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Long-Term Outcomes After Cardiac Arrest: Protocol for the Extended Follow-Up Sub-Study of the STEPCARE Trial

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ABSTRACT

Background: The international multi-center randomized controlled STEPCARE-trial will investigate optimal management of sedation, temperature, and mean arterial pressure (MAP) during intensive care in out-of-hospital cardiac arrest (OHCA) patients due to various etiologies. The primary outcome is mortality at 6 months. This protocol describes an extended follow-up sub-study of the STEPCARE-trial with the main objective to provide detailed long-term outcomes for survivors and caregivers. It will focus on potential neuroprotection and improved recovery for different targets of sedation, temperature, and MAP management at 6 and 12 months post-OHCA.

Methods: All survivors and one caregiver per survivor at selected STEPCARE sites will be invited to participate. Randomization is stratified by site. This sub-study extends the main STEPCARE follow-up at 6 months by undertaking detailed assessments, face-to-face meetings, inclusion of a caregiver, and repeating the assessments at 12 months. Our main outcome for survivors is cognitive function measured by the Montreal Cognitive Assessment, and for caregivers, the caregiver burden measured by the Zarit Burden Interview. Additional outcomes include symptoms of anxiety, depression, post-traumatic stress disorder, fatigue, physical function, life satisfaction, and life impact (disability), assessed by psychometrically robust measures. The estimated sample size is 600. Efforts to improve interrater reliability and decrease missing data are integral to the study design.

Conclusion: These detailed long-term outcomes will explore the possible benefits or risks of fever, sedation, and blood pressure management in post-OHCA survivors. Additionally, this study will explore survivorship after cardiac arrest from various perspectives, including different causes of arrest.

ClinicalTrials.gov: NCT0207942.

Marjaana Tiainen and Naomi Hammond contributed equally to this study.

For affiliations refer to page 10.

1 | Background and Rationale

Cardiac arrest is associated with a high risk of death and neurologic impairment [1, 2]. The Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation (STEPCARE)-trial will compare optimal levels of sedation, temperature management, and mean arterial pressure (MAP) targets for patients admitted to an intensive care unit (ICU) following out-of-hospital cardiac arrest (OHCA) [3–5].

Current treatment recommendations for these interventions are largely based on limited or weak evidence. Guidelines for temperature management after OHCA suggest actively preventing fever [6, 7], based on observational data and low certainty evidence [8]. Clinical practice recommendations for blood pressure management differ, and the optimal target remains unknown [6, 9]. Similarly, the optimal sedation strategy is not well established, with a weak recommendation for "short-acting agents", but with insufficient guidance on depth or duration of sedation [6]. Each of these strategies is hypothesized to offer neuroprotective benefits [6, 10–12]. However, studies assessing long-term effects on patient outcomes, including potential benefits and risks, have yet to be conducted.

In the STEPCARE trial, the primary outcome is mortality at 6 months, and secondary outcomes include functional outcome, measured by the modified Rankin Scale (mRS) and overall health evaluated by the EuroQol Visual Analogue Scale (EQ-VAS) at the same time-point [3–5]. Using crude but recommended measures like the mRS, most post-OHCA survivors have a good outcome, with only 10% having a poor functional outcome [13]. Studies using more detailed measures report that approximately half of the survivors experience mild to moderate cognitive impairment [14, 15], which is associated with decreased health, psychological problems, and reduced societal participation [1, 16]. The main STEPCARE trial does not collect detailed information on cognitive function.

Distressing ICU memories and symptoms of post-traumatic stress disorder (PTSD) are commonly reported after an ICU stay, with a pooled prevalence of 20% for PTSD after cardiac arrest [17]. Although a lighter sedation has been suggested to increase the risk of PTSD, a recent meta-analysis reported no influence on subsequent PTSD by the level of sedation, but the certainty of evidence was low [18]. While symptoms of anxiety and depression after cardiac arrest tend to increase over time, PTSD has been less studied. Consequently, studies with extended follow-up times and a greater focus on PTSD are needed [17].

Limitations in physical function are common after critical illness, particularly among patients with a duration of critical care ≥ 7 days of ICU stay, possibly related to ICU-acquired weakness, neurological impairment, or other factors [19]. A neuroprotective intervention, or reduced sedation that allows for earlier awakening and mobilization, may positively affect physical function and long-term outcomes.

Fatigue is the most reported symptom by cardiac arrest survivors. In stroke and traumatic brain injury, mental fatigue is commonly thought to be associated with acquired brain injury and cognitive impairment. In general ICU survivors, fatigue was associated with prolonged immobilization, malnutrition, ICU length of stay, age, sex [20], as well as physical, cognitive, and mental health symptoms [21].

Families of ICU-survivors may experience the Post Intensive Care Syndrome-Family (PICS-F) [22, 23]. In cardiac arrest, caregiver burden and poorer mental health among caregivers have been linked to worse outcomes for survivors, including poor functional outcomes and cognitive impairment [16]. Improving survivors' outcomes may reduce caregiver strain and improve their well-being.

2 | Objectives

The main objective of this extended follow-up study within the STEPCARE-trial is to provide comprehensive information on long-term outcomes for both survivors and their caregivers in relation to potential neuroprotection and improvements in recovery for different targets of sedation, temperature, and MAP management at 6- and 12-months following OHCA due to various etiologies.

3 | Methods

This manuscript is based on the SPIRIT-PRO extension guidelines for inclusion of patient-reported outcomes in clinical trial protocols [24]. The full protocol is available at: www.stepcare.org/extended-follow.

3.1 | Trial Design and Interventions

This sub-study (ClinicalTrials.gov: NCT0207942) is part of the multi-center, international, parallel group, non-commercial, randomized, factorial, superiority STEPCARE-trial (ClinicalTrials.gov: NCT05564754) with a 2×2×2 allocation to: (I) Sedation: Continuous sedation for 36 h or minimal sedation [4], (II) Temperature: Fever management with or without a TTM device for 72 h [3], and (III) Blood pressure: A MAP target of > 85 mmHg or > 65 mmHg for 72 h [5]. The interventions are described in detail in the main protocols [3–5, 25].

The first STEPCARE patient was recruited in August 2023 with the first 6-month follow-up in February 2024. The last inclusion is expected in 2026, with the last 12-month follow-up due in 2027.

3.2 | Study Setting

Over 60 hospitals across Europe, the Middle East, Asia, New Zealand, and Australia will participate in the STEPCARE trial. Selected sites with resources and experience in follow-up will participate in the extended follow-up sub-study, with randomization stratified by site as per the main trial allocation.

3.3 | Eligibility Criteria

Adults (≥ 18 years) with OHCA due to cardiac or non-cardiac cause (hypoxia, pulmonary embolism, overdose, asphyxia/

TABLE 1 | Inclusion and exclusion criteria of the STEPCARE trial.

Inclusion criteria	Exclusion criteria
Out-of-hospital cardiac arrest	Trauma or hemorrhage being the presumed cause of arrest
A minimum of 20 min of spontaneous circulation without chest compressions	Suspected or confirmed intracranial hemorrhage
18 years of age or older (adults)	On ECMO prior to randomization
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	Pregnancy
Eligible for intensive care without restrictions or limitations	Previously randomized in the STEPCARE trial
Inclusion within 4 h of Return of Spontanoues Circulation	

strangulation or other medical cause) with sustained return of spontaneous circulation ≥ 20 min. All patients randomized at a center participating in the extended follow-up, who survive and provide consent, will be eligible, with no further inclusion or exclusion criteria beyond those for the STEPCARE-trial [3–5], as detailed in Table 1.

For caregivers, eligibility requires living with or having weekly or more frequent contact (in person or via telephone/digital means) with the post-OHCA survivor. Only one nominated caregiver per survivor will be included in the sub-study.

3.4 | Outcomes

The main outcome for the survivors in this sub-study is cognitive function, while for caregivers, the main outcome is caregiver burden. Table 2 presents an overview of exploratory outcomes. The main outcomes for the extended follow-up sub-study will be assessed at 6 months post-OHCA. This timing was chosen based on previous studies indicating that most neurological recovery has occurred by this time [2, 26, 27]. Since other outcomes, such as functional outcome [27] and health [26, 28], may continue to improve, an additional follow-up will be performed 12 months after inclusion in line with current recommendations [29]. The follow-ups should be completed as close to ±14 days of the follow-up date as possible, at both 6 and 12 months.

3.5 | Sample Size

We assume that half of the STEPCARE participants will be eligible for this sub-study ($n = 1750$ of 3500), with an estimated mortality rate of 60%, leaving approximately 700 survivors for follow-up at 6- and 12-months. We expect a missing rate of 10%–15%, with the final sample size estimated at $N = 600$ in total, with $N = 300$ post-OHCA survivors for each of the three intervention groups (temperature, sedation and MAP) according to the factorial design. A priori power calculations and thresholds for minimally important differences are presented in Table 3. With the expected sample size, the power will be close to 100% for all included outcome assessments.

TABLE 2 | Main and exploratory outcomes for the STEPCARE extended follow-up sub-study.

	Post-OHCA survivor	Caregiver
Main outcome	Cognitive function at 6 months	Caregiver burden at 6 months
Exploratory outcomes	Cognitive function at 12 months Mental health symptoms at 6 and 12 months • Depression • Anxiety • Posttraumatic stress disorder Fatigue at 6 and 12 months Physical function at 6 and 12 months Life impact at 6 and 12 months • Disability • Occupational status • Overall health status (at 12 months) • Life satisfaction • Functional outcome (at 12 months)	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 • Overall health status • Life satisfaction

3.6 | Recruitment

All patients included in the STEPCARE-trial at sub-study participating sites are also eligible for this sub-study. Prior to discharge, information about contact details will be collected using a master screening log to increase patient retention. This log will be kept at site and will include essential information, for example, names, addresses, email, and telephone numbers for both the survivor and the caregiver.

TABLE 3 | Power and sample size calculations.

Outcome assessment	Mean	SD	MID	Required sample size	Power by current estimated sample size
MoCA[a] [30, 31]	25	5	2	264 (132 + 132)	1.00
ZBI [16]	15	13	6	208 (104 + 104)	1.00
WHODAS 2.0 (12 items) [32, 33]	15.6	14.7	6	256 (128 + 128)	0.99
HADS anxiety [34–36]	4.6	4.1	2	178 (89 + 89)	1.00
HADS depression [34–36]	3.4	3.7	2	146 (73 + 73)	1.00
MFIS [37–40]	21.1	19.7	8	256 (128 + 128)	1.00
SDMT[a]	−1.05	1.38	0.69	170 (85 + 85)	1.00
PCL-5 [41, 42]	22	18	9	170 (85 + 85)	1.00
WVS life Satisfaction[a]	7.88	1.99	1	168 (84 + 84)	1.00
EQ-VAS[b]	76.1	18.7	9	190 (95 + 95)	1.00

Note: 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 critically ill and other types of acquired 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. Bold text indicates the main outcome for survivors and caregivers.

Abbreviations: EQ-VAS = EuroQol Visual Analogue S; ES = Effect size; HADS = Hospital Anxiety and Depression Scale; MFIS = Modified Fatigue Impact Scale; MID = Minimally Important Difference; MoCA = Montreal Cognitive Assessment; PCL-5 = Post-Traumatic Stress Disorders Checklist updated for Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5); SD = Standard Deviation; SDMT = Symbol Digit Modalities Test;

WHODAS = World Health Organization Disability Assessment Schedule; WVS Life satisfaction = World Value Survey life Satisfaction; ZBI = Zarit Burden Interview.

[a]Information based on unpublished data from the TTM2-trial.

[b]Information for caregivers based on a Swedish normative population ($n = 25{,}867$) [43].

3.7 | Blinding

Outcome assessors conducting the structured follow-up will be blinded to group allocation. Given the factorial design of the study, it can be assumed that survivors and caregivers will have minimal awareness of the complex combinations of allocation groups. However, since they may notice information during the patients' ICU stay that could reveal the allocation group, outcome assessors will inform the survivors and caregivers that they should not reveal any related information regarding the trial treatment to them.

3.8 | Data Collection Methods

Eligible survivors for this sub-study will be invited to face-to-face follow-up at 6- and 12-months, together with a relative or close friend (preferably the allocated caregiver), either as a clinical visit, home visit, or by a web-based digital meeting. Approximately 2–4 weeks prior to the follow-up, questionnaires will be sent to the survivor and caregiver to complete. At the follow-up, the blinded outcome assessors will review the questionnaires and perform a structured interview along with performance-based assessments.

The blinded outcome assessors may have a professional background as a nurse, occupational therapist, physical therapist, physician, psychologist, or other allied health care specialists. All outcome assessors are trained for the study and provided with a written trial manual that includes detailed guidelines for assessment conduct. During the trial, they have access to support from the trial follow-up coordinating team.

To prevent missing data, efforts will be made to facilitate participation among survivors, including for example, the use of reminders, the master screening log, and alternative modes of follow-up, if necessary, as follow-up by telephone or postal mail. If needed, an authorized interpreter will be used. For participants unable to attend due to, for example, severe cognitive impairment, data may be collected through a proxy, except for the outcomes related to mental health and life satisfaction that are then not collected.

3.9 | Outcome Measures

The outcome measures for the extended follow-up sub-study are presented below, with more detailed information available in Table 4. During the sub-study's initial development, patient and caregiver input on the selected questionnaires was 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 that the overall burden for completion was acceptable. Two patient representatives also provided input and support for the Australian grant submission, including the proposed extended follow-up.

3.9.1 | Main Outcome Measure for the Survivors

Montreal Cognitive Assessment (*MoCA*) is recommended for cognitive screening after cardiac arrest [13], demonstrating excellent

TABLE 4 | Detailed information on outcome assessments at 6 and 12 months.

Main outcome domain	Specific outcome domain	Respondent		Outcome measure	Abbreviation	Administration			Scoring
		Survivor	Caregiver			Clinician reported	Performance based	Self-reported	
Cognitive function	Global cognition	X		Montreal Cognitive Assessment	MoCA		X		10 items, total score of 0–30 (lower worse). Scores < 26 indicates cognitive impairment.
	Mental processing speed	X		Symbol Digit Modalities Test	SDMT		X		Raw scores 0–110 (lower worse), 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.
Fatigue	General impact of fatigue	X		Modified Fatigue Impact Scale	MFIS			X	Recall period 4 weeks, 21 items, score range 0–4 (higher worse), total score 0–84. Scores > 37 indicates fatigue. Three subscales: physical, cognitive, and psychosocial impact of fatigue.
Mental health	Anxiety and depression	X	X	Hospital Anxiety and Depression Scale	HADS			X	Recall period 4 weeks, 14 items (7 for anxiety and 7 for depression), score range 0–3 (higher worse), scores are calculated into two subscales (depression and anxiety), with a total score for each subscale 0 to 21. The cut off is > 7.
	Post Traumatic Stress	X	X	Post-Traumatic Stress Disorders Checklist, DSM-5, civilian version	PCL-5			X	Recall period last month, 20 items, score range 0–4 (higher worse), total score 0–80. The cut-off for significant symptoms of PTSD is 33. 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.
	Caregiver burden		X	Zarit Burden Interview	ZBI			X	22 items, score range 0–4, total score 0–88. A score > 20 indicates caregiver burden; with little to moderate burden (21–30), moderate to severe burden (41–60), severe burden (61–88).
Physical function	Lower extremity strength	X		Timed Stands Test	TST		X		Measures the time in seconds (with one decimal) to rise 10 times, with the maximum time 60 s (used if the participant is unable). Based on age and gender normative data three categories are generated: normal TST, abnormal TST or unable.
	Upper extremity strength[a]	X		Jamar hand grip dynamometer	JAMAR		X		Three trials with each hand. Raw scores for the right vs. left hand used to calculate a mean of the three trials and compared with age and gender normative data. Values > 2 SD of the mean are considered impaired.

(Continues)

TABLE 4 | (Continued)

Main outcome domain	Specific outcome domain	Respondent		Outcome measure	Abbreviation	Administration			Scoring
		Survivor	Caregiver			Clinician reported	Performance based	Self-reported	
Life impact	Total disability	X	X	World Health Organization Disability Assessment Schedule 2.0	WHODAS 2.0			X	36 items version for survivors and 12 items version for caregivers. Recall period 30 days. Complex scoring performed by a SPSS syntax, with a total disability score, range 0–100 (higher worse). For the 36 item version subscales for cognition, mobility, personal care, relationship, daily activities, participation are generated with the same score range (0–100).
	Life Satisfaction	X	X	World Value Survey Life Satisfaction item	WVS Life Satisfaction			X	VAS scale of 1–10 (lower worse). The norm median is approximately 7 but differs between countries.
	Functional outcome[b]	X		Modified Rankin Scale	mRS	X			Hierarchical ordinal scale including 7 categories from no symptoms to dead, range 0 to 6 (higher worse).
	Overall health status[b]	X	X	EQ-5D 5 level response version and EQ Visual Analogue Scale	EQ-5D-5L EQ-VAS			X	The EQ-5D-5L includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression measured on a 5-level scale that range from no problems (1) to extreme problems (5). The dimension scores can also be converted to a utility index (EQ index), range −0.593 to 1.00 (higher = better health). The EQ VAS is scored separately, range 0 to 100 (lower worse). An EQ-VAS score ≤ 70 indicates health problems.
	Ability to work	X	X	Occupational status at time of the cardiac arrest and occupational status at time of the follow-up	RTW			X	Collected 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, on sick leave, retired (due to age), unemployed/retired (health reasons), unemployed (other reasons) or other (specify).

[a]Only selected sites.
[b]At 6-months included as a part of the main STEPCARE-trial.

TABLE 5 | Patient and caregiver characteristics.

	Respondent				
	Survivors			Caregivers	
	Time-point for data collection				
	Hospital stays*	6-months	12-months	6-months	12-months
Sex	X			X	
Age	X			X	
Pre-arrest clinical frailty score by the Clinical Frailty Scale	X				
Bystander CPR performed	X				
Time to return of spontaneous circulation	X				
Cause of cardiac arrest[a]	X				
Mobilization during the intensive care stay[b]	X				
Delirium during the intensive care stay[c]	X				
Native language		X			
Neurological disease		X	X		
Diabetes		X	X		
Hypertension		X	X		
Education		X		X	
Living situation		X			
Participation in rehabilitation or other support		X	X	X	X
Previous psychiatric history		X			
Sleep less/more/the same by two questions from the Mental Fatigue Scale		X	X		
Relationship to the post-OHCA survivor[#]				X	
If witnessed the cardiac arrest/performed CPR/were present during the ICU stay				X	

Abbreviations: ACS = Acute Coronary Syndrome; CPR = Cardiopulmonary Resuscitation; ICU = Intensive Care Unit; OHCA = Out-of-Hospital Cardiac Arrest; STEMI = ST-elevation myocardial infarction; VF = Ventricular Fibrillation; VT = Ventricular Tachycardia.
*As a part of the main STEPCARE-trial.
[a]Cause of arrest is collected as cardiac (option: STEMI, NSTEMI/ACS, Arrhythmia (non-ischemic VT/VF), Heart failure, other cardiac) or non-cardiac (options: hypoxia, pulmonary embolism, overdose, asphyxia/strangulation, other medical cause).
[b]Daily during the first 5 days by the Intensive care Mobility Scale (IMS).
[c]Daily during the first 5 days by a standardized assessment either the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) based on at least two observations a day.

sensitivity [44, 45]. In the TTM2 trial, the MoCA was found to be feasible and well accepted, with 91% of participants in the follow-up completing the MoCA [14]. A full MoCA [46] requires a face-to-face visit, either in person or via a web-based digital meeting. Alternatively, a modified telephone version (T-MoCA) can be used [47]. For analyses combining the full MoCA and the T-MoCA, the T-MoCA will be converted to a 30-item MoCA [14, 47].

3.9.2 | Main Outcome Measure for the Caregivers

Zarit Burden Interview (*ZBI*) captures caregiver burden and the consequences of caregiving on various aspects such as health, psychological wellbeing, finances, social life, and relationship [48]. ZBI has been used in cardiac arrest [16, 49]. While the psychometric properties of ZBI have not been studied in cardiac arrest populations, they have been extensively explored in similar groups experiencing cognitive problems, such as dementia and acquired brain injury [50].

3.9.3 | Additional Outcome Measures

Modified Rankin Scale (*mRS*) is recommended to assess overall functional outcome post-OHCA [29], and is a secondary outcome measure in the main STEPCARE-trial at 6-months [3–5]. In the extended follow-up sub-study, the mRS will also be repeated at 12-months.

EQ-5D 5 level version (*EQ-5D-5L*) is recommended for patient-reported overall health assessment following cardiac arrest [29], and included in the main STEPCARE-trial at 6-months [3–5]. As a part of the extended follow-up study, the EQ-5D-5L and the EQ-VAS will also be repeated at 12-months for survivors and added for caregivers at both 6- and 12-months.

Symbol Digit Modalities Test (*SDMT*) is recognized as one of the most sensitive assessments of cognitive function and is used to complement the MoCA by providing additional information on processing speed. The combined use of MoCA and SDMT for OHCA demonstrated an increased sensitivity in cognitive screening compared to either assessment used alone [45]. However, the SDMT requires a physical visit and is not suited for other modes of follow-up.

Hospital Anxiety and Depression Scale (*HADS*) is a patient-reported questionnaire designed to assess symptoms of anxiety and depression. It has been widely used in OHCA contexts [17, 51], and is incorporated in sub-studies of the TTM [34] and TTM2-trials [52, 53].

Post-Traumatic Stress Disorders Checklist updated for DSM-5 (*PCL-5*) will be employed for patient-reported assessment of PTSD, encompassing all aspects according to DSM-5 criteria [41, 54]. The PCL-5 has been used for OHCA-patients [42], including a sub-study of the TTM2 trial (ACTRN12619001038189).

Modified Fatigue Impact Scale (*MFIS*) assesses patient-reported fatigue, encompassing both impact and type of fatigue (physical, cognitive, psychosocial), and has been used in cardiac arrest patients [37, 38].

Timed Stands Test (*TST*) is a performance-based measure of lower extremity strength and general physical function, used for OHCA patients in the previous TTM2 trial [55]. The TST can only be conducted for those participating in a physical meeting.

Jamar Hydraulic Hand Dynamometer (*Lafayette Instrument Europe*, *Loughborough*, *UK*) is employed to assess hand grip strength. It has been validated and extensively used in various patient populations [56] and is included in one cardiac arrest trial [57]. Jamar can only be used for those participating in a physical visit and requires a Jamar dynamometer, limiting its use to a selected number of sites.

World Health Organization Disability Assessment Schedule (*WHODAS*) *2.0* is a standardized assessment that evaluates outcomes related to activity and participation, based on the WHO's International Classification of Functioning, Disability, and Health (ICF). It has been previously employed and psychometrically evaluated in general ICU populations, including cardiac arrest [32]. The 36-item version of the WHODAS 2.0 generates a total disability score and six individual domain scores, includingcognition, mobility, self-care, relationships, daily activities, and participation. For the caregivers, a modified 12-item version of the WHODAS 2.0 will be used, generating a total disability score only.

Ability to work is a part of the WHODAS 2.0, but more detailed information on occupational status at the time of OHCA and at the time of the follow-up will be collected separately. Additionally, the date of return to work will be recorded.

Life satisfaction will be assessed using a single question with a VAS scale (1–10) from the World Value Survey. This question was previously used in the TTM2 trial [55]. Country-specific normative data are available.

3.9.4 | Characteristics

Characteristics of participants will be collected as a part of the main STEPCARE-trial for survivors, with additional information collected at the 6- and 12-month follow-up for survivors and caregivers, as presented in Table 5.

3.10 | Data Management

Trial data will be collected in an electronic case report form (eCRF). STEPCARE participants are assigned a trial number and pseudonymised.

3.11 | Statistical Methods

This substudy adheres to the general statistical analysis plan for the main STEPCARE-trial [25]. The main outcome for survivors (MoCA 0–30) will be analyzed separately for each intervention, using mixed-effects linear regression adjusted for site (random intercept) and the other interventions (fixed effects). Further analyses will be performed adjusted for age (continuous) and sex (male/female). Additional supporting analyses will be conducted by including deceased patients (assigned a MoCA score worse than possible for survivors, −1) to confirm that the randomized design is not influenced by survival bias. The main outcome for the caregivers (ZBI 0–88) will be analyzed, using the same methods as for the main outcome of survivors. Transformation of the MoCA and ZBI scores will be performed if the model's assumption for linear regression is violated.

Analyses of exploratory outcomes will be hypothesis-generating only and performed similarly to the main outcome analyses. If the model assumptions of the regression model are violated, categorization of variables will be considered by using pre-specified cutoff values as specified in Table 3. Associations between survivors' and caregivers' outcomes will be explored.

Missing data will be presented descriptively, and we will consider reporting sensitivity analyses and/or multiple imputation according to recommendations on how to handle missing data [58]. During the data analyses, information on the allocation group will be available. Analyses will be two-sided. The results will be published in peer-reviewed journals.

3.12 | Monitoring

The follow-up data will be reviewed regularly by the central follow-up coordinating team to ensure data quality. This

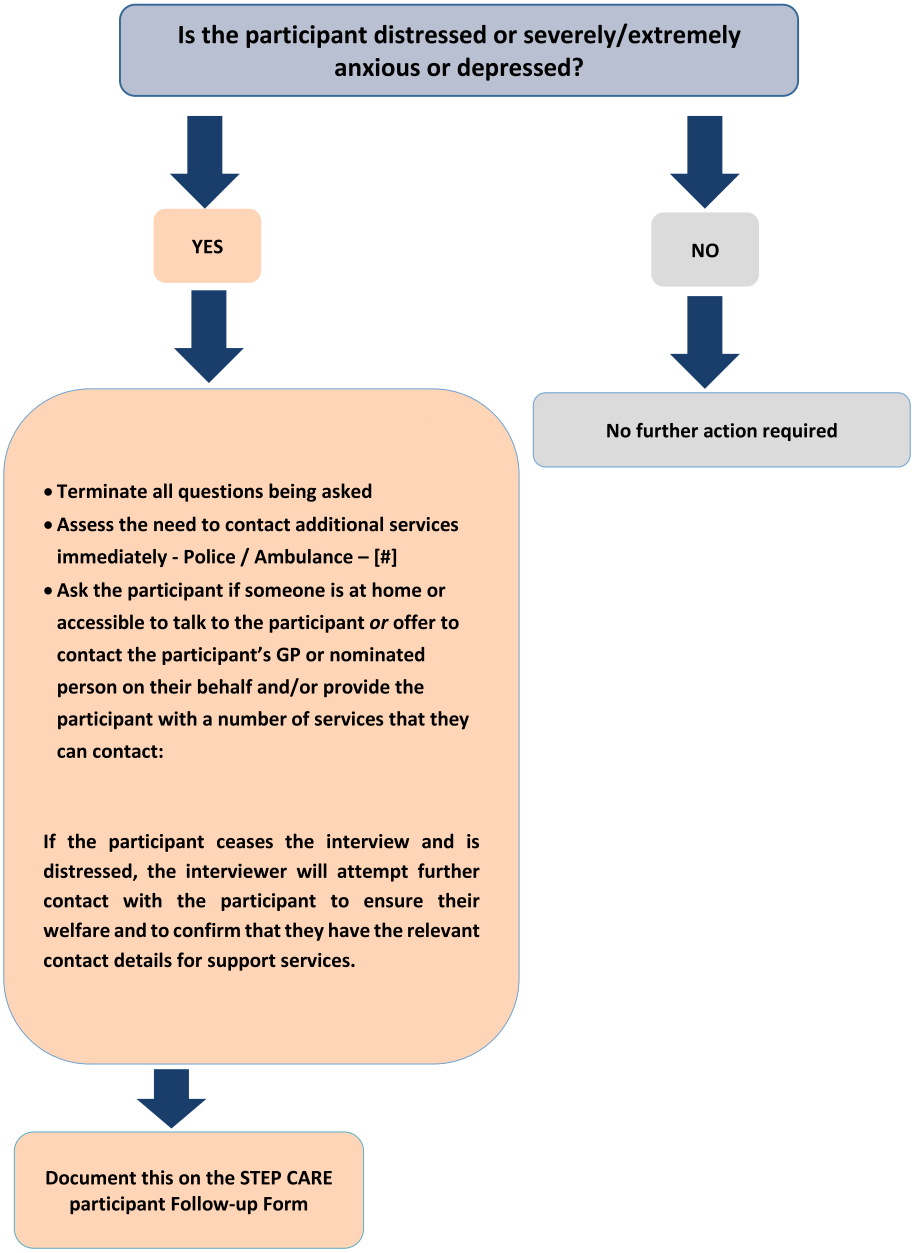

FIGURE 1 | Escalation plan.

approach will help facilitate the retention of participants by increasing outreach and enabling adjustments, if necessary, during the study.

3.13 | Ethics

Ethics applications have been approved by relevant ethics boards in participating countries according to local regulatory requirements and good clinical practice (GCP). The consent process for the trial aligns with local regulatory approvals but involves written and oral information about the trial. Caregivers are asked to provide consent separately for the caregiver follow-up. All trial data will be securely stored according to local requirements and the European regulations Directive 2001/20/EU of the European Parliament and of the Council and according to the General Data Protection Regulation 2016/679. If a participant is distressed or severely anxious or depressed during the follow-up, the outcome assessors will follow the escalation plan, as presented in Figure 1.

4 | Discussion

This extended follow-up sub-study of the STEPCARE-trial will report on detailed outcomes in relation to three different clinical interventions and include a comprehensive perspective on long-term sequelae for both the survivors and their caregivers, also adding significant information on survivorship after OHCA due to various etiologies.

Cognitive function reflects one of the most significant outcomes among survivors of cardiac arrest reported by patients, partners, and researchers [29], and will add important information

to the STEPCARE trial. Additionally, the large sample size and the psychometrically robust instruments used will enable additional analyses to explore changes in cognitive function between 6- and 12-months and associations with patient and caregiver characteristics.

The in-depth focus on the caregiver impact of cardiac arrest will enable detailed investigations of the caregivers' experience at 6- and 12-months in relation to the burden of care, mental health, and life impact of caring for and living with a post-survivor who has been randomized to different targets of sedation, temperature, and MAP management.

The top 10 research priorities in cardiac arrest, determined in partnership with survivors and family members, include a strong focus on survivorship [59]. While previous studies mainly include post-OHCA survivors due to a cardiac cause only, this extended follow-up study will explore survivorship for patients with OHCA of different etiologies, providing opportunities for novel subgroup analyses of differences in outcome.

A strength of this study is the multicenter design; however, this may also increase the risk of higher interrater variability and missing data. Several strategies to improve comparability (inter-rater reliability) are included in the study design, such as structured assessments, training of outcome assessors, central monitoring, and ongoing support. The training sessions provided by the trial coordinating team are also an important strategy to decrease avoidable missing data.

5 | Summary

The detailed outcomes that will be investigated in the STEPCARE extended follow-up sub-study will contribute to exploring the possible benefits or risks of the three clinical interventions, which could improve long-term outcomes in OHCA-survivors. The large international data set will facilitate the exploration of survivorship after OHCA from various perspectives, including the family perspective and different causes of arrest.

Author Contributions

G. Lilja drafted the manuscript together with M. Tianinen and N. Hammond. All other authors contributed to the study design and critically revised the manuscript. All authors approved the final version.

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Conflicts of Interest

Matthew P Wise reports: Diagnostics for the Real World (personal fee, Advisory Board), NICE Advice Service (personal fee, Clinical Expert) and INhaled Sargramostim In Groups of Healthy and inTensive care unit patients to study Alveolar Macrophage function—INSIGHT AM Newcastle University (Chair DSMB). No other authors report any conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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