STEPCARE Trial Protocol - Summary of Changes

Superseded Document:	**STEPCARE Trial Protocol Version 1.1, 17 February 2023**
New Document:	**STEPCARE Trial Protocol Version 1.2, 25 April 2024**
Additions are in red text, deletions are ~~strikethrough text~~	

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
General	General minor administrative changes have been made throughout document		
Title page	Version number: 1.1, 17 February 2023	Version number:1.2, 25 April 2024	Administrative change for version control
Title page – header	Version number: 1.1	Version number:1.2	Administrative change for version control
Title page	**Sponsor:** Region Skåne – Skånes Sjukhus Nordväst - Helsingborgs Hospital S Vallgatan 5, 251 87 Helsingborg, Sweden	**Sponsor:** Region Skåne – ~~Skånes Sjukhus Nordväst~~ - Helsingborgs Hospital S Vallgatan 5, 251 87 Helsingborg, Sweden	Administrative change
Title page (Page 1)	**Study Chair**: Niklas Nielsen, MD, PhD, DEAA, EDIC Department of Anesthesiology and Intensive Care, Helsingborg Hospital Lund University, Faculty of Medicine	**Study Chair:** Niklas Nielsen, MD, PhD, DEAA, EDIC Department of Anesthesiology and Intensive Care, Helsingborg Hospital Department of Clinical Sciences, Lund University, Faculty of Medicine	Administrative change
Overview	**Last paragraph:** 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	**Last paragraph:** 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	Administrative change

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
	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.	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, and a common statistical analysis plan will be published.	
2.2 Temperature target: TEMP-CARE	N/A	The INTREPID (Impact of Fever Prevention in Brain Injured Patients) trial is an international multicenter randomized controlled clinical trial that compared the use of a surface cooling device to prevent and treat fever. The study included 667 patients treated in the ICU following either ischaemic stroke, intracerebral haemorrhage or traumatic brain injury. The study was stopped prematurely for futility. The results are not yet published but are available on the ClinicalTrials.goc website (https://clinicaltrials.gov/study/NCT02996266?tab=results). It appears that whilst the study intervention decreased fever burden of patients the intervention did not improve functional outcome.	Updated section based on recent publications and current evidence
2.3 Mean arterial pressure target: MAP-CARE	N/A	The current treatment Guidelines from the European Resuscitation and the European Society of Intensive Care Medicine suggest targeting a MAP higher than 65 mmHg. On the other hand, the recently published American Heart Association Scientific Statement for post cardiac arrest care advocate a blood pressure	Updated section based on recent publications and current evidence

STEPCARE Trial Protocol - Summary of Changes

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
		target >80 mm Hg unless the patient has advanced cerebral monitoring in place, defined as monitoring of intracranial pressure, brain tissue oxygen and cerebral blood flow autoregulation. It is unclear to what extent this form of monitoring is used clinically.	
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 **	~~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 **	Updated wording of the inclusion criteria
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	1.Trauma or being hemorrhage as presumed cause of arrest 2.Suspected or confirmed intracranial hemorrhage 3. On ECMO prior to randomization 4. Pregnancy 5. Previously randomized in the STEPCARE trial	Updated exclusion criteria Changed order of criteria

STEPCARE Trial Protocol - Summary of Changes

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
4.4 Note on differences between in and out-of-hospital Cardiac arrest	**Last Paragraph:** 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.	**Last Paragraph:** 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. Cardiac arrests in outpatients in for example a hemodialysis unit, in dental care, at a doctors office etc. are considered out-of-hospital.	Clarification of out-of-hospital cardiac arrest locations
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.	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 admitted to the participating ICU, 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.	Administrative update and clarification
6.2 Interplay between this trial and other recent or ongoing trials on post cardiac arrest care	**Second Paragraph:** 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	**Second Paragraph:** The TAME trial (NCT03114033) ~~has finished including patients and should be~~ was published in ~~the first half of~~ 2023. The trial ~~compares~~ compared moderate hypercapnia (PaCO2 6.7-7,3 kPa) to	Updated section based on recent publications and evidence

STEPCARE Trial Protocol - Summary of Changes

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
	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	normocapnia (PaCO2 4.5-6.0 kPa) in 1700 patients treated in the ICU after OHCA. There was no difference in outcome between the groups and this trial will not affect the conduct of STEPCARE. ~~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	

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
	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.	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~~	

STEPCARE Trial Protocol - Summary of Changes

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
		~~change the STEPCARE protocol.~~	
8.0 Data collection	Individualized data collection points	eCRF data collection points summarised in a table format	eCRF has been updated. Data summary in table format is reflective of what will be collected from participants
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	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 (deferred consent or consent to continue), since the interventions must be regarded as an emergency procedure and must be started as soon as the participants are admitted to the hospitals.	Clarification update
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 trial will be externally monitored by national monitoring offices coordinated by the clinical trial manager and Clinical Studies Sweden, Forum South or by the National Sponsor remotely and/or on-site.	Clarification and administrative update
13. Publication of Data (last paragraph)	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	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	Clarification and administrative update

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
	manuscripts. A detailed authorship plan will be decided upon the first interim analysis.	detailed authorship plan will be decided upon before the first interim analysis and posted on www.stepcare.org.	
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 nordvast- 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.	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 nordvast~~ 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.	Clarification and administrative update
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)	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 Grants from the South Swedish Health Region	Clarification and administrative update including all funders

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
	Health Research Council of New Zealand	The Academy of Finland Finska Läkaresällskapet Sigrid Juselius Stiftelse Medicinska Understödsföreningen Liv och Hälsa Svenska Kulturfonden Stiftelsen Dorothea Olivia, Karl Walter och Jarl Walter Perkléns minne Medical Research Future Fund (Australia) Health Research Council of New Zealand Luxembourg funding body: Clinical Research Programme Directorate of Health Ministry of Health and Social Security	
18. References		New references added	Updated references
17.1 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,	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,	Administrative update

Changes to Protocol [Page – untracked document]	Original Text	New/Amended Text	Reason/Justification for Change
	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	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 Matt P Wise, Intensive Care, Cardiff, United Kingdom Frances Bass, The George Institute, Sydney, Australia	
18. References		New references added	Updated references