Extended follow-up substudy of the Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation – STEPCARE trial

SED-CARE
TEMP-CARE
MAP-CARE

Extended Follow-up Protocol

Study synopsis

Title	Extended follow-up substudy of the Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation -STEPCARE trial
Short Title	STEPCARE Extended follow-up substudy
Aim	To provide detailed information on long-term outcomes in relation to potential neuroprotection and improvements in recovery for different targets of sedation, temperature, and pressure management in post out of hospital cardiac arrest (OHCA) survivors at 6 and 12 months. In addition, the impact of caring for a post OHCA survivor will be explored.
Population	Survivors of out of hospital cardiac arrest and their caregivers
Design	This extended follow-up substudy is incorporated into the multi-center, international, factorial randomized STEPCARE trial.
Intervention	OHCA participants will be randomized to different targets of sedation, temperature, and MAP management in the main STEPCARE trial.
Sample Size	The extended follow-up substudy is estimated to enroll approximately 600 post OHCA survivors. This will leave 300 survivors for each group of TTM, sedation, and MAP, with a power close to 100% for all outcome assessments included in the extended follow-up substudy.
Eligibility Criteria	All OHCA participants randomized in the STEPCARE trial at the extended follow-up substudy participating sites, who survive and provide consent, will be eligible to participate, with no further inclusion or exclusion criteria.
Primary outcomes	**Post OHCA survivors:** Cognitive function at 6 months **Caregivers:** Caregiver burden at 6 months
Exploratory outcomes	**Post OHCA survivors:** 1. Cognitive function at 12 months 2. Mental health; including symptoms of depression, anxiety and posttraumatic stress disorder at 6 and 12 months 3. Physical function at 6 and 12 months 4. Fatigue at 6 and 12 months 5. Life impact; including functional outcome at 12 months, disability at 6 and 12 months, occupational status at 6 and 12 months, health related quality of life at 12 months, and life satisfaction at 6 and 12 months **Caregivers:** 1. Caregiver burden at 12 months 2. Mental health; including symptoms of depression, anxiety and posttraumatic stress disorder at 6 and 12 months 3. Life impact; including disability, occupational status, health related quality of life and life satisfaction at 6 and 12 months

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According to SPIRIT 2013 and SPIRIT-PRO extension checklist[1]

Administrative information

1. **Title:** Extended follow-up substudy of the Sedation, Temperature and Pressure after Cardiac Arrest and Resucitation -STEPCARE trial

2. **Trial registration:** ClinicalTrials.gov ID NCT06207942. Main trial: ClinicalTrials.gov ID NCT05564754

3. **Protocol version:** V1.0, 27th December 2023. V1.1, 6th of June 2024

4. **Funding:** This substudy is funded by external foundations for medical research and included as a part of the main STEPCARE trial follow-up, currently funded by the Swedish Research Council, the ALF-project funding within the Swedish Research Council, The Academy of Finland and Medical Research Future Fund (Australia).

5. **Roles and responsibilities:**
    a. *Gisela Lilja*, Neurology, Department of Clinical Sciences, Lund University, Lund, Sweden and Neurology Dapartment, Skåne University Hospital, Lund, Sweden; extended follow-up substudy Co-chair
    Naomi Hammond, The George Institute for Global Health, Sydney; Malcolm Fisher Department of Intensive Care, Royal North Shore Hospital, Sydney, Australia; extended follow-up Co-chair
    Marjaana Tiainen, Department of Neurology, Helsinki University Hospital, Helsinki, Finland; extended follow-up Co-chair
    Niklas Nielsen, Helsingborg hospital; Principal investigator/ trial chair STEPCARE
    Dorit Töniste, Neurology, Department of Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund, Sweden; Management committee
    Frances Bass, The George Institute for Global Health, Sydney; Malcolm Fisher Department of Intensive Care, Royal North Shore Hospital, Sydney, Australia; extended follow-up, Management committee
    Janus Christian Jakobsen, Copenhagen Trial Unit, Copenhagen, Denmark, Methodology
    b. Trial Sponsor: Region Skåne, Skånes Sjukhus Nordväst, Helsingborg hospital
    c. Role of study sponsors and funders: Study sponsors and funders have no involvement or influence in the study design, data collection, management, analysis, interpretation of the data, writing of the report and the decision to submit the report for publication.
    d. Gisela Lilja, Naomi Hammond and Marjaana Tiainen share the responsibility for the extended follow-up substudy. The extended follow-up substudy will like the main STEPCARE follow-up be centrally coordinated from Skåne, Sweden with Gisela Lilja as the coordinating investigator. The management committee team including Gisela Lilja, Naomi Hammond, Marjaana Tianinen, Frances Bass and Dorit Töniste have regular meetings approximately two times a month, or more regularly if needed.

Introduction

6. **Background and rationale**
    Cardiac is associated with high risk of death and neurologic impairment. In post cardiac survivors discharged from hospital the frequency of neurological disability varies.[2,3]. Using crude, but recommended, clinician reported outcome scales such as the Cerebral Performance Category (CPC) Scale, Glasgow Outcome Scale-Extended

(GOSE), or the modified Rankin Scale (mRS), the overall functional outcome is good in the majority, with only 10% having a poor outcome associated with severe

neurological disability.[2] In studies using more detailed instruments, mild or moderate cognitive impairment is reported in up to 40-50% of survivors,[4] and cognitive impairment post cardiac arrest is associated with decreased quality of life, emotional problems, lower societal participation, and increased caregiver burden.[5,6]

Targeted temperature management (TTM)

The TTM2-trial[7] randomized 1900 out of hospital cardiac arrest (OHCA) patients to TTM at 33°C or to a TTM-strategy to maintain normothermia with active treatment of fever (≥37.8° C). The TTM2-trial reported no difference in survival nor functional outcome between groups, indicating that cooling to subnormal temperatures does not provide benefit compared to targeting normothermia and avoiding fever. The clinical treatment recommendation following the TTM2-trial is to not cool to sub-normal levels, but to avoid fever in OHCA patients.[8] Fever is suggested as a risk factor for death after cardiac arrest, but the practice and guideline recommendation to treat fever is based on observational data, and it is not known whether there is a causal and modifiable relationship. While TTM with devices targeting normothermia may prevent a potentially harmful fever, it may also cause side effects as there is a requirement for increased sedation and may prolong ICU stay. Long term effects of fever after OHCA have not been studied.

Sedation

Deep sedation was introduced for cardiac arrest patients as an essential part of the TTM regime to counteract undesirable physiological effects. In all modern TTM-trials both groups have been similarly sedated up to 1.5-2 days after cardiac arrest. Based on physiological reasoning and animal data, sedation has also been proposed as a potential brain protective and seizure prophylactic intervention.[2,9,10] For mechanically ventilated patients, sedation can increase comfort, and improve ventilator synchrony. However, while sedation may be beneficial it may also cause adverse effects including increased length of mechanical ventilation, delirium, delayed awakening, and prolonged stay in the intensive care unit (ICU). Sedation also interferes with neurological prognostication after cardiac arrest e.g. is a confounder for clinical neurological examination and EEG patterns.

Blood pressure

Blood pressure is essential for perfusion to all organs, particularly the brain, heart and kidneys. Most cardiac arrest patients need treatment for low blood pressure during the first 48 hours after cardiac arrest. Small pilot trials suggest that an even higher blood pressure than currently used in ICU care could be organ protective and safe, and a biomarker sensitive to brain injury (neurofilament light, NFL) was found to indicate potential neuroprotective effects in a group with higher mean arterial pressure (MAP),[11] but the long-term effects are unclear.

STEPCARE trial

The STEPCARE (Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation) trial (ClinicalTrials.gov: NCT05564754) is an international, multicenter, parallel group, non-commercial, randomized, factorial, superiority trial where optimal levels of sedation, temperature management and MAP targets will be studied. These three interventions represent different aspects of basic management for patients who are admitted to an intensive care unit after cardiac arrest. All participants in the STEPCARE trial will be randomized to three allocation groups, but each intervention will be studied separately regarding safety and reporting of results. The primary outcome in the STEPCARE trial is mortality at 6 months. The main secondary

outcomes are poor functional outcome defined as an mRS score of 4-6 and overall patient reported Health related quality of life (HRQoL) using the EQ-VAS scale (a part

of the EuroQol 5 Dimensions 5 Levels response version (EQ-5D-5L) health survey), both at 6 months.

Cognitive impairment

Cognitive impairment after cardiac arrest is related to hypoxic ischemic brain injury, and potential neuroprotective interventions, such as fever control or higher MAP, may decrease the number of patients with cognitive impairment. In survivors of critical illness long term cognitive impairment is also associated to delirium, sedation, time to awakening and mobilization among others. Cognitive and neurological disability is reflected as one of the most important outcomes from the patient perspective in the development of a Core Outcome Set for Cardiac Arrest trials (COSCA).[12] The primary and secondary outcomes in the main STEPCARE trial do not provide detailed information on cognitive function.

Additional outcomes

Distressing ICU memories and symptoms of posttraumatic stress disorder (PTSD) are commonly reported after an ICU stay. Less sedation in critically ill patients has been reported to have no through positive effects for long term mental health outcomes.[13] For cardiac arrest survivors, potential associations between sedation, delirium, PTSD, or other mental health outcomes have not been explored.

Limitations with physical function is commonly reported after critical illness, especially for patients with seven or more days of ICU stay. Limitations with physical function has recently become a focus area and recognized as an important outcome after OHCA.[2,14] The underlying cause of limitations with physical function after cardiac arrest is unknown, and may be related to neurological impairment, ICU acquired weakness, or other factors. It is possible that a potential neuroprotective intervention may have positive effects on physical function, and less sedation allows for earlier awakening and mobilization, which in turn may be related to better physical function in the long-term.

Fatigue is the most commonly reported symptom by cardiac arrest survivors, and is a key barrier for recovery.[15,16] Fatigue is multidimensional and could be more or less related to a physical or a mental type of fatigue. The most common type of fatigue, and its associated factors is not investigated after cardiac arrest. In stroke and traumatic brain injury, mental fatigue is often reported as associated to the acquired brain injury and cognitive impairment. Fatigue is also common among general ICU survivors[17] of which especially a physical type of fatigue is frequently reported.[18] In general ICU-survivors fatigue is associated to prolonged immobilization in the bed, malnutrition, ICU length of stay, age, sex [19], and physical, cognitive and mental health symptoms.[20] Fatigue, irrespective of cause, may have negative impacts on the patients' rehabilitation, functional outcome, return to work, and HRQoL.

Descriptions of cognitive impairment, mental health problems, limitations in physical function and fatigue do not in itself provide information on life impact and the survivors' ability to function in their daily life, including roles in work, school, family or other social situations. In the main STEPCARE trial, functional outcome will be accessed by the mRS, but this scale does not provide detailed information. To allow for detailed evaluations of patients' health state, the World Health Organization (WHO) provides "the International Classification of Functioning, Disability and Health, (ICF)" as a framework to describe health, health-related states and the individuals functioning in the society. Disability by ICF reflects impairment, activity limitations and participation

restrictions. Ability to return to work as a part of participation is of special importance for the patient, their families, and the society, as it is associated with financial consequences.

Caregiver outcomes

Families of survivors may also experience negative outcomes related to poor mental health and societal participation including professional life and social engagement. These sequalae have collectively been described as the Post Intensive Care Syndrome- Family (PICS-F).[21,22] Caregiver burden and the impact of caring for and living with a post OHCA survivor has been poorly described. Increased burden and poorer health in the caregivers to cardiac arrest survivors are associated to the survivors' outcome, especially poor functional outcome and cognitive impairment.[6]

7. Objectives

The main objective of the STEPCARE extended follow-up substudy is to provide detailed information on long-term outcomes in relation to potential neuroprotection and improvements in recovery for different targets of sedation, temperature, and MAP management for OHCA survivors at 6 and 12 months.

Primary objectives: Post OHCA survivor:

I. Investigate differences for OHCA survivors, of continuous deep sedation compared to minimal sedation and allowance of early awakening, on cognitive function at 6 months.
II. Investigate differences for OHCA-survivors, with fever management with or without a feed-back controlled device, on cognitive function at 6 months.
III. Investigate differences for OHCA survivors, with a MAP target of >85mmHg compared to those with a MAP target of >65 mmHg, on cognitive function at 6 months.

Exploratory objectives: Post OHCA survivor:

IV. Investigate potential changes between 6 and 12 months for OHCA survivors in respects to cognitive function, and in relation to different targets of sedation, temperature, and MAP management, and explore the association to age, sex, education, prearrest clinical frailty, and life impact.
V. Describe mental health at 6 and 12 months for OHCA survivors, and in relation to different targets of sedation, temperature, and MAP management, and explore the association to age, sex, education, prearrest clinical frailty, cognitive function, physical function, fatigue, and life impact.
VI. Describe mobilization and delirium in the ICU, and the association to age, sex, education, prearrest clinical frailty, sedation, cognitive function, physical function, mental health, fatigue, and life impact at 6 and 12 months.
VII. Describe the prevalence, impact, and type of fatigue at 6 and 12 months, and explore the association to age, sex, education, prearrest clinical frailty, cognitive function, physical function, mental health, sleep, and life impact.

Primary objective: Caregiver:

i. Investigate the caregiver's experience of burden of care for cardiac arrest survivors who has been randomised to different targets of sedation, temperature, and MAP management at 6 months.

Exploratory objective: Caregiver:

ii. Investigate the caregiver's experience at 6 and 12 months in relation to burden of care, mental health, and life impact of caring for and living with a post cardiac arrest survivor who has been randomised to different targets of sedation, temperature, and MAP management.

8. Trial design

This extended follow-up substudy is incorporated into the multi-center, international, randomized STEPCARE trial with a 2x2x2 allocation: https://stepcare.org/protocol (extended follow up substudy described in section 8.2.3 and Appendix A 20.3). A selected number of sites will participate in this extended part of the trial, with randomization stratified by site as per the main trial allocation.

Methods: participants, interventions, outcomes

9. Study settings

In the STEPCARE trial >60 hospitals will be participating from Europe, New Zealand, Australia and Asia. Only selected sites with resources and experience with follow-up for post cardiac arrest survivors will be participating in the extended follow-up substudy. Apart from Sweden, Australia, and Finland the aim is to recruit sites in Belgium, Czech Republic, Germany, Italy, Luxembourg, the Netherlands, New Zealand, Norway, Singapore, Switzerland, and the United Kingdom. We expect approximately half of the OHCA participants in the STEPCARE trial to be eligible for the extended follow-up substudy. The extended follow-up will be performed primarily as a face-to-face meeting, that could be either by a physical meeting (in the clinic or in the patient's home) or by a web based digital meeting.

10. Eligibility criteria

All OHCA participants randomized in the STEPCARE trial at the extended follow-up participating sites, who survive and provide consent, will be eligible to participate, with no further inclusion or exclusion criteria. The inclusion and exclusion criteria for the STEPCARE trial are:

- Inclusion criteria: out-of-hospital cardiac arrest of non-traumatic origin, minimum of 20 minutes without chest compressions (defined as stable return of spontaneous circulation. ROSC), unconsciousness (defined as not being able to obey verbal commands equal to a FOUR-score motor response of <4, or being intubated and sedated because of agitation after sustained ROSC, eligible for intensive care without restrictions or limitation, inclusion within 4 hours (240 minutes) of ROSC (or 220 minutes of stable ROSC).

- Exclusion criteria: on ECMO prior to randomization, pregnancy, suspected or confirmed intracranial hemorrhage, previously randomized in the STEPCARE trial.

For caregivers, the eligibility will be that they live with, or have weekly or more frequent contact (in person or over the telephone) with the post OHCA survivor. Only one nominated caregiver per post OHCA survivor will be able to be included in the study. This would typically be the caregiver that would identify as the primary caregiver of the post OHCA survivor if needed, but may also be another close family member.

11. Interventions

We refer to the main STEPCARE trial protocol for detailed information on the three intervention arms and control groups.

12. Outcomes

The outcome assessments used to collect information on outcomes for the extended follow-up substudy are presented below. More detailed information on the outcome, outcome assessments, time point, scaling and scoring are available in the *Appendix (number 25)*. Consumer perspectives on the selected questionnaires, design and

overall burden were received from three cardiac arrest survivors and two separate relatives in collaboration with the Swedish Cardiac Arrest network, a part of the patient

organization Swedish Heart and Lung Association. They all supported the selected questionnaires and indicated the overall burden for completion to be acceptable.

Overview of post OHCA survivor outcomes

Primary outcome:

- Cognitive function at 6 months

Exploratory outcomes:

- Cognitive function at 12 months
- Mental health symptoms at 6 and 12 months
  - Depression
  - Anxiety
  - Posttraumatic stress disorder
- Physical function at 6 and 12 months
- Fatigue at 6 and 12 months
- Life impact at 6 and 12 months
  - Functional outcome (at 12 months)
  - Disability
  - Occupational status
  - Health related quality of life (at 12 months)
  - Life satisfaction

Post OHCA survivor outcome assessments

Cognitive function (primary outcome):

- *Montreal Cognitive Assessment (MoCA*) recommended for performance-based cognitive screening after cardiac arrest,[2] with excellent sensitivity .[23] In the TTM2 trial the MoCA was shown feasible and well accepted for this purpose, with 91% of participants in the follow-up having an available MoCA score.[24] A full MoCA requires a face-to-face visit, either by a physical meeting or by a web based digital meeting (e-MoCA). As an alternative a modified telephone version (T-MoCA) can be used.

Cognitive function:

- *Symbol Digit Modalities Test (SDMT)* complement the MoCA with additional information on processing speed, that is not included as a domain in the MoCA test. The performance-based SDMT is known to be one of the most sensitive assessments on cognitive function available, but requires a physical visit and will therefore not be possible for other modes of follow-up. SDMT has been previously used for cardiac arrest.[24,25]
- *Cognition domain of the World Health Organization Disability Assessment Schedule (WHODAS) 2.0* used for patient reported information on cognitive problems including e.g., concentration, problem-solving, memory and communication.

Mental health:

- *Hospital Anxiety and Depression Scale (HADS)* for patient-reported symptoms of anxiety and depression. HADS is well used in OHCA trials and included in substudies of both the TTM1[26] and TTM2 trial.[14,27]
- *Posttraumatic Stress Disorders Checklist updated for DSM-5 (PCL-5)* for patient-reported symptoms of PTSD, including all aspects according to the

DSM-5 criteria [28]. PCL-5 was previously used for cardiac arrest in a TTM2 substudy.

Fatigue:

- *Modified Fatigue Impact Scale (MFIS)* patient-reported outcome measure including both impact and type of fatigue (physical, cognitive, psychosocial). MFIS has previously been used in cardiac arrest.[29,30]

Physical function:

- *Timed Stands Test (TST)* is a performance-based measure for lower extremity strength and general physical function. TST was used in the previous TTM2 trial. TST could only be used for those participating in a physical meeting *Jamar dynamometer hand grip test* is used to assess upper extremity strength. Jamar has not been previously used in cardiac arrest but has been used extensively in other patient populations and shown evidence to be a valid measure for its purpose. Jamar could only be used for those participating in a physical visit and in addition requires a Jamar dynamometer. Jamar will therefore only be performed at selected sites.
- *Mobility domain of WHODAS 2.0* for patient-reported information on mobility.

Life impact:

- *modified Rankin Scale* (mRS) a clinician-reported ordinal scale for functional outcome used as secondary outcome in the main STEPCARE trial, here repeated at 12 months.
- *WHODAS 2.0 36 item version* is a standardized generic assessment of disability related to the activity and participation domains of the ICF. WHODAS 2.0 could be used either as an interview, self, or proxy report. We here will use the self-report version, except for cases when the patient clearly can't participate. In these cases, the proxy version will be used. Except from the total disability score the WHODAS 2.0 36 item version also generates six individual domain scores, including cognition, mobility, self-care, relationships, daily activities, and participation.
- *Occupational status* ability to work is included as a part of the WHODAS 2.0, but more detailed information will be collected regarding the survivor's occupational status at time of the OHCA and at time of the follow-up at 6 and 12 months by the following categories: paid work full time, paid work part time (health reasons), paid work part time (other reasons), self-employed (such as own your business or farming), non-paid work (such as volunteer or charity), student, keeping house/ homemaker, retired (due to age), unemployed/retired (health reasons), unemployed (other reasons) or other (specify). In addition, the date of return to work will be collected.
- *EQ-5D-5L* patient-reported HRQoL a part of the secondary outcomes in the main STEPCARE trial, and here repeated at 12 months
- *Life satisfaction* a single question of overall life satisfaction from the World Value Survey. This item was previously used in the TTM2 trial.[31] Country-specific norm data is available.

Overview of caregiver outcomes

Primary outcome:

- Caregiver burden at 6 months

Exploratory outcomes:

- Caregiver burden at 12 months

- Mental health symptoms at 6 and 12 months
  - Depression
  - Anxiety
  - Posttraumatic stress disorder

- Life impact at 6 and 12 months
  - Disability
  - Occupational status
  - Health related quality of life
  - Life satisfaction

Caregiver outcome assessments

Caregiver burden

- *Zarit Burden Interview (ZBI)* capture caregiver burden and consequences of caregiving and was previously used for cardiac arrest.[6,32]

Mental health:

- *HADS* used similar to the post OHCA survivor, to capture symptoms of anxiety and depression. HADS is previously used to caregivers of OHCA survivors.[33]
- PCL-5 will be used also for the caregivers. PCL-5 was previously used for caregivers to OHCA survivors in a TTM2 trial substudy.

Life impact

- *WHODAS 2.0 12 item version* will be used for the caregivers. It is a modified version of the 36-item version and generates a total disability score only.
- *Occupational status* at time of the OHCA and at time of the follow-up at 6 and 12 months will be collected from the caregivers in the same way as for the post OHCA survivor (see above).
- *EQ-5D-5L* an assessment to collect information of the caregivers' overall HRQoL.
- *Life satisfaction:* the same question from the World Value Survey as for the survivors will be used for the caregivers.

Characteristics:

Characteristics for the post OHCA surviors will be collected as a part of the main STEPCARE trial including pre-arrest CFS, age and sex, pre-hospital characteristics as bystander CPR, time to ROSC, and variables in the ICU including daily information on mobilization and delirium. Additional information on post OHCA survivor and caregiver characteristics will be collected at the at 6 and 12 months follow-up, including:
Post OHCA survivor: native language, pre-arrest neurological disease, diabetes, hypertension, education, living situation, participation in support and rehabilitation, previous psychiatric history, sleep less/more/the same (by two questions from the Mental Fatigue Scale).
Caregiver: sex, age, relationship to the post OHCA survivor, if witnessed the cardiac arrest/ performed CPR/were present during the ICU stay, education, if participated in formal emotional support such as counseling, psychologist, peer support group attendance.

13. Participant timeline:

Participants in the main STEPCARE trial are enrolled and randomized at the time they are admitted to the hospital after OHCA. To evaluate long-term outcome, the 6-month time point was chosen for data collection as previous studies show that at this time most neurological recovery has occurred. It is suggested that other outcomes, such as functional outcome and HRQoL may continue to improve, at least 1 year after OHCA. Therefore, for the extended follow-up substudy an additional follow-up will be

performed 12 months after inclusion. It is recommended that the follow-up should be completed within +/- 14 days of the follow-up date at 6 and 12 months. The follow-up should never be performed prior to this timeline, but may if needed be delayed, with the aim to be as close to the suggested time as possible.

14. Sample Size:

The main STEPCARE trial will include 3500 OHCA participants. We assume half of the main trial OHCA participants will be eligible for this extended follow-up substudy (n=1750), and with an predicted mortality of 60% leaving approximately 700 survivors to be invited to the follow-up at 6 months. We expect a missing rate of 10-15%, therefore the final sample size for the extended follow-up substudy is estimated at n=600. This will leave approximately 300 post OHCA survivors for each group of TTM, sedation, and MAP. With this sample size the power will be close to 100% for all extended follow-up substudy included outcome assessments, as presented in the *Appendix* (number 26).

15. Recruitment:

All STEPCARE OHCA participants randomized at those sites participating in the extended follow-up substudy will be eligible for recruitment. The first patient recruitment in the STEPCARE trial was in 2023 with the first 6-months follow-up in the beginning of 2024, and the last follow-up is expected to be in 2026. Caregivers will be invited to participate in the extended follow-up substudy, preferably at the same time as the patient consent to the study, or at time of the follow-up. Since missing data is a main problem in follow-up studies, methods to decrease missing data is an important part of the study design, for further information see data collection and methods (number 18).

Methods: assignment of interventions

16. Allocation:

- Sedation: Continuous sedation for 36 h OR minimal sedation (SEDCARE)
- Temperature: Fever management with OR without a TTM device for 72 h (TEMPCARE)
- Blood pressure: A MAP target of >85mmHg OR >65mmHg for 36 hours (MAPCARE)

17. Blinding:

Outcome assessors will be blinded to group allocation. We assume due to the factorial design that patient and caregivers will have minimal awareness of the complex combination of allocation groups. However, since patients and caregiver may notice information during the patients ICU stay that potentially could reveal allocation group, outcome assessors will inform the patients and caregiver that they should not reveal any information related to the trial treatment to them. During analyses of the data information on allocation group will be available.

Methods: data collection, management and analyisis

18. Data collection methods:

To prevent missing data is an important part of the methodology, and efforts to ensure that every possible survivor will attend the follow-up will be an important part of the study management.

Prior to discharge

Contact details will be collected via a master screening log to increase patient retention. The master screening log will be kept at site and include e.g. name, address, email, telephone number for both post OHCA survivor and caregiver.

At 6- and 12-months

Survivors eligible for this substudy will be invited to a face-to-face visit together with a relative or close friend (preferably the caregiver), either a clinical visit, home visit or by a web-based digital meeting. Approximately 2 weeks prior to the follow-up the questionnaires (WHODAS 2.0, Life satisfaction, MFIS, HADS, PCL-5 and ZBI) will be sent via mail to the post OHCA survivor and caregiver to complete and be returned by a pre-paid envelope, or by bringing to the meeting. At the follow-up the blinded outcome assessors will review the questionnaires and perform a structured interview and administer the performance-based tests. If the post OHCA survivor can't take part in the follow-up e.g., due to severe cognitive impairment, data could be collected from a proxy, except for the outcomes of mental health and life satisfaction that are then excluded. To avoid missing data alternative strategies for follow-up will be used, as follow-up by telephone or postal mail only. If needed an authorized interpreter will be used.

The blinded outcome assessors that perform the structured follow-up may have a professional background such as an occupational therapist, physician, intensive care nurse, research nurse, physical therapist, psychologist, or other allied health specialists. All outcome-assessors will be specifically trained for the study and provided a written trial manual with detailed guidelines for performing the questionnaires and assessments to improve the quality of data collection and comparability of the results (interrater reliability). The training sessions provided by the trial coordinating team are also an important strategy to decrease avoidable missing data. During the trial the outcome assessors will have access to continuing support by the trial follow-up coordinating team to e.g. decrease loss to follow-up. Data will also be reviewed regularly to increase data quality and enable adjustments if necessary, during the study.

19. Data management:

Trial data will be collected in an electronic case report form (eCRF) directly into the trial database.

20. Statistical methods

We plan to have three different data sets for the primary outcome in relation to allocation group, and if valid (underlying the assumption of no interaction effect) these will be treated as three different analyses, with one separate publication for each of the three interventions (Objectives I-III). All analyses will be 2 sided. Thresholds for minimally important differences are presented in the *Appendix* (number 26).

The results from the primary objective for the caregivers will be presented in one additional publication (Objective i.) but could be separated into >1 depending on the results from paper I-III.

Missing data will be presented descriptively and we will consider to report sensitivity analyses and/or multiple imputation according with recommendations on how to handle missing data by Jakobsen et al.[34]

Methods: monitoring

21. Monitoring

Monitoring for the substudy including consents and data completeness will be incorporated into the main study monitoring plan. See section 10.2 and 10.3 of the main trial protocol. Additional monitoring for the extended follow-up substudy will be performed by the trial management committee team.

22. Harms

For more information see main STEPCARE protocol

23. Auditing

For more information see main STEPCARE protocol

Ethics and dissemination

24. Research ethics approval

Ethics applications will be submitted to all relevant ethics boards in participating country and will follow local regulatory requirements.

25. Protocol amendements

n/a

26. Consent or assent

Survivors of cardiac arrest will be asked for written consent as soon as they are able to make an informed decision, with the extended follow-up included in the STEPCARE consent form for those sites participating in the extended follow-up. The caregivers will be asked separately for written consent. 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 OHCA participant or legally acceptable surrogate and by the investigator seeking the consent if this is required by national legislation.

27. Confidentiality

All OHCA participants in the main STEPCARE trial are assigned a trial number and will not be identified in the eCRF. Trial data will be stored according to European regulations Directive 2001/20/EC of the European Parliament and of the Council and according to the General Data Protection Regulation 2016/679.

28. Declaration of interest

Investigators have no financial or other competing interest for this trial

29. Access to data

In partnership with the patient organization a suggestion for the mina STEPCARE trial was to have a structured platform to report results back to OHCA participants and their family members. Therefore, a website will be developed to inform trial participants and the broader society of the results of the trial. In addition results will be reported in seminars, webinars, through patient organizations and via public media.

30. Ancillary and post-trial care

If any problems are discovered during the follow-up screening at 30 days or 6 and 12 months, such as suspected or reported cognitive impairment or emotional difficulties, outcome assessors will ask the survivor and/or caregiver if they have received support

for this. Such interventions are not part of the trial but in line with good clinical practice (GCP), the organization that you work for should have and agreed local policy/strategy in case it is deemed necessary. See Escalation plan *Appendix* (35).

31. Dissemination Policy

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 committee team, national investigators, and additional names, based on recruitment and fulfillment of responsibilities. After the author list there will be added: "and the STEPCARE extended follow-up substudy group" and a reference to an appendix with all sites, site investigators and number of participants enrolled.

Appendix 25: Detailed information on outcome assessments used in the extended follow-up substudy

Main outcome domain	Specific outcome domain	Respondent	Outcome measure	Administration	Time point				No. of items	Scoring	Prior use in OHCA
					At ICU	30 days	6 months	12 months			
Cognitive function	Global cognition	Post OHCA survivor	Montreal Cognitive Assessment (MoCA) e-MoCA if used by a web based meeting T-MoCA if used by telephone	Performance based			X	X	10	Total scores 0-30 (higher better). Scores <26 indicates cognitive impairment. Total scores for T-MOCA 0-22. Scores less than 19 indicates cognitive impairment.	Yes
	Mental processing speed	Post OHCA survivor	Symbol Digit Modalities Test (SDMT)	Performance based			X	X	1	Total scores (range 0-110) are transformed to z-scores based on age and education adjusted norm data. A z-score -1 is considered as low and at a group level indicates cognitive impairment.	Yes
Mental health	Anxiety and depression	Post OHCA survivor Caregiver	Hospital Anxiety and Depression Scale (HADS)	Self-reported Recall period 4 weeks			X	X	7 depression 7 anxiety	Score 0-3 on each item, summed into a total score of 0-21 for the two subscales separately (depression vs. anxiety). Higher values represent more symptoms. The cut off for indicating symptoms is >7.	Yes
	Posttraumatic Stress Disorder	Post OHCA survivor Caregiver	Posttraumatic Stress Disorders Checklist updated for DSM-5 (PCL-5), civilian version	Self-reported Recall period last month			X	X	20	Score 0-4 on each item, summed into a total score of 0 to 80. Higher values represent more symptoms of PTSD. The cut-off for significant symptoms of PTSD is 33. Symptoms of PTSD can also be indicated if the participant scores 2 or more on at least one re-experiencing symptom, one avoidance symptom, two symptoms of negative alterations in cognition and mood, and two arousal symptoms.	Yes
	Caregiver burden and consequence of caregiving	Caregiver	Zarit Burden Interview 22 items (ZB-22I)	Caregiver reported			X	X	22	Score 0-4 on each item, summed into a total score of 0-88. A score >20 indicates burden, and more specific: Little to moderate burden (21-30), moderate to severe burden (41-60), severe burden (61-88)	Yes

Physical function-	Lower extremity strength	Post OHCA survivor	Timed Stands Test (TST)	Performance based			X	X	1	The score equals to the time in seconds (with one decimal) to rise 10 times. The maximum time is 60 seconds, also used if the participant is unable. Based on age and gender normative data three groups will be generated: normal TST, unnormal TST or unable.	Yes
	Upper extremity strength	Post OHCA survivor	Jamar hand grip dynamometer	Performance based			X	X	6 (3 for right hand and 3 for left hand)	The raw score from three trials of right hand respective of left hand. The mean of the three trials can be compared with normative data for gender and age. From a statistical point of view, values within two standard deviations (SD) of the mean are within normal limits.	No
Fatigue	Fatigue Subscales differing physical cognitive and psychosocial impact on fatigue	Post OHCA survivor	Modified Fatigue Impact Scale (MFIS)	Patient reported			X	X	21	Score 0 to 4 on each item, summed into a total score of 0 to 84, with higher score indicating greater impact of fatigue. The cut off for significant impact of fatigue is >37.	Yes
Disability	Total disability score Subscales for cognition mobility, personal care, relationship, daily activities (in home and at work) and participation	Post OHCA survivor Caregiver	World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)	Self-reported Proxy reported version used when needed Recall period 30 days			X	X	36 (post OHCA survivors) 12 (caregivers	36 items version, score 0-100 12 items version, score 0-48 Complex scoring will be used with scores converted to a percentage overall and within each domain where 0= no disability; 100=full disability. Scoring is performed by a SPSS syntax	No Used in general ICU populations
Life satisfaction		Post OHCA survivor Caregiver	Life Satisfaction VAS scale from the World Value Survey	Patient-reported			X	X	One	Visual Analogue Scale of 1-10 (higher better) The norm median is approximately 7, but differ between countries	Yes

Health-related Quality of Life	Overall health related quality of life and five domains of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	Post OHCA survivor Caregiver	EuroQol 5 Dimensions 5 Levels response version health survey (EQ-5D-5L) including the EuroQol Visual Analouge Scale (EQ-VAS)	Patient-reported			X For Post OHCA survivor's part of the main STEPCARE trial	X	6 (five domains and a VAS scale score)	The EQ-5D-5L domains are presented as 0 (no problems) to 4 (extreme problems). A utility score (EQ index) could be calculated from the individual responses, and ranges from −0.593 (score of 0 is equivalent to death) to 1.00 (full health), with higher values indicating better health states. For the EQ VAS, respondents are asked to indicate their present health state on a VAS scale ranging from the worst imaginable health state (score of 0) to the best imaginable health state (score of 100).	

Appendix 26: Power and sample size calculations

Outcome assessment	Mean	SD	MID	Required sample size	Power by current estimated sample size
MoCA*[35,36]	25	5	2	264 (132+132)	1.00
ZBI [6]	15	13	6	208 (104+104)	1.00
WHODAS 2.0 (12 items) [37,38]	15.6	14.7	6	236 (118+118)	0.99
HADS anxiety [26,33,39]	4.6	4.1	2	178 (89+89)	1.00
HADS depression [26,33,39]	3.4	3.7	2	146 (73+73)	1.00
MFIS [29,30,40,41]	21.1	19.7	8	256 (128+128)	1.00
SDMT*	-1.05	1.38	0.69	170 (85+85)	1.00
PCL-5 [42,43]	22	18	9	170 (85+85)	1.00
WVS Life Satisfaction*	7.88	1.99	1	168 (84+84)	1.00
EQ-VAS#	76.1	18.7	9	190 (95+95)	1.00

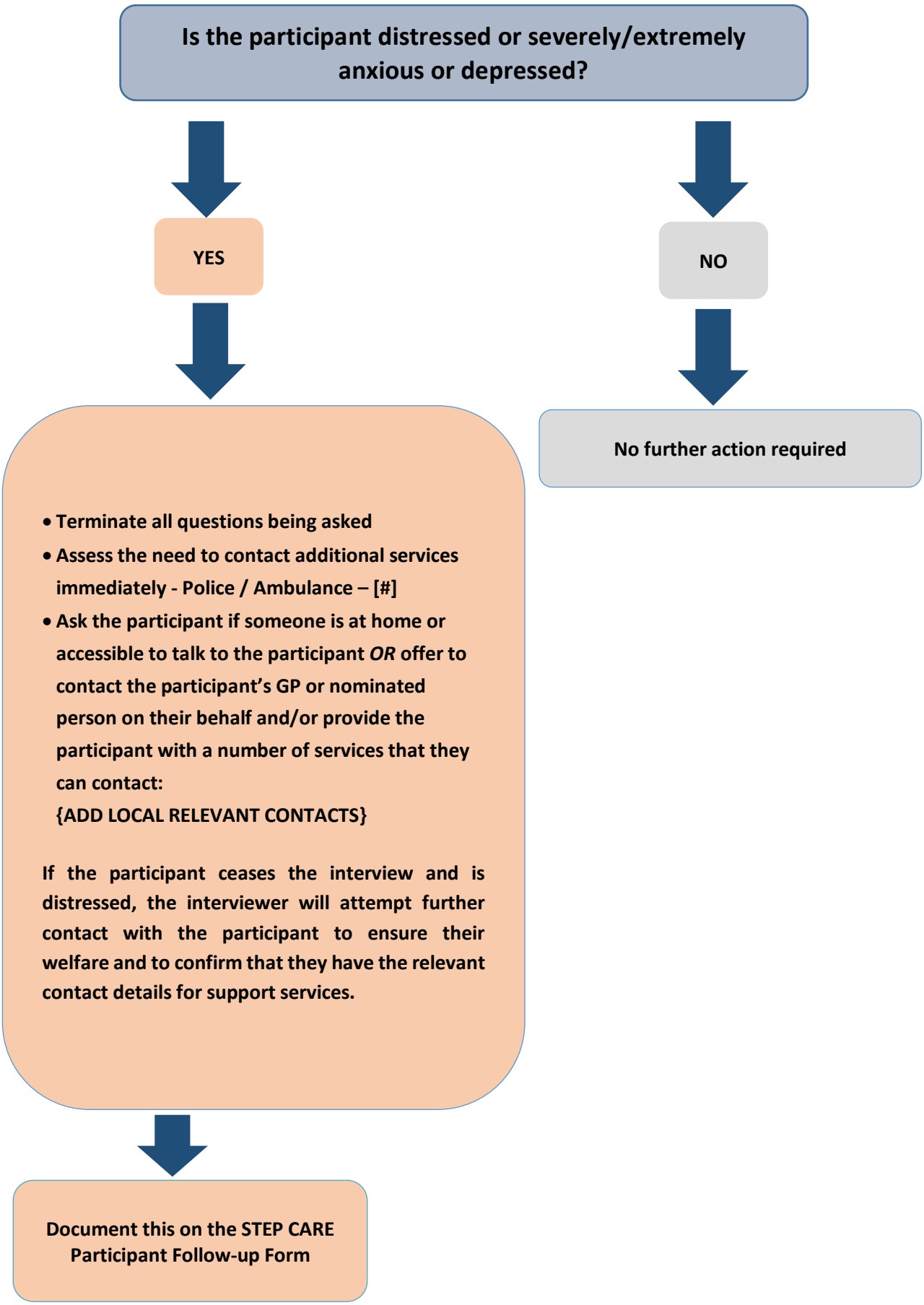
We are planning to include 300 experimental subjects and 300 independent controls with a ratio of 1:1 (N=600). Mean, SD and MID are based on previous studies with cardiac arrest. If no previous studies of cardiac arrest, data from similar patient groups as e.g., critically ill and brain injury were used. The MID was established by a combination (triangulation) of distribution (ES 0.5) and anchor-based methods (when available). The Type I error probability used for the null hypothesis was 0.05. The probability (power) to be able to reject the null hypotheses used for the sample size calculations was 0.90 (90%). Sample size and power calculations were performed by PS: power and sample size calculation program version 3.1.6.

* Information based on unpublished data from the TTM2 trial.

Information for caregivers based on a Swedish normative population (n= 25 867).[44]

Abbreviations: SD= Standard Deviation; MID= Minimally Important Difference; MoCA=Montreal Cognitive Assessment: SDMT=Symbol Digit Modalities Test; HADS=Hospital Anxiety and Depression Scale, PCL-5=PTSD Checklist for DSM-5; WHODAS= World Health Organization Disability Assessment Schedule; WVS Life satisfaction= World Value Survey Life Satisfaction; MFIS= Modified Fatigue Impact Scale: ZBI= Zarit Burden Interview: EuroQol Visual Analogue Scale (EQ-VAS)

Appendix 27: Escalation plan



Appendix 28: Schedule of events

STEPCARE trial: Schedule of follow-up visits		
30-days follow-up (telephone)		
	Post OHCA survivor	**Caregiver**
modified Rankin Score (mRS)	**X**	
6 and 12-months follow-up (Physical or web based digital meeting, or by telephone)		
	Post OHCA survivor	**Caregiver**
modified Rankin Score (mRS)*	**X**	
EuroQol Health Questionnaire - EQ 5D 5L*	**X**	**X**
Montreal Cognitive Assessment (MoCA)	**X**	
Hospital Anxiety and Depression Scale (HADS)	**X**	**X**
Posttraumatic Stress Disorder (PTSD) Checklist (PCL-5)	**X**	**X**
World Health Organization Disability Assessment Scale (WHODAS) 2.0	**X (36 items)**	**X (12 items)**
Modified Fatigue Impact Scale (MFIS)	**X**	
Life satisfaction (VAS Scale by the World Value Survey)	**X**	**X**
Detailed questions about rehabilitation and support provided	**X**	**X**
Detailed questions about occupational status	**X**	**X**
6 and 12-months follow-up (Physical face to face visit only)		
Symbol Digit Modalities Test (SDMT)	**X**	
Time Stands Test (TST)	**X**	
Jamar hand grip strength#	**X**	

*mRS and EQ-5D-5L are included as secondary outcomes in the main STEPCARE trial for the survivors at 6 months and as part of the extended follow-up study at 12 months
#only selected sites

Appendix 29: References

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