury, survival is a global assessment of the interventions' effect on all organ systems. The estimated 60% mortality of the target population yields a high power to detect differences in a reasonably sized trial.

We recognize 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 out-of-hospital cardiac arrest-survivors ranges from a vegetative state to complete recovery.

To complement and support the primary outcome we will therefore use the mRS-scale to evaluate functional outcome. The mRS-scale is increasingly used in cardiac arrest and is currently recommended in an ILCOR consensus statement as part of the Utstein template. The scale is also part of the core outcome set (COSCA) for cardiac arrest trials, which was developed by an ILCOR consensus group including patient and partner representatives. To facilitate clinical interpretation of the trial results, and to provide an understandable effect size the primary analysis will be performed as a binary analysis, with the mRS-scale dichotomised (0-3 vs. 4-6).[45]

It is of utmost importance to both assess beneficial and harmful effects of any intervention. We have therefore predefined safety outcomes including the most common, and those most plausibly related to the interventions.

To include patient reported outcome measures, HRQoL is recommended by guidelines for out- come reporting after cardiac arrest and is part of COSCA's recommendations. The EQ5D-5L including the EQ-VAS was chosen as the 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.[46]

An intervention might be associated with an increased short-term mortality but have a protective effect over time. We will therefore include survival, assessed as a time-to-event in an exploratory analysis. We will also include an ordinal analysis of the mRS-scale among the exploratory outcomes which might reveal differences in functional outcome which are not apparent in a dichotomous analysis.

3.6 Assessing functional outcome

Participants with either a very poor outcome or a very good outcome may be less likely than others to attend follow-up. Accordingly, limiting the assessment of functional outcome to patients in whom it is possible to perform a structured follow-up might therefore lead to biased results. We will invite participants to follow up either by telephone, digital meeting, or a physical visit. For participants that cannot be assessed face-to-face or by telephone/video, good or poor outcome using the mRS scale will be quantified by medical records, information from a family member, a primary care provider, or other sources. The dichotomization will be based on whether the participant is independent in basic activities of daily life (moving indoors, eating, dressing, personal hygiene) or not. We recognize that there may be a slight overlap for this definition and a mRS-score of 3.

4 Eligibility

The trial population will be adults (18 years of age or older) who experience a cardiac arrest with return of spontaneous circulation (ROSC).

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

4.1 Inclusion criteria

1. Out-of-hospital cardiac arrest of non-traumatic origin
2. A minimum of 20 minutes without chest compressions*
3. Unconsciousness defined as not being able to obey verbal commands (FOUR-score motor response of <4) or being intubated and sedated because of agitation after sustained ROSC
4. Eligible for intensive care without restrictions or limitations
5. Inclusion within 4 hours of ROSC **

4.2 Exclusion criteria

1. On ECMO prior to randomization
2. Pregnancy
3. Suspected or confirmed intracranial hemorrhage
4. Previously randomized in the STEPCARE trial

*20 minutes of spontaneous circulation without the need for chest compressions is called “stable ROSC”, see below 4.3

** 240 minutes from ROSC or 220 minutes from stable ROSC, see below 4.3

4.3 Note on inclusion window

Theoretically the inclusion window starts from when ROSC occurs and lasts until 4 hours after ROSC occurred. However, a patient is not eligible for participation in the trial until stable ROSC has occurred and that is defined in the eligibility criteria as a time period of 20 minutes elapsing without the need for CPR (inclusion criteria 2). In practical terms, this means that the inclusion window is from stable ROSC (20 minutes after ROSC with. no chest compressions), until 240 minutes after ROSC.

If a potential participant experiences sequential cardiac arrests, which is not uncommon, eligibility assessment should factor in conscious level (inclusion criteria 4) and the presence of stable ROSC (inclusion criteria 2 and 3).

The following scenarios might occur:

Example 1.
A potential participant is resuscitated from an out-of-hospital cardiac arrest and is unconscious on admission to hospital. *Before 20 minutes* have passed, a second cardiac arrest occurs, after which the patient is successfully resuscitated and has stable ROSC for greater than 20 minutes. The patient is within 4 hours of ROSC from the first cardiac arrest. - This patient is eligible for inclusion as the second cardiac arrest is considered a continued event. Time to ROSC should be recorded as the time to stable ROSC which is after the second arrest plus 20 minutes, and the inclusion window starts at this time point.

Example 2.
A potential participant is resuscitated from an out-of-hospital cardiac arrest and is unconscious on admission to hospital. *After 20 minutes* have passed from the initial cardiac arrest, a second cardiac arrest occurs, after which the patient regains stable ROSC after further resuscitation. - This patient is eligible for inclusion. Time to ROSC should be recorded as the time to stable ROSC (which is after resuscitation from the first cardiac arrest plus 20 minutes); the inclusion window starts at this time point.

Example 3.
A potential participant has an out-of-hospital cardiac arrest, is transported to hospital with ongoing CPR and ROSC occurs in the emergency room or angiography suite. - This patient is *eligible* for inclusion, as the initial event occurred outside the hospital walls.

Example 4.
A potential participant has an out-of-hospital cardiac arrest and is conscious on admission to hospital. This is followed by a second cardiac arrest, stable ROSC, and unconsciousness.
- This patient is *ineligible* as the event is considered an in-hospital arrest

4.4 Note on differences between in- and out-of-hospital cardiac arrest.

In-hospital cardiac arrests in monitored beds due to ventricular arrhythmias do not usually result in coma. In-hospital cardiac arrests due to other causes are often associated with severe illness, and for those patients who are initially resuscitated death often occurs due to the condition for which they were hospitalized, rather than brain injury. Out-of-hospital cardiac arrests are characterized by a higher proportion of cardiac causes of arrest and are associated with a prolonged cerebral ischemia resulting in coma and brain injury.

Cardiac arrests occurring in-hospital for non-patients (those not yet admitted to the emergency department, family members, staff, and outpatients) are more similar to out-of-hospital cardiac patients and will therefore be considered eligible for the trial. Only cardiac arrests among patients already admitted to hospital will therefore be considered in-hospital arrests.

5 Trial design

The trial is a multicenter, international, randomized trial with a 2x2x2 allocation. The trial is investigator-initiated and non-commercial. Outcome assessors, prognosticators, statisticians, steering group writers of the manuscript and the data safety monitoring committee will be blinded to group allocation.

5.1 Screening and randomization

Screening can be performed either in the emergency room, angiography suite, or in the ICU. Clinical investigators at each participating site will be responsible for screening of all patients who are resuscitated from an out-of-hospital cardiac arrest. A screening log will be compiled and include all out-of-hospital cardiac arrest-patients with sustained ROSC, whether they are eligible for inclusion, or not. Informed consent will be obtained according to national ethical approval. If a patient is screened and not included the main reason will be recorded.

Trial sites will have access to an internet-based randomization 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 randomization number. Randomization will be performed with permuted blocks, stratified for trial site.

5.2 Sedation Intervention

If needed, patients should be initially sedated to ensure safe transport, imaging, coronary angiography and other invasive procedures. Following randomization, the Richmond Agitation Scale (RASS) score and motor response will be collected every four hours.

For patients randomized to *continuous sedation*, sedation will be targeted to a RASS from −4 to -5 upon admission to the ICU and continued until 36h after randomization. In patients randomized to *minimal sedation* sedative agents should be used only as needed for clinical care.

After the 36-hour intervention period, sedation strategy for both groups will be at the discretion of the treating physician as needed for clinical care.

5.3 Temperature Intervention

The intervention period will commence immediately after randomization. Core body temperature will be continuously measured (preferentially via a bladder catheter, but an alternative core temperature site such as esophagus and blood will be allowed).

For participants allocated to *fever management with a device*, temperature management devices will be started to achieve a core body temperature of ≤37.5°C if temperature reaches the trigger of ≥37.8°C before 72h after randomization. For participants allocated to *fever management without a device*, fever will be managed as per standard fever treatment in the ICU, including for instance exposure and pharmacological agents.

The temperature intervention will last until 72 hours after randomization, or until extubation, whichever occurs first. After 72 hours, or earlier if the participant regains consciousness and is extubated, and after ICU discharge the management of temperature will be at the discretion of the treating physician.

5.4 Mean arterial pressure Intervention

All patients must have invasive monitoring of blood pressure. The intervention period will commence immediately after randomization, but titration of vasopressors to the MAP target may be delayed until the patient has completed required diagnostic work-up (e.g., CT-scan and coronary angiography) and is admitted to ICU.

Participants will be randomized to a MAP target of either >85 mmHg or >65 mmHg. The means to achieve this will be up to the treating clinician but the primary recommendation is to titrate a vasopressor unless the patient is hypovolemic, in which case judicious fluids should be prescribed.

The MAP intervention will last until 72 hours after randomization, or until extubation, whichever occurs first. After 72 hours, or earlier if the participant regains consciousness and is extubated, and after ICU discharge the management of MAP will be at the discretion of the treating physician.

5.5 General ICU care

General ICU-care should be delivered similarly in all allocation groups according to local standardized care plans at the discretion of the treating physicians. Management of respiration, metabolic disturbances, ulcer-, and deep venous thrombosis-prophylaxis and other aspects of intensive care should 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 catheterization (coronary angiography) should not be delayed by the trial interventions. Apart from the interventions adhering to international and national guidelines for post-resuscitation care is recommended.

5.5.1 Shivering

Shivering will be assessed according to the Bedside shivering assessment scale (BSAS) on day 1-3. The treatment goal for shivering will be to maintain a BSAS score of 0 or 1. To ensure adequate control of shivering local protocols should be followed. Interventions to minimize shivering will be as per the treating clinician but might include paracetamol, magnesium, buspirone, increased sedation and administration of a non-depolarizing neuromuscular blockade agent.

5.5.2 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

5.6 Prognostication

Evaluating interventions that cannot be blinded to the treating clinicians, the STEPCARE trial will employ a conservative and strict protocol for neurological prognostication based on the ERC and European Society of Intensive Care Medicine recommendations.[4,47]

Prognostication will be performed on *all* participants who are not awake and obeying verbal commands, and who are still in the ICU at 72 hours after randomization. The clinical examination used for prognostication may not be performed earlier than 72h after cardiac arrest but may be delayed due to practical reasons (such as weekends or national holiday). Results from additional examinations performed <72 h may be included in the assessment if performed according to ERC/ESICM recommendations. The physician performing the prognostication will be a neurologist, intensivist or other specialist experienced in neuroprognostication after cardiac arrest and who has not been involved in patient care of this patient. The prognosticator will be blinded for group allocations, but not for relevant clinical data. Prognostication will be based on results of clinical examinations, neurophysiology, biomarkers of brain injury and imaging.

The result of the prognostication will be categorized as "YES" or "NO", based on the answer to the question *"Does this patient fulfil the STEPCARE criteria for a likely poor neurological outcome?"*. This assessment will be recorded in the case report form and will be communicated to the treating clinician. Results of neurological prognostication and the potential decision to withdraw active intensive care are closely related but will be considered separate entities.

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 sufficiently delay prognostication to ensure that any lingering effects of sedative agents will not affect the assessment.

5.6.1 Clinical neurological examinations

A clinical neurological exam is ***mandatory*** and should include:

- Daily assessment of the best motor response according to the Full Outline of UnResponsiveness (FOUR)-M-score[48] recorded daily until day 7 in the ICU.
- Daily assessment of status myoclonus (continuous and generalized myoclonus persisting for at least 30 min) until day 7 in the ICU.
- The presence or absence of pupillary AND corneal reflexes at hospital admission, at 24 h and if applicable, at the time-point of neurological prognostication.

Absent, extensor or flexion motor response to pain (FOUR- score motor response 0-2) at 72 h or later in a patient who is considered unaffected by sedative agents, will be a prerequisite to consider the neurologic prognosis poor. Bilateral absence of pupillary and corneal reflexes at 72h after CA or later and or the presence of an early status myoclonus (within 72 h) are criteria indicative of a poor prognosis.

5.6.2 Additional prognostic examinations

Prognostication should always be multimodal and include ≥2 prognostic methods as recommended by the ERC/ESICM guidelines.

- The choice of additional prognostic examinations within the STEPCARE are at the discretion of the treating physicians unless sites participate in the neuroprognostication substudy.
- For sites recruiting for the early neuroprognostication substudy, a CT and an EEG from 24 h post-randomization as per clinical praxis is mandatory in patients still unconscious (see Appendix B for further information).

5.6.2.1 EEG

An EEG ≥24 h after randomization ***is recommended*** in line with ERC/ESICM guidelines.

The STEPCARE employs a more conservative evaluation of EEG than the ERC/ESICM guidelines, also including reactivity. An EEG with a "highly malignant pattern"[49,50], and without reactivity to sound and pain is indicative of a poor prognosis if lingering effects of sedation are ruled out.

5.6.2.2 Brain CT

A brain computed tomography (CT) as per clinical praxis is mandatory for unconscious patients ≥24 h after randomization within the ultra-early neuroprognostication substudy. For all other patients, a brain CT ***should be considered***.

If a brain-CT shows signs of diffuse and extensive hypoxic ischemic injury, such as: generalized oedema with reduced grey/white matter differentiation and sulcal effacement, this is indicative of a poor prognosis, regardless of the time-point of examination.[51,52]

5.6.2.3 Brain MRI

A brain magnetic resonance imaging (MRI) may be incorporated into prognostication if it has been performed. Signs of diffuse and extensive hypoxic injury on MRI is indicative of a poor prognosis at 2-5 days post-arrest.[4]

5.6.2.4 Neuron specific enolase

Thresholds for high Neuron specific enolase (NSE) levels in blood must be established in collaboration with the local laboratory considering the analytical method. High serial blood levels of NSE (suggested at least > 60 ng/mL at 48-h and/or 72-h) are indicative of a poor prognosis. Hemolysis, malignancies, and other intracranial pathologies are potential confounders and should be excluded.

5.6.2.5 SSEP

SSEP N20-responses may be used for prognostication if the technical quality is adequate. Absent SSEP N20-responses bilaterally ≥24 h are indicative of a poor prognosis.

5.6.3 STEPCARE criteria for a likely poor neurological outcome

In STEPCARE the prognosis is considered *likely poor* if criteria A, B and C are all fulfilled:

A. Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out. The ERC/ESICM recommend awaiting 5 half-lives of the sedative with the longest half-life prior to clinical evaluation.
B. The patient has no response, a stereotypic extensor response or a stereotypic flexor response to bilateral central and peripheral painful stimulation at ≥ 72 h after randomization.
C. At least two of the below mentioned signs of a poor prognosis are present:

C1. No pupillary AND corneal reflexes ≥72 hours after randomization
C2. Bilaterally absent SSEP N20-potentials
C3. Early generalized and persisting myoclonus ≤72 hours after randomization
C4. Highly malignant and unreactive EEG-pattern >24 hours after randomization
C5. Diffuse and extensive hypoxic brain injury on CT/MRI
C6. High NSE >60 ng/mL at 48 and/or 72 hours after randomization

Note: *Participants with suspected ongoing status myoclonus at the time of assessment should still be assessed for a response to pain. An increase in the frequency or amplitude of myoclonic jerks when a painful stimulus is applied should not be considered as a motor response. If the participant localizes to pain or EEG-background is continuous, the prognosis should not be stated as "likely poor neurological outcome", as this state may be compatible with a diagnosis of Lance-Adams syndrome.*

5.7 Withdrawal of life supporting therapies (WLST)

All participants in the trial will be actively treated until **72 hours** after randomization. There will be two exemptions from this rule.

1. Participants in whom further treatment is considered unethical due to irreversible multi-organ failure; or, following inclusion in the trial, information becomes available such as an advanced medical comorbidity (e.g., generalized malignant disease) or a pre-existing Advance Care Directive that prohibits treatment.
2. Participants in whom brain death is established according to local legislation, however this will be defined as death and not WLST. We recommend that the clinical diagnosis of brain death should be avoided during the first 24 hours after ROSC and be supported by radiological evidence of herniation and loss of intracerebral blood-flow when there is any doubt about the diagnosis.

The assumption of a poor prognosis as a result of hypoxic brain injury alone will not be considered sufficient to employ withdrawal of active intensive care prior to 72 hours after randomization. After prognostication has been performed, WLST due to a presumed poor prognosis will be allowed as per the treating clinician and if the STEPCARE criteria for a likely poor neurological outcome are fulfilled.

Participants who have an unclear prognosis at 72 h after randomization should be reexamined daily and WLST may be considered if neurological function does not improve and, metabolic and pharmacological reasons for prolonged unconsciousness are ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing life-supporting therapies will be recorded. However, supporting therapy may also be continued regardless of the neurological assessment of prognosis, at the discretion of the treating physician.

5.8 Follow up

A first formal follow-up will take place at 30 days after cardiac arrest by telephone/digital meeting. For some participants this follow-up will take place face-to-face in hospital. For those participants who are assessed after discharge, follow-up as outlined in section 3.6; participants will be assessed according to the mRS-scale.

At six months, participants will be invited to a follow-up as outlined in section 3.6. Information will be collected by specially trained, blinded assessors in structured interviews.

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 trial manual with detailed guidelines for performing the assessment. Training sessions will be provided by the trial coordinating team. At the end of each training session participants will perform mRS scoring on several practice cases.

5.9 Blinding

The clinical team responsible for the participant (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 interventions (sedation, temperature, and arterial pressure). 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 make a first prognostic evaluation of the patient at 72 hours after randomization and make a statement on neurological prognosis. The treating intensive care physician will not be allowed to share any information regarding the allocation groups. Participants, their legal representatives, and family will only be informed that the patient has been part of the trial but not the allocation groups. Health personnel responsible for outcome assessment at follow-up will also be blinded to the allocation of the interventions.

The steering group, writers of the manuscript, outcome assessors, prognosticators, statisticians, and the data safety monitoring committee will be blinded to group allocation. The intervention groups will be coded as "A" and "B", “1” and “2”, and “X” and “Y”. Two conclusions from all outcomes in the main manuscript will be drawn: one assuming one is the experimental group and the other is the control group - and one assuming the opposite. All conclusions must be approved by the author group before the code is broken.

6 Factorial Design

In certain circumstances, testing multiple interventions simultaneously might be highly advantageous as more than one research question can be answered, and data collection can be more efficient. In other circumstances, a factorial design might not be possible due to logistical issues, or because of mechanistic interactions between the interventions affecting outcome assessment.

The three interventions in STEPCARE have potential physiological interactions with each other but there is no data suggesting that these interactions affect the outcomes being assessed.

Sedation#Temperature
Sedative agents such as propofol may promote heat loss through vasodilatation and might also directly impair hypothalamic temperature regulation.[53] Drug pharmacokinetics might also be affected by active temperature reduction, however this interaction is likely negligible in the absence of induced hypothermia.

Sedation#Blood Pressure
Many continuously administered sedative agents cause vasodilatation and may have effects on cardiovascular function; targeting deep sedation may result in hypotension and vasodilation and may influence the achievement of different MAP targets. However, it is standard practice in intensive care to titrate sedation and vasoactive agents to achieve clinician prescribed cardiovascular targets. Additionally, feasibility and safety of blood pressure strategy has been demonstrated in pilot studies. Targeting a higher blood pressure is unlikely to affect drug pharmacodynamics and may affect consciousness.

Temperature#Blood Pressure
It appears unlikely that targeting different MAP levels would influence the occurrence of fever however vasoconstriction might reduce heat loss.

Interactions with regards to patient outcome
We do not believe that there is evidence for any interactions between the interventions in respect to the study outcomes. However, if higher doses or levels of sedation, inotropic / vasopressor support, or external cooling are required because of between-group interactions, differential adverse effects of these interactions are theoretically possible. We will therefore monitor the trial during its conduct to identify such possible interactions, with particular focus on patient safety (Section 3.2).

6.1 Co-enrolment in other trials

Study participants may be included in any observational trial which does not affect protocol adherence in the STEPCARE-trial. Pursuant to approval by from the trial management group, co-enrolment in other randomized or intervention trials may be possible. We will assess co-enrollment suggestions based on the Spice-8 co-enrolment guidelines.[54]

6.2 Interplay between this trial and other recent or ongoing trials on post cardiac arrest care

There are major trials currently running or that have recently completed randomization focusing on management of both oxygen and carbon dioxide after cardiac arrest. Oxygenation, carbon dioxide levels and MAP may all influence cerebral oxygenation.[55]

The TAME trial (NCT03114033) has finished including patients and should be published in the first half of 2023. The trial compares moderate hypercapnia (PaCO2 6.7-7,3 kPa) to normocapnia (PaCO2 4.5-6.0 kPa) in 1700 patients treated in the ICU after OHCA.

It is not likely that either the treatment of patients with moderate hypercapnia or aiming to actively avoid hypercapnia would change the effect of MAP on patient outcome including brain and myocardial injury. In support of this lack of likely interaction, the COMACARE trial included different interventions for MAP, oxygen and carbon dioxide and did not find any interaction between these interventions and the primary outcome, the level of the brain injury biomarker NSE at 48 hours. [3,44] Therefore, the STEPCARE trial will not protocolize the management of PaCO2 or arterial oxygen saturation. If the results of these trials, which are likely to be reported during the conduct of the STEPCARE trial, change practice, there should consequently be no requirement to change the STEPCARE protocol.

The EXACT study (Reduction of Oxygen After Cardiac Arrest) (NCT03138005) is a phase 3 multicenter randomized trial comparing reduced oxygen administration targeting low-normal arterial oxygen saturations (90%–94%) to a more liberal use of oxygen targeting an oxygen saturation of 98-100% during transport to hospital and in the ED prior to hospital admission. The study was stopped prematurely and included approximately 400 OHCA patients. The study did not find any evidence of improved outcome with the lower oxygen target, and on the contrary found that survival to hospital discharge was 10% lower in the low oxygen group and more patients experienced hypoxia.[56] Whether these results will influence the current recommendations of post cardiac arrest is not known but nonetheless any change in recommended oxygen targets during ICU care is not likely to influence the feasibility of the STEP CARE trial.

It is not likely that either the treatment of patients with moderate hypercapnia or aiming to actively avoid hypercapnia would change the effect of MAP on patient outcome including brain and myocardial injury. In support of this lack of likely interaction, the COMACARE trial included different interventions for MAP, oxygen and carbon dioxide and did not find any interaction between these interventions and the primary outcome, the level of the brain injury biomarker NSE at 48 hours. Therefore, the STEPCARE trial will not protocolize the management of PaCO2 or arterial oxygen saturation. If the results of these trials, which are likely to be reported during the conduct of the STEPCARE trial, change practice, there should consequently be no requirement to change the STEPCARE protocol.

Blood Pressure and Oxygenation were assessed in the BOX trial (NCT03141099) with approximately 800 participants in two large Danish hospitals and reported in August 2022. There was no difference between a blood pressure target of 63mmHg and a target of 77mmHg. The separation between the trial arms was however less than planned (10 mm Hg) and thus was the MAP-CARE research question not answered. The BOX-trial results did not find any adverse events with either target. Similarly, the BOX-trial oxygen results do not affect standard care for oxygenation after cardiac arrest.[40,57]

There is a randomized temperature trial that is yet to be reported, the ICECAP-trial (NCT04217551) is currently randomizing patients to different cooling durations after out-of-hospital cardiac arrest. This study does not have a normothermic control arm and will therefore not impact the temperature intervention.

7 Trial Interventions

7.1 Sedation strategy

Sedation depth according to RASS will be recorded throughout the intervention. All patients should be assessed for pain and delirium using local protocols. Pain should be treated, according to local protocols, before a sedative agent is considered. Multimodal pain management should be adopted, including non-pharmacological techniques, acetaminophen (paracetamol), and opioids by either continuous or intermitted intravenous infusion. Pain management and treatment for delirium should follow the principles outlined by the SCCM.[58]

Participants in both trial groups regaining consciousness and obeying commands will be extubated and discharged according to standard local hospital criteria. Patients judged to require a tracheostomy will have this performed according to local standard practice. Discontinuation of sedation and mechanical ventilation following tracheostomy in both trial groups will be according to local hospital practice.

In both study groups, if sedative medications are required, short-acting drugs by continuous infusion (such as propofol) should be preferred to benzodiazepines (by either continuous infusion or bolus dosing) for most patients. Clinicians might consider certain patients have a particular indication for a benzodiazepine-based sedation regimen: for example, those requiring very high rates of propofol infusion, those who have demonstrated seizure activity, and those with marked hemodynamic instability. In such patients, the requirement for ongoing benzodiazepine use (vs. an alternative) should be reassessed continuously.

In both study groups, sedative medications should only be used to achieve the prescribed sedation target, and only after measures to control pain and delirium have been initiated. For patients receiving neuromuscular blocking agents the level of sedation should be titrated to avoid awareness, as per treating physician, no matter of allocation group.

7.1.1 Sedation – Continuous sedation for 36h

For patients randomized to *continuous sedation* a continuous infusion of a short-acting sedative agent (such as propofol) should be started at randomization. During the first 36 hours this infusion should be increased if the patient becomes rousable, with a RASS target of -4 to -5 until 36h after randomization. After 36h, the sedation goal will be a RASS of -2 to 0 (unless there is a clinical indication for deeper sedation), continued until the time of liberation from mechanical ventilation, at which time all sedative medications should be discontinued as soon as judged safe.

7.1.2 Sedation – Minimal sedation

In patients randomized to minimal sedation sedative agents shall not be used unless needed for clinical care. During the first few hours of post-cardiac arrest care patients may require deeper sedation to facilitate safe transfers, imaging, and invasive procedures, but weaning from sedatives should be performed as early as possible, ideally within 6 hours of randomization if not at the time of ICU admission.
Patients randomized to minimal sedation will be continuously assessed for extubation as soon as possible after admission to the ICU according to local criteria. If the patient is alert, obeys commands and is otherwise stable the patient may be extubated. A patient that does not fulfill criteria for safe extubation should remain intubated and receiving sedations as needed.
No opioid or sedative medications will be given unless the patient demonstrates a requirement for analgesia or sedation to safely tolerate mechanical ventilation and/or other treatments. If such medications are required, analgesia should be administered first, according to local protocols. Multimodal pain management should be adopted, including non-pharmacological techniques, acetaminophen (paracetamol), and opioids by either continuous or intermittent intravenous administration in line with clinical guidelines. If sedation is required after pain is treated, short-acting agents (e.g., propofol) should be used, targeting a level of sedation that is as light as possible

but still deep enough to enable safe treatment and adequate patient comfort. The sedation target should be RASS 0 to -2, unless there is a clinical indication for deeper sedation, in which case a deeper sedation target is acceptable.
Deeper sedation may be used in the minimal sedation arm if required to manage clinical situations such as refractory status epilepticus, myoclonus, severe hypoxemia or, confirmed or suspected raised intracranial pressure.

7.1.3 Sedation – Changing sedation

The clinical situation may require continuous sedation to be started in a patient in the minimal sedation group. This is at the discretion of the treating physician. If continuous sedation is started within the first 36 hours the reason for this will recorded and classified as follows:

Was continuous sedation started within 36 hours of randomization?

- No
- Yes – to facilitate general intensive care
- Yes –for seizures

7.2 Temperature strategy

7.2.1 Fever management with a device

Temperature will preferentially be recorded via a bladder thermometer. If the patient is oliguric, or if a bladder recording is not available then core temperature will be assessed by an esophageal or intravascular probe.

Participants who have an initial temperature between below 33°C may be actively rewarmed to 33°C, at which point active rewarming should be suspended. However, passive rewarming below 33°C may also be used, if preferred by the treating physician. Participants with an initial body temperature above 33°C will not be actively rewarmed to normothermia. 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
- Complete exposure of the patient

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 ≥37.8°C, regardless of whether the temperature is deemed to be of infectious origin or a response to neurological injury within 72 hours after randomisation.

If the criterion for insufficient fever control is fulfilled a temperature management device will be applied and set at 37.5°C using:

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

The treating physician may prescribe the application of a device (insert an endovascular catheter of apply a surface device) if a rise in temperature is encountered. However, the device will not be switched on until a core body temperature of ≥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 72 hours after randomization.

In a patient that wakes up, is alert, obeys command and is extubated, temperature control with a device may be discontinued even if the 72-hour mark has not been passed.

7.2.2 Fever management without a device

Temperature will be preferentially 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 esophageal or intravascular probe.

Participants who have an initial temperature below 33°C may be actively rewarmed to 33°C, at which point active rewarming should be suspended. However, passive rewarming below 33°C may also be used, if preferred by the treating physician. Participants with an initial body temperature above 33°C will not be actively rewarmed to normothermia.

Fever management in this group should not differ from other critically ill patients in the ICU. No specific temperature target will be set. Antipyretics and non-pharmacological cooling measures may be used on the same indications as for any ICU patient. It might therefore be reasonable to use paracetamol, steroids or NSAIDS under certain circumstances but their use is not protocolized.

7.2.3 Fever management outside of the 72-hour intervention period

Fever management outside of the intervention should not differ from any other critically ill patient in the ICU. No specific temperature target will be set. Antipyretics and non-pharmacological cooling measure may be used on the same indications as for any ICU patient. It might therefore be reasonable to use paracetamol, steroids or NSAIDS under certain circumstances but their use is not protocolized.

Fever management after 72h in both groups will be at the discretion of the treating physician. If cooling is ongoing at the end of the intervention period, this management may continue.

Active cooling with a device may be started at any time in both groups at the discretion of the treating physician in situations of very high temperature and severely deranged physiology, similarly to situations in which a cooling device might be used in a general ICU patient.

7.2.4 Temperature – use of a device

The reason for a use of a device will be collected and categorized as follows

Temperature control device started

- No
- Yes – according to intervention (Temperature >37.7°C)
- Yes - Clinical team error (not according to intervention)
- Yes – Very high temperature and severely deranged physiology not responding to other treatments (not according to the intervention, but not regarded as a protocol violation)

7.3 Mean Arterial Pressure Strategy

7.3.1 Achieving the MAP target

Titration of vasopressors to the MAP target may be delayed until the patient has completed the required (clinician defined) initial diagnostic work-up (e.g., CT-scan and coronary angiography) and is admitted to ICU.

In both groups the means of achieving the targeted MAP will be up to the treating clinician according to local protocols. The most common vasoactive and inotropic drugs in the cardiac intensive care unit include noradrenaline, adrenaline, phenylephrine, vasopressin, milrinone, dobutamine, dopamine and levosimendan.

Fluid therapy should be guided by standard procedures for hemodynamic support such as fluid responsiveness, urinary output, hemodynamic and laboratory values and echocardiography. In case of suspected hypovolemia and fluid responsiveness (based on for example stroke volume variation or the results of a passive leg raising test), a fluid bolus may be administered. Excessive fluid loading should only be performed after careful consideration.[59]

If the target is not achievable despite adjustment of vasoactive/inotropic therapies, then a lower target may be accepted, and the reason will be recorded.

If the MAP is higher than the allocated target and the patient is on vasopressors, then the vasopressor should be titrated down to achieve the target.

Hypertensive urgencies occurring in the absence of vasoactive medications will be managed in accordance with usual practice in both the low MAP and high MAP arms.

7.3.2 Low MAP target

Participants allocated to targeting a MAP of 65 mmHg will have their vasopressor infusions titrated until a MAP of at least 65 mmHg is achieved for the first 72 hours after randomization. In case of suspected hypovolemia fluid boluses of a crystalloid may be administered.

The MAP target should not be continued in participants ready to be discharged from ICU before 72 hours.

If the patient is extubated the MAP target will be up to the treating clinician. If the patients is reintubated before 72 hours the MAP target will be 65 mmHg.

After the 72-hour intervention period, the MAP target is decided by the treating clinician.

7.3.3 High MAP target

Participants allocated to a MAP target of at least 85 mmHg will have their vasopressor infusions increased until a MAP of at least 85 mmHg is achieved for the first 72 hours after randomization. In case of suspected hypovolemia crystalloid fluid may be administered.

The MAP target should not be continued in participants ready to be discharged from ICU before 72 hours.

If the patient is extubated the MAP target will be up to the treating clinician. If the patients is reintubated before 72 hours the MAP target will be 85 mmHg

After the 72-hour intervention period, the MAP target is decided by the treating clinician.

7.3.2 – Adjusting the MAP target

The overall intention is to achieve the MAP target throughout as much of the 72h intervention period as possible; the clinical situation may however require an adjustment of the MAP-target.

If necessary, the MAP target should be adjusted in increments or decrements of 5 mmHg. Subsequently, if there is a change in the clinical status of the patient, further attempts to achieve the targeted MAP may be considered.

The reason for the deviation from the allocated target will be collected and categorized according to the description below.

MAP-target changed or abandoned before extubation or 72h?

- No

- Yes –Lower target - Escalation of vasoactive treatment not achieving a higher MAP
- Yes – Lower target because of cardiac reasons.
  (Cardiac reasons include severe arrhythmias, worsening pulmonary oedema, worsening cardiogenic shock, LVOT-obstruction, aortic insufficiency, or other reasons where the clinician suspects that an increase in vasopressor dose is causing a clinically important decline in cardiac output)
- Yes – Lower target because of major surgery
- Yes – Lower target because of intracranial bleeding.
- Yes – Lower target because of bleeding (extracranial)
- Yes – Lower target because of other reason

- Yes – Higher target because clinical team forgot
- Yes – Higher target because of renal perfusion
- Yes – Higher target because of ischemic stroke or critical carotid stenosis
- Yes – Higher target because of other reasons.

7.4. Discontinuation and reinstitution of the interventions

For participants that are de-sedated and extubated before the end of the intervention period of 72 hours for the temperature and MAP intervention, and where the interventions have been discontinued, the interventions should be reinstituted in the event of re-intubation/re-sedation if within the intervention period. After 72 hours the targets for temperature and MAP are to the discretion of the physician.

If the participant is evaluated for likely brain death according to national criteria, the sedation, temperature, and MAP targets will be at the clinicians discretion.

8. 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 data that will be collected. Full definitions are available in the electronic case record form (eCRF).

Data will be obtained from hospital records, relatives, and ambulance services and will be entered into a web-based eCRF by site personnel. The site investigator must sign all eCRFs before trial completion to verify that the recorded data is correct and complete. The software for the web-based form will be provided by Spiral, New Zealand. The primary database server will be located in Stockholm, Sweden. Data from the web-based forms will be migrated to a trial database, which will be handled by the coordinating team. A separate data management plan will be provided as per the General Data Protection Act of the European Union.

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)

8.1 Baseline data

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

- **Pre-randomization- characteristics**
- Inclusion and exclusion criteria
- Age
- Sex
- Time and date of ROSC
- Time and date of Cardiac Arrest
- Miracle 2 SCORE.
  - Witnessed arrest / Unwitnessed arrest
  - Shockable initial rhythm, yes/no
  - Pupillary reflex, yes/no
  - Age
  - Changing rhythms (Any two of VF/PEA/asystole), yes/no
  - First available pH (arterial)
  - Epinephrine given

- Presumed cause of arrest
    - Cardiac – ST-elevation myocardial infarction / acute coronary occlusion
    - Cardiac – non-ST elevation myocardial infarction
    - Cardiac – Arrhythmia – not related to acute ischemia
    - Cardiac – Heart Failure
    - Pulmonary Embolism
    - Hypoxia
    - Other medical causes (Electrolyte disorders, sepsis etc)
    - Asphyxia (strangulation, foreign body etc.)
    - Drowning
    - Drug Overdose

- Perceived prognosis by randomizing physician (Good vs. Poor neurological function)
- **Pre-hospital data**
    - Scene of arrest (home, work, public place, nursing facility, other)
    - Witnessed arrest (Y/N)
    - Bystander CPR (Y/N)
    - Bystander defibrillation performed (Y/N)
    - First monitored rhythm at arrival of EMS (asystole, PEA, VF, non-perfusing VT, ROSC after bystander defibrillation, unknown (shockable or unshockable))
        - Defibrillation performed
        - Time of emergency call
        - Minutes until CPR started. (No-Flow time)
        - Amount of adrenaline (mg)

- **Background data**
    - Height
    - Weight
    - Pre-arrest functional status (Independent / Not independent, in basic activities of daily life)
    - Frailty
    - Previous percutaneous coronary intervention? [Y/N]
    - Previous coronary artery bypass grafting? [Y/N]
    - Previous heart failure with pharmacological treatment [Y/N]
    - Previous implantable cardioverter defibrillator (ICD)? [Y/N]
    - Previous hypertension with pharmacologic treatment? [Y/N]
    - Previous diabetes mellitus [Y/N]
    - Previous stroke or transitory ischemic attack [Y/N]
    - Current smoker [Y/N]
    - Pre-arrest frailty using the Clinical Frailty Score (1-9)

8.2 Data on hospital admission

- First recorded tympanic temperature (bilateral, highest value)
- FOUR motor score
- Preserved pupillary reflexes
- Preserved corneal reflexes
- First lactate (arterial or venous)
- First creatinine
- First troponin
- STEMI - New ST-segment elevation ≥1 mm in ≥2 contiguous ECG leads or posterior STEMI
- ECG rhythm (sinus / atrial fibrillation or flutter / other)
- Shock on admission, Systolic blood pressure <90mmHg for at least 30 minutes or the need for supportive measure to maintain a systolic blood pressure ≥90mmHg and end-organ hypoperfusion (cool extremities, or urine output of less than 30ml/hr, and a HR >60 beats per minute

8.3 In the ICU

8.3.1 Data 0-72h

At 0, 2, 4, 6, 8, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 48, 56, 72 hours

- Temperature (bladder or alternative)
- Systolic, diastolic, and mean arterial pressure
- Heart rate

At 0, 4, 8, 12, 16,20,24,28,32,36,40,48,72 hours

- RASS-score
- Propofol dose mg/kg/h
- Dexmedetomidine dose
- Noradrenaline dose mcg/kg/min
- Midazolam infusion (check if yes)
- Dobutamine infusion (check if yes)
- Adrenaline infusion (check if yes)
- Responds to commands (check if yes)
- Delirium (assessed using CAM ICU or ICDSC) in the previous 24h (Yes/No)

At 0,12, 24, 48 and 72 hours

- Mechanically ventilated (check if yes)
- PaO2 (arterial)
- PaCO2 (arterial)
- Lactate (arterial)
- Respiratory rate, Peak end-expiratory pressure, Tidal volume, Pressure or volume control ventilation, Plateau pressure (for volume control), Inspiratory pressure (pressure control), FiO2, SaO2
- Highest BSAS
- FOUR motor score
- Presence of status myoclonus
- Presence of corneal and pupillary reflexes
- Tonic/clonic seizures during the previous 24h
- Highest ICU Mobility Scale previous 24h

At 72 hours

- Cumulative doses of propofol, midazolam, dexmedetomidine
- Cumulative doses of remifentanil, fentanyl, alfentanil, oxicodone, morphine
- Any use of milrinone (0-72 hours)
- Any use of vasopressin (0-72 hours)
- Any use of levosimendan (0-72 hours)

8.3.2 Daily ICU stay at day 4,5,6,7:

- Highest body temperature
- Blood Pressure
- Delirium (assessed using CAM ICU or ICDSC) in the previous 24h (Yes/No)
- Highest ICU Mobility Scale previous 24h

8.3.3 Neurology

- The stated prognosis from the blinded examiner, dichotomized as poor outcome likely (Y/N, based on the definition in the trial protocol) and which criteria are fulfilled. The local results of prognostic examinations will be collected for CT, MRI, EEG and SSEP findings. The rawdata of original prognostic examinations (CT, MRI, EEG and SSEP) may be collected for pseudononymized evaluation by blinded study examiners.

8.3.4 At ICU discharge

- Time of ICU discharge
- Was the patient readmitted to ICU (yes/no)
- Time and results of coronary angiography (1-vessel, 2-vessel, 3-vessel disease)
- Culprit lesion found on coronary angiography (yes/no)
  - Was the culprit lesion an acute thrombotic occlusion (yes/no)
  - Where was the culprit lesion (RCA, Cx, LAD or graft)
- PCI performed (yes/no)
- Continuous EEG performed
  - Indicative of a poor prognosis (yes/no)
- EEG performed
  - Indicative of a poor prognosis (yes/no)
  - Earliest normal background (hours from randomization)
- SSEP performed
  - Indicative of a poor prognosis (yes/no)
- CT brain performed
  - Indicative of a poor prognosis (yes/no)
- MRI-brain performed
  - Indicative of a poor prognosis (yes/no)
- NSE locally samples
  - Indicative of a poor prognosis (yes/no)
  - NSE concentrations
  - Potential confounders malignancies, hemolysis, ECMO other (yes/no)
- NFL locally samples
  - Indicative of a poor prognosis (yes/no)
  - NFL concentrations
- Use of mechanical cardiac support and when this was started.
  - Impella (or other pVAD)
  - ECMO
  - IABP
- Use of haloperidol, olanzapine, quetiapine (yes/no)
- Use of antiseizure medication (yes/no)
- Discharge facility (coronary care unit/general ward/other ICU/dead)
- Use of temperature control device (No/Yes/Type)
- Time of final extubation (or still intubated)
- Time of awakening
- Renal Replacement Therapy (yes/no)
- Safety events

8.4 At hospital discharge

- Time of hospital discharge
- Discharged to: nursing home/rehabilitation unit/other hospital/home/dead
- Death (Yes/No, time of death)
    - Presumed cause of death (Neurological vs. Non-neurological)
- Probable cause of cardiac arrest
- Last creatinine
- Additional data on observational parameters (including data such as, but not limited to, circulatory indices, EEG, imaging, pupillometry, near infrared spectroscopy etc.)

8.5 30 days after randomization

- 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
- mRS assessment by telephone interview
- Last and first memory in relation to the cardiac arrest

8.6 6 months after randomization

- Survival status obtained from hospital or civil registries
- Date of death
- mRS assessment
- EQ5D-5L VAS and domains

8.7 Planned investigations

Most investigations and interventions are performed at the discretion of the treating physician. However, an EEG as early as possible after 24 hours is encouraged for all patients who remain unconscious, according to guidelines.

8.8 Predefined substudies

8.8.1 Biomarker substudy

There will be an optional biomarker substudy with consecutive blood sampling. Details of data collection are described in Appendix A.

8.8.2 Early neuroprognostication substudy

There will be an optional extended observational ultra-early neuroprognostication substudy. Details of data collection are described in Appendix B.

8.8.3 Extended follow up substudy

There will be an optional extended follow up substudy. Details of data collection are described in Appendix B.

8.8.4 Additional substudies

There may be additional substudies added to the STEPCARE protocol.

9 Ethics and informed consent

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 the interventions must be regarded as an emergency procedure and must be started as soon as the participants are admitted to the hospitals. We judge that this strategy is justifiable according to the Declaration of Helsinki article 30 available from the World Medical Association. Participants 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 if this is required by national legislation. It is of importance that ethical applications contain a request to use data also for deceased participants, to avoid survival bias.

10 Data management

10.1 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. Data will be entered into the electronic database (eCRF) produced by Spiral, New Zealand with the main data server placed in Stockholm, Sweden. The electronic data capture module fulfils all criteria for handling of patient data according to General Data Protection Act of the European Union and is FDA (Food and Drug Administration) and HIPAA (Health Insurance Portability and Accountability ACT) compliant. 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 at least 15 years to allow inspection by relevant authorities. The trial database will be maintained for at least 15 years and anonymized if requested for revision.

10.2 Quality control and quality assurance

The trial will be externally monitored by national monitoring offices 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 participants and data handling. At a minimum, there will be a pre-trial meeting, 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 randomization, and a protocol for medical treatment will be distributed to all sites. Sites will also receive training on how to perform assessments at follow-up visits. The site investigator will be responsible for that all relevant data are entered into the electronic CRFs. The CRFs will be constructed to assure data quality with predefined values and ranges on all data entries. Data management activities will be performed and organized by the trial coordinating team.

10.3 Remote monitoring

Remote monitoring will be performed to ensure data completeness and plausible data. Quality control with regard to achievement of correct levels of sedation, blood pressure and temperature will also be monitored remotely. This monitoring will be automated and coordinated by a data quality group, which will meet regularly. A protocol for the data quality group will be available.

The data quality group will recommend the trial management group to suspend randomizations at a site if:

1) Data is not entered into the eCRF within two weeks of a randomization
2) Queries are not answered.
3) The interventions are not delivered as planned in consecutive patients without adequate explanation.

11 Safety events

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

11.1 Definitions

An **adverse event** 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** 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
- Results in a congenital anomaly/birth defect

Death is an expected outcome among survivors of cardiac arrest. More than half of all 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 unexpected or caused by the intervention. Additionally, when TTM at 33°C and 36°C was compared in the TTM1-trial, only hypokalemia (which occurred in the majority of patients) differed between temperature groups. Serious adverse events will therefore not be reported.

To strike a balance between over-reporting, and maximize the probability of finding any true and important differences only the following safety events will be recorded.

Safety 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.
- Arrhythmia or cardiac arrest **requiring** defibrillation/cardioversion or chest compressions.
  - Ventricular Fibrillation
  - Ventricular Tachycardia
  - PEA or Asystole
  - Atrial fibrillation or other supraventricular tachycardia
- Venous thromboembolism
  - Pulmonary embolism verified with imaging.
  - Other venous thrombosis verified with imaging (catheter- or device-related thrombus, deep-vein thrombosis in extremity)
- Reintubation
- Non-planned extubation
- Ischemic complications
  - Gut ischemia verified by imaging, endoscopy, or requiring surgery
  - Limb or digital necrosis

Other unexpected serious complications

- Events which might reasonably occur as a consequence of the trial intervention and which are not part of the natural history of critical illness, the process which caused the cardiac arrest, or the cardiac arrest itself. These events should only be reported if they are life-threatening, prolong hospitalization or result in meaningful harm to the participant.

11.2 Reporting of safety events

All safety events described in 11.1 will be reported in the eCRF during the intensive care unit stay. Events that occur after discharge from the intensive care unit will not be reported. The specific safety events described above will be reported whether they are considered related to the intervention or not. As the specific safety evens in many circumstances may be considered expected, they will not automatically mandate further follow-up.
At each daily assessment all other serious unexpected complications either observed by the investigator or other caregivers must be recorded and evaluated. The event should be reported within 24 hours from awareness of the event using the eCRF. The nature and circumstances of the event should be described. Expected events is this population of participants include, but are not limited to hemodynamic instability, cardiac arrhythmias, electrolyte abnormalities, reintubation, worsening neurological function, cerebral oedema and complications related to the condition that led to cardiac arrest, and do not mandate reporting. An event which is considered expected in this population might still be considered unexpected in an individual participant. If this is the case, the event should be categorized as an unexpected serious adverse event and reported as such.

The relatedness between the trial interventions and the unexpected serious complications should be determined by the local investigator. The relatedness will be categorized as:

Possibly related: There is a possible temporal relationship between the intervention and the event, but it could have been caused by other factors

Probably related: There is a plausible temporal relationship between the intervention and the event, and the event is not reasonably explained by other factors.

The local investigator is required to follow each participant with an unexpected serious adverse event until resolution of symptoms. Reports of unexpected serious adverse events will be assessed for safety by a qualified physician in the trial coordinating team (medical monitor). The frequency of all serious adverse events (dichotomised by ≥1 event vs. no events) by will be reported to the DSMC

12 Statistical plan and data analysis

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

12.1 Sample size

Previous RCTs of cardiac arrest in the intensive care setting have based calculations on a minimal important difference corresponding to an absolute risk reduction (ARR) of up to 25%. In TTM1 and 2 we used 10% and 7.5% ARR, respectively which we believe are clinically relevant. With an overall survival of less than 50% we suggest a trial should strive for detecting or rejecting a 5% ARR risk reduction (clinically highly relevant but also realistic in terms of expectations on an intervention).

Based on the results of the TTM1-trial, TTM2-trial, and information in the International cardiac arrest registry, (INTCAR) we estimate a total mortality of approximately 60%. The power calculation is based on a 60% mortality in control arms and a 54.4% mortality in the intervention arms, at 6 months for all three interventions.

To demonstrate a relative risk of 0.91 with 90% power at a significance level of 0.05, 1638 participants are required in each group, a total of 3278 participants. The sample size calculation corresponds to a relative risk reduction (RRR) of 9.3%, and an ARR of 5.6%.

Factors that might influence the power calculation include adjustments for site, a significant interaction effect between two allocation arms, loss to follow-up, withdrawn consent and a large intervention effect in one on the three studied interventions.

We have investigated the possible effects of adjustment for site and possible interactions between interventions using simulations. These simulations indicate that no adjustment of sample size is needed to account for site effects, but that a slight increase in sample size (~5%) would be needed to account for possible interactions.

The combined effect of withdrawn consent and missing data on the primary outcome in the TTM2-trial resulted in a reduced sample size by approximately 2%. We assume a similar result in the current trial (1.8%).

A large intervention effect is an inherent limitation to trials with a factorial design and we have not taken this into account when deciding on the final sample size.

Taking the above-mentioned factors into account we will increase the sample size by 6.8% and recruit 3500 participants a sample size which is compatible with funding and a realistic time frame.

The analyses of the outcomes will be based on the intention-to-treat (ITT) principle, i.e., all randomized participants will be included in the analysis regardless of how much treatment they have received.

12.1.2 Sample size calculation

Test used: Power calculation for two proportions
Probability of death in the control group: 60%
Probability of death in the intervention group: 54.4%
Effect size: 2*asin(sqrt(p1))-2*asin(sqrt(p2)) = 0.113
Required sample size: 3278
Final sample size: Required sample size + 6.8% =3500

12.2 Analysis methods

Dichotomous outcomes will be analyzed using mixed effect logistic regression and continuous outcomes will be analyzed using mixed effect linear regression. All outcomes will initially be performed with adjustments made for site as a random intercept.

12.2.1 Primary outcome

The primary outcome will be analyzed as a binary variable (alive versus dead) at six months.

12.2.2 Secondary outcome

Functional outcome will be evaluated by dichotomizing the modified Rankin scale (0-3 versus 4-6), or if this is missing; dependent or independent in basic activities of daily life (moving indoors, eating, dressing, personal hygiene). The secondary outcome HRQoL will be presented as the difference in the continuous VAS-scale included in the EQ5D-5L among survivors.

12.3 Missing data

Missing data will be reported in the publication. If further analyses reveal substantial missing- ness, multiple imputation will be considered. We will follow recommendations for the handling of missing data as recommended by Jakobsen.[60]

12.4 Subgroup analysis

Subgroups will be analyzed according to pre-defined variables

- Age (higher or lower than the median)
- Sex at birth
- Bystander CPR
- Initial rhythm – Shockable vs. Non-Shockable.
- Time to ROSC (higher or lower than the median)
- Circulatory status on admission (Presence or absence of circulatory shock)[61]
- Severity (Miracle2-score)
- Presumed cause of arrest at randomization (Cardiac vs. Others)
- Previous hypertension

12.5 Data safety monitoring committee

There will be an independent data safety and monitoring committee (DSMC) arranging an independent statistician to conduct blinded interim analysis. The DSMC will be chaired by Dr Paul Mouncey, ICNARC, London, UK. 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 trials and can initiate analysis at any time they request. Lan-DeMets group sequential monitoring boundaries will be used if multiple interim analyses are needed. The DSMC may stop or pause an intervention, or the entire trial if:

- Group difference in the primary outcome measure is found in the interim analysis according to pre-defined stopping rules
- Group difference in serious adverse events is found in the interim analysis
- Evidence of interaction causing increased mortality.
- Results from other studies show benefit or harm with one of the allocation arms

13 Publication of Data

The results of the three main comparisons will be published in three separate articles. The trial will be analyzed by two independent statisticians and the results interpreted by the authors. The analysis process will be performed with the allocation code unbroken and with the trial arms unknown. Two abstracts for each intervention will be prepared before the allocation code is broken, with the different arms inter-changed. All authors must approve both versions before the code is broken. The final manuscripts will be submitted to a peer-reviewed international journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement and fulfilment of the author's respective roles. The author list will include the management group, national investigators, and additional names, based on recruitment and fulfillment of responsibilities.

After the author list there will be added: "and the STEPCARE-trial group" and a reference to an appendix with all sites, site investigators and number of participants enrolled. The main publication will report the primary and secondary outcomes. In doing so, survival, functional outcome and HRQoL will be reported. Exploratory outcomes will, due to complexity of reporting be submitted to a peer-reviewed journal as multiple separate manuscripts. A detailed authorship plan will be decided upon after the first interim analysis.

14 Insurance

When preexisting insurance is not available, indemnity to meet the potential legal liability of investigators/collaborating hospitals for harm to participants arising from the conduct of the research will be provided by the STEPCARE-Trial through the sponsor: Region Skåne – Skånes sjukhus nordväst – Helsingborg hospital. The insurance negotiated with a major insurance company for each country will be specified in each site agreement before the commencement of patient inclusion at that site.

15 Funding

The trial will be funded by external foundations 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

ALF-project funding within the Swedish Health Care

The Academy of Finland

Medical Research Future Fund (Australia)

Health Research Council of New Zealand

16 Timeline

2022	Trial design, ethics application, site recruitment, application for funding
2023	First patient recruitment, run-in period, site initiations
2023-24	Patient recruitment and interim analysis
2025-26	Continued recruitment, follow up and presentation of results.

17 Trial organization

There will be a site principal investigator at each participating hospital, and the site principal investigator will organize co-investigators and local trial personnel.

For each country there will be one national coordinating investigator, coordinating national sites and suggesting site principal investigators. The national investigator will participate in the trial steering group.

In countries with significant contribution to the trial there might be additional national investigators appointed.

For the day-to-day management of the trial there will be a trial management group (representing conception of the trial and countries with significant funding of the trial). See 17.2

The steering group will be chaired by the chief principal investigator (study chair) and consist of the national investigators and the trial management group.

Representatives for patient organizations will be invited to the steering group.

Additional coordinating investigators may be recruited to the trial to liaise with national investigators, site principal investigators and sites.

There will be intervention and procedure specific groups assigned for sedation, temperature, mean arterial pressure, prognostication, follow-up.

All minor and daily decisions will be taken by the trial management group (consensus).

All major decisions will be taken by the steering group (majority).

17.1 Trial Management Group

Study chair:
Niklas Nielsen, Intensive Care, Helsingborg, Sweden

Study co-chair:
Markus Skrifvars, Intensive Care, Helsinki, Finland

Trial management group members:
Josef Dankiewicz, Cardiology, Lund, Sweden
Naomi Hammond, The George Institute, Sydney, Australia
Johanna Hästbacka, Intensive Care, Helsinki, Finland
Janus Jakobsen, Copenhagen Trial Unit, Copenhagen, Denmark
Gisela Lilja, Rehabilitation, Lund, Sweden
Marion Moseby-Knappe, Neurology, Lund, Sweden
Helena Levin, Center for Cardiac Arrest, Lund, Sweden
Matti Reinikainen, Intensive Care, Kuopio, Finland
Manoj Saxena, The George Institute, Sydney, Australia
Marjaana Tiainen, Neurology, Helsinki, Finland
Paul Young, Intensive Care, Wellington, New Zealand

17.2 Investigators

See clinicaltrials.gov

17.3 Homepage

www.stepcare.org

17.3 Investigator responsibilities

The trial site investigator is responsible for:

- Organizing all local site activities to run the trial according to protocol
- Screening and listing eligible patients
- Performing randomization
- Achieving intervention 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 who regain consciousness
- Reporting safety events
- 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 randomization at national sites
- Ethical Review Board - application and approval
- Dissemination of protocols and updates to sites
- Proposing suitable candidates for vacant site investigator positions

18. References

1. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369(23):2197–206.

2. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. N Engl J Med 2021;384(24):2283–94.

3. COMACARE study group, Jakkula P, Pettilä V, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med 2018;44(12):2091–101.

4. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021;47(4):369–421.

5. Moulaert VRMP, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: A systematic review. Resuscitation 2009;80(3):297–305.

6. Treggiari MM, Romand J-A, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness*: Crit Care Med 2009;37(9):2527–34.

7. Kress JP. Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation. N Engl J Med 2000;7.

8. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. 2010;375:6.

9. Olsen HT, Nedergaard HK, Strøm T, et al. Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. N Engl J Med 2020;382(12):1103–11.

10. Vossler DG, Bainbridge JL, Boggs JG, et al. Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee. Epilepsy Curr 2020;20(5):245–64.

11. Hausburg MA, Banton KL, Roman PE, et al. Effects of propofol on ischemia-reperfusion and traumatic brain injury. J Crit Care 2020;56:281–7.

12. Oddo M, Crippa IA, Mehta S, et al. Optimizing sedation in patients with acute brain injury. Crit Care 2016;20(1):128.

13. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. Brain Resuscitation Clinical Trial I Study Group. N Engl J Med 1986;314(7):397–403.

14. May TL, Riker RR, Fraser GL, et al. Variation in Sedation and Neuromuscular Blockade Regimens on Outcome After Cardiac Arrest. Crit Care Med 2018;46(10):e975–80.

15. Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. Neurochem Res 2015;40(12):2583–99.

16. Stamatakis EA, Adapa RM, Absalom AR, Menon DK. Changes in Resting Neural Connectivity during Propofol Sedation. PLoS ONE 2010;5(12):e14224.

17. Murphy M, Bruno M-A, Riedner BA, et al. Propofol Anesthesia and Sleep: A High-Density EEG Study. Sleep 2011;34(3):283–91.

18. May TL, Ruthazer R, Riker RR, et al. Early withdrawal of life support after resuscitation from

cardiac arrest is common and may result in additional deaths. Resuscitation 2019;139:308–13.

19. Sandroni C, D'Arrigo S, Cacciola S, et al. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med 2020;46(10):1803–51.

20. Bjelland TW, Dale O, Kaisen K, et al. Propofol and remifentanil versus midazolam and fentanyl for sedation during therapeutic hypothermia after cardiac arrest: a randomised trial. Intensive Care Med 2012;38(6):959–67.

21. Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, et al. Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest. N Engl J Med 2022;386(8):724–34.

22. Bernard SA, Gray TW, Buist MD, et al. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. N Engl J Med 2002;346(8):557–63.

23. Hypothermia Hypothermia after Cardiac Arrest Study Group. Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. N Engl J Med 2002;346(8).

24. Nielsen N, Friberg H, Gluud C, Herlitz J, Wetterslev J. Hypothermia after cardiac arrest should be further evaluated—A systematic review of randomised trials with meta-analysis and trial sequential analysis. Int J Cardiol 2011;151(3):333–41.

25. Sandroni C, Nolan JP, Andersen LW, et al. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Intensive Care Med 2022;1–9.

26. Holgersson J, Meyer MAS, Dankiewicz J, et al. Hypothermic versus Normothermic Temperature Control after Cardiac Arrest. NEJM Evid [Internet] 2022 [cited 2022 Aug 26];Available from: https://evidence.nejm.org/doi/10.1056/EVIDoa2200137

27. Wolfrum S, Roedl K, Hanebutte A, et al. Temperature Control After In-Hospital Cardiac Arrest: A Randomized Clinical Trial. Circulation 2022;146(18):1357–66.

28. Fernando SM, Santo PD, Sadeghirad B, et al. Targeted temperature management following out-of-hospital cardiac arrest: a systematic review and network meta-analysis of temperature targets. Intensive Care Med 2021;1–11.

29. Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. Resuscitation 2021;167:160–72.

30. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia After Cardiac Arrest Is Associated With an Unfavorable Neurologic Outcome. Arch Intern Med 2001;161(16):2007.

31. Young PJ, Nielsen N, Saxena M. Fever control. Intensive Care Med 2018;44(2):227–30.

32. Saxena MK, Taylor C, Hammond N, et al. A multicentre audit of temperature patterns after traumatic brain injury. Crit Care Resusc 2015;17(2):6.

33. Holgersson J, Ceric A, Sethi N, Nielsen N, Jakobsen JC. Fever therapy in febrile adults: systematic review with meta-analyses and trial sequential analyses. BMJ 2022;e069620.

34. Hassager C, Schmidt H, Møller JE, et al. Duration of Device-Based Fever Prevention after Cardiac Arrest. N Engl J Med 2022;NEJMoa2212528.

35. Deye N, Cariou A, Girardie P, et al. Endovascular Versus External Targeted Temperature Management for Patients With Out-of-Hospital Cardiac Arrest: A Randomized, Controlled Study. Circulation 2015;132(3):182–93.

36. Skrifvars MB, Åneman A, Ameloot K. Individualized blood pressure targets during postcardiac arrest intensive care: Curr Opin Crit Care 2020;26(3):259–66.

37. Ameloot K, Jakkula P, Hästbacka J, et al. Optimum Blood Pressure in Patients With Shock After Acute Myocardial Infarction and Cardiac Arrest. J Am Coll Cardiol 2020;76(7):812–24.

38. Ameloot K, De Deyne C, Eertmans W, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. Eur Heart J 2019;40(22):1804–14.

39. Wihersaari L, Ashton NJ, Reinikainen M, et al. Neurofilament light as an outcome predictor after cardiac arrest: a post hoc analysis of the COMACARE trial. Intensive Care Med 2021;47(1):39–48.

40. Kjaergaard J, Møller JE, Schmidt H, et al. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med 2022;NEJMoa2208687.

41. Hoiland RL, Ainslie PN, Wellington CL, et al. Brain Hypoxia Is Associated With Neuroglial Injury in Humans Post–Cardiac Arrest. Circ Res 2021;129(5):583–97.

42. Sekhon MS, Gooderham P, Menon DK, et al. The Burden of Brain Hypoxia and Optimal Mean Arterial Pressure in Patients With Hypoxic Ischemic Brain Injury After Cardiac Arrest*: Crit Care Med 2019;47(7):960–9.

43. Gräsner J-T, Lefering R, Koster RW, et al. EuReCa ONE□27 Nations, ONE Europe, ONE Registry. Resuscitation 2016;105:188–95.

44. Grand J, Wiberg S, Kjaergaard J, Wanscher M, Hassager C. Increasing mean arterial pressure or cardiac output in comatose out-of-hospital cardiac arrest patients undergoing targeted temperature management: Effects on cerebral tissue oxygenation and systemic hemodynamics. Resuscitation 2021;168:199–205.

45. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Circulation 2018;

46. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727–36.

47. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: An advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation 2014;85(12):1779–89.

48. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: The FOUR score. Ann Neurol 2005;58(4):585–93.

49. Westhall E, Rossetti AO, Rootselaar A-FF van, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology 2016;86(16):1482–90.

50. Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol 2021;38(1):1–29.

51. Lang M, Nielsen N, Ullén S, et al. A pilot study of methods for prediction of poor outcome by head computed tomography after cardiac arrest. Resuscitation 2022;179:61–70.

52. Lang M, Leithner C, Scheel M, et al. Prognostic accuracy of head computed tomography for prediction of functional outcome after out-of-hospital cardiac arrest: Rationale and design of the prospective TTM2-CT-substudy. Resusc Plus 2022;12:100316.

53. Díaz M, Becker DE. Thermoregulation: Physiological and Clinical Considerations during Sedation and General Anesthesia. Anesth Prog 2010;57(1):25–33.

54. Reade MC, Bass F, Howe B, Seppelt I, Shehabi Y. Considerations for co-enrolment in randomised controlled effectiveness trials in critical care: the SPICE-8 co-enrolment guidelines. Crit Care Resusc 2017;19(2):5.

55. Rosenthal G, Hemphill JC, Sorani M, et al. Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury*: Crit Care Med 2008;36(6):1917–24.

56. Bernard SA, Bray JE, Smith K, et al. Effect of Lower vs Higher Oxygen Saturation Targets on Survival to Hospital Discharge Among Patients Resuscitated After Out-of-Hospital Cardiac Arrest: The EXACT Randomized Clinical Trial. JAMA 2022;328(18):1818.

57. Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med 2022;NEJMoa2208686.

58. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU: Crit Care Med 2018;46(9):e825–73.

59. Bogaerts E, Ferdinande B, Palmers PJ, et al. The effect of fluid bolus administration on cerebral tissue oxygenation in post-cardiac arrest patients. Resuscitation 2021;168:1–5.

60. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol 2017;17(1):162.

61. Dankiewicz J, Cronberg T, Lilja G, et al. Targeted hypothermia versus targeted Normothermia after out-of-hospital cardiac arrest (TTM2). A randomized clinical trial – Rationale and design. Am Heart J 2019;

20. Appendix A – Substudies

20.1 Biomarker substudy

All sites enrolling in the STEPCARE trial will be eligible for participation in the optional biomarker substudy. Blood samples will be drawn from an existing central or arterial line at 12, 24, 48 and 72 hours after randomization. Samples will be processed and aliquoted according to a separate protocol. All samples will be re-identified, coded, and labelled at the site level and initially stored locally prior to being transported to a core laboratory at Luxembourg Institute of health, Luxembourg. Blood samples may be analyzed for routine clinical laboratory measurements and prognostic biomarkers, including markers of brain and organ injury, inflammation, and mitochondrial content. No analysis of nuclear DNA will be performed within the scope of the trial. No measurements will take place before the end of the trial, and no results from the biomarker substudy will be published in the initial manuscript. All analyses will be performed after the end of trial. All remaining samples will be destroyed after analysis.

Samples will be collected at:

- **12h after randomization:** serum vial 6 ml and plasma vial 6 ml
- **24h after randomization:** serum vial 6 ml and plasma vial 6 ml
- **48 h after randomization:** serum vial 6 ml and plasma vial 6 ml, pax-RNA tube 2.5 ml
- **72h after randomization:** serum vial 6 ml and plasma vial 6 ml

20.2 Substudy on early neurological prognostication

The STEPCARE trial will perform a separate substudy on early neurological prognostication (EARLY-NEURO) aiming to examine whether brain injury markers in blood, EEG and CT can be used for prediction of outcome already at 24 hours post-arrest.

The hypotheses of the EARLY-NEURO substudy are:
1) The combination of clinical examinations, blood levels of the brain injury marker NFL, EEG and CT predict poor outcome already at 24 h post-arrest without false positive predictions.
2) Any guideline recommended method (clinical examination/EEG/CT/SSEP) fulfilling criteria for a poor outcome according to ERC/ESICM, will have highly elevated blood levels of NFL, indicating the presence of severe brain injury.
3) Extensive sedation will not affect the prognostic accuracy of the prognostic methods EEG, CT, SSEP and NFL.

Prospective substudy of the STEPCARE with selected centers committed to:
1) Routinely perform EEG and CT in all unconscious patients as early as possible after 24 h post-arrest.
2) Participate in the STEPCARE biomarker substudy.
3) Export rawdata for central blinded evaluation for EEG (European Data Transfer, EDT), SSEP and CT/MRI (DICOM format).

Sites participating in the EARLY-NEURO substudy will commit to participation in the biomarker substudy and routine examination with CT and EEG, whilst prediction of outcome and decisions on WLST will strictly adhere to the ERC/ESICM guidelines and the STEPCARE protocol.

20.3 Substudy on detailed follow up

The STEPCARE trial will include an extended follow up substudy, with the aim to provide more detailed information on cognitive, physical, mental health, and life impact for different targets of sedation, temperature, and blood pressure management in the survivors at 6 and 12 months after the randomization. An additional aim will be to describe their caregivers' situation at 6 and 12 months in relation to burden, mental health, and life impact of caring for and living with a cardiac arrest survivor. The extended follow up will be performed as a face-to-face interview at either a clinical visit or a web based digital meeting, by a blinded outcome assessor trained by the study team. Eligible participants will be all survivors at sites participating in the extended follow up substudy, to keep the randomized design. Eligible caregivers are those that lives with or has weekly (or more frequent contact in person or over the telephone) with the participant and would identify as the primary caregiver of the participant if needed.

The assessment for the extended follow up substudy are:

Cognitive function

Montreal Cognitive Assessment (MoCA)*
Symbol Digit Modalities Test (SDMT)* (clinical visit only)
Informant Questionnaire on Cognitive Decline in the Elderly – Cardiac Arrest version (IQCODE-CA)#

Physical function

Optional: Time Stands Test (TST)* and Hand Grip Strength* (clinical visit only)

Mental health

Hospital anxiety and Depression Scale (HADS)
Post-traumatic stress disorder (PTSD) Checklist (PCL-5)

Life impact

World Health Organization Disability Assessment Scale (WHODAS) 2.0 36 items version
Modified Fatigue Impact Scale (MFIS)
Life satisfaction (VAS Scale by the World value survey)
Detailed questions about return to work, and rehabilitation provided*

Burden

Zarit Burden Interview (ZBI)#
*=survivors only
#=caregivers only

21. Appendix B - The modified Rankin Scale (mRS)

Score	Description
0	**No symptoms at all**
1	**No significant disability despite symptoms**; able to carry out all usual duties and activities
2	**Slight disability**; Able to look after own affairs without assistance, but unable to carry out all previous activities
3	**Moderate disability**; requires some help, but able to walk unassisted
4	**Moderately severe disability**; unable to attend own bodily needs without assistance OR unable towalk unassisted
5	**Severe disability**; Requires constant nursing care and attention, bedridden
6	**Dead**