**Title**

The effect of sedation, temperature management and blood pressure targets on cerebral oximetry, transcranial doppler, optic nerve sheath diameter, and pupillometry in comatose survivors of cardiac arrest: protocol for neuromonitoring sub-studies in the STEPCARE randomised controlled trial.

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**Authors (list to be finalised)**

1. Peter McGuigan\*

Regional Intensive care Unit, Royal Victoria Hospital, Belfast, UK.

Wellcome-Wolfson Institute for Experimental Medicine, Queen’s University Belfast, UK.

Peter.mcguigan@belfasttrust.hscni.net

Telephone; 0044 2890 633286

Fax; 0044 2890 236167

ORCID 0000-0001-5766-990X

\*Corresponding author

1. Yew Woon

Cardiac Intensive Care Unit, Tan Tock Seng Hospital, Singapore.

Yong Loo Lin School of Medicine, National University of Singapore.

Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

1. Anders Aneman

Liverpool Hospital, Sydney South West Local Health District, Sydney, Australia.

South Western Clinical School, University of New South Wales, Sydney, Australia. The Ingham Institute for Applied Medical Research, Liverpool, Australia.

1. Chiara Robba

IRCCS Policlinico San Martino, Genova, Italy.

Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Italy.

1. Toby Betteridge

Intensive Care Unit, Christchurch Hospital, Christchurch, New Zealand.

1. Josef Dankiewicz

Department of Clinical Sciences Lund, Lund University, Lund, Sweden.

Department of Cardiology, Skåne University Hospital, Lund, Sweden.

1. Bruno M Fernandes

Adult Critical Care, University Hospital of Wales, Cardiff, UK.

1. Mattias Haenggi

Institute of Intensive Care Medicine, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland.

1. Matthias P Hilty

Institute of Intensive Care Medicine, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland.

1. Manuela Iten

Department of Intensive Care Medicine, University Hospital Bern, University of Bern, Freiburgstrasse, CH-3010 Bern, Switzerland.

1. Janus Christian Jakobsen

Copenhagen Trial Unit, Centre for Clinical Intervention Research, Capital Region of Denmark.

Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Denmark.

1. Thomas R Keeble

Essex Cardiothoracic Centre, Mid and South Essex NHS trust, Basildon, Essex, UK.

Medical Technology Research Centre, Anglia Ruskin School of Medicine, Chelmsford, Essex, UK.

1. Anja Levis

Department of Anesthesiology and Pain Medicine, University Hospital Bern, University of Bern, Freiburgstrasse, CH-3010 Bern, Switzerland.

1. Marion Moseby-Knappe

Department of Clinical Sciences Lund, Lund University, Lund, Sweden.

Department of Neurological Rehabilitation, Skåne University Hospital, Lund, Sweden.

1. Alistair Nichol

University College Dublin Clinical Research Centre, St Vincent’s University Hospital, Dublin, Ireland.

The Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia.

The Alfred Hospital, Melbourne, Australia.

1. Alastair Proudfoot  
   Barts Heart Centre, London, UK.   
   Queen Mary University of London, London, UK.
2. Manoj Saxena

St, George Hospital and The George Institute for Global Health, University of New South Wales, Sydney, Australia.

1. Markus B. Skrifvars

Department of Emergency Care and Services, University of Helsinki, Finland.

Helsinki University Hospital, Helsinki, Finland.

1. Judith White

Centre for Healthcare Evaluation, Device Assessment and Research, Cardiff and Vale University Health Board, Cardiff, UK.

1. Matt P Wise

Adult Critical Care, University Hospital of Wales, Cardiff, UK.

1. Niklas Nielsen

Clinical Sciences Lund, Lund University, Lund, Sweden.  
Department of Anesthesiology and Intensive Care Medicine, Helsingborg hospital, Helsingborg, Sweden.

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**Abstract**

**Introduction**

The STEPCARE trial (NCT05564754) will randomise 3500 comatose survivors of cardiac arrest to sedation, temperature management, and blood pressure targets. These interventions may modify cerebral metabolic rate and cerebral blood flow, potentially influencing cerebral oxygenation and intracranial pressure (ICP). We aim to assess the effects of these interventions on multimodal neuromonitoring modalities including regional cerebral oximetry (rScO2), Pulsatility Index (PI, an index derived from cerebral blood flow velocities measured using transcranial Doppler, TCD), optic nerve sheath diameter (ONSD), non-invasive estimates of ICP and quantitative pupillary light reflex (q-PLR).

**Methods**

In addition to routine radiology, neurophysiology and biomarkers, we will conduct a series of neuromonitoring sub-studies. These will record multimodal monitoring data, including rScO2, ONSD, PI, non-invasive estimates of ICP and q-PLR at baseline, 24, 48 and 72 hours. Pulsatility Index will be calculated from TCD flow velocities (peak systolic flow velocity – end diastolic flow velocity)/mean flow velocity. We will use PI and ONSD to derive non-invasive estimates of ICP.

**Results**

We will report the difference in neuromonitoring data between intervention groups. We will model the relationship between neuromonitoring data and mortality and functional outcome (assessed using modified Rankin Scale) at 6 months using regression models.

**Conclusions**

As part of the STEPCARE trial, we will examine the effects of the interventions on multimodal neuromonitoring and the association between neuromonitoring values and mortality and functional outcomes.

**Key words**

Cardiac arrest

Cerebral oximetry

Optic nerve sheath diameter

Transcranial Doppler

Pupillometry

**Introduction**

In Europe, out of hospital cardiac arrest (OHCA) is the third commonest cause of death with an annual incidence of 84 per 100,000 population. [1,2] Mortality is high with just 8% of patients surviving to hospital discharge. [2] For those admitted to ICU following OHCA, two thirds of deaths are primarily attributable to hypoxic ischaemic encephalopathy (HIE).[3] The majority of patients have life sustaining therapy withdrawn based on predicted poor neurological outcome. [4] One in five survivors suffer from moderate to severe disability. [4]

Currently, the ability to ameliorate primary brain injury that occurs at the time of cardiac arrest is limited. However, optimising cerebral oxygenation and reducing intracranial pressure (ICP) may limit secondary brain injury. [5] The STEPCARE trial (NCT05564754) will assess the effect of depth of sedation, temperature management, and blood pressure targets on mortality following OHCA. These interventions may modify cerebral metabolic rate and cerebral blood flow, potentially influencing cerebral oxygenation, ICP, and HIE. [6,7]

Recently, the American Heart Association identified transcranial doppler (TCD), optic nerve sheath diameter (ONSD), and quantitative pupillometry as promising areas for research in cardiac arrest survivors. [8] These may provide surrogate measures of ICP, prompting invasive ICP monitoring or use of pharmacological and non-pharmacological ICP lowering therapies. [8] Similarly, there have been calls for further research into cerebral oximetry following cardiac arrest. [9] However, there is currently insufficient evidence to support their use in clinical decision making. [10]

In addition to guiding therapy, neuromonitoring may identify patients at higher risk of poor outcomes [8,10]. Of these neuromonitoring modalities, only automated pupillometry is included in current neuroprognostication guidelines. [11,12]

**Objectives**

We aim to assess the effects of sedation, temperature management and blood pressure targets separately on regional cerebral oximetry (rScO2), Pulsatility Index (an index of cerebral blood flow velocities measured using TCD), optic nerve sheath diameter (ONSD), non-invasive estimates of ICP and quantitative pupillary light reflex (q-PLR) in comatose survivors of OHCA. We may also evaluate other neuromonitoring modalities where these are routinely recorded at sites. This will be achieved in a series of neuromonitoring sub-studies conducted as part of the STEPCARE trial.

We hypothesise that:

* Continuous sedation, in comparison to minimal sedation, results in higher rScO2, lower Pulsatility Index, lower ONSD, lower non-invasive estimated ICP, and higher q-PLR at 72 hours
* , lower Pulsatility Index, lower ONSD, lower non-invasive estimated ICP, and higher q-PLR at 72 hours, and
* , lower Pulsatility Index, lower ONSD, lower non-invasive estimated ICP, and higher q-PLR at 72 hours.
* There is an association between low rScO2, raised Pulsatility Index, raised ONSD, raised non-invasive estimates of ICP and low q-PLR at 72 hours and mortality and poor neurological outcome following OHCA.

**Methods**

**Trial design**

The STEPCARE trial (NCT05564754) is a multicentre, randomised, factorial trial in which sedation, temperature management, and blood pressure targets will be studied in 3,500 comatose survivors of OHCA. The STEPCARE protocol is available at <https://stepcare.org/protocol>. In brief, randomisation will be performed using permuted blocks of varying size, stratified by site. The clinical team responsible for participant care will be aware of treatment allocations. Outcome assessors, those who conduct prognostication assessments, statisticians, steering group writers of the manuscript and the data safety monitoring committee will be blinded as to the treatment allocation. Trial Management Group composition, Data Monitoring Committee composition, role and reporting structures and monitoring plan are outlined in the STEPCARE protocol.

**Ethics and consent**

The trial protocol (including sub-studies) has been approved by the ethics committees in each participating country. The trial will recruit comatose survivors of OHCA. Written informed consent will be obtained from a legal surrogate, deferred or waived depending on circumstances and legal requirements within each jurisdiction. Deferred informed consent will be obtained if patients regain capacity.

**Participants**

**Eligibility criteria**

Adult patients (≥ 18 years) who experience an OHCA with return of spontaneous circulation (ROSC) will be eligible if they meet all the inclusion and none of the exclusion criteria outlined in Table 1.

**STEPCARE Interventions**

In the STEPCARE trial, patients will be randomised to:

1. Continuous sedation to a target Richmond Agitation Sedation Score of -4 to -5 versus minimal sedation until 36 hours after randomisation.
2. Fever management with a feedback device versus fever management without a device until 72 hours after randomisation. Patients randomised to fever management with a feedback device will have a device applied and set at 37.5°C when core body temperature ≥37.8°C.
3. Target MAP of >85 mmHg versus >65 mmHg until 72 hours after randomisation.

**STEPCARE Outcomes**

Participants will be followed up for six months to assess survival, functional outcome and health related quality of life. The primary outcome measure is all-cause mortality 6 months after randomisation. Functional outcome will be assessed using modified Rankin Scale (mRS)-scale, dichotomised as good (mRS 0-3) or poor (mRS 4-6) (Supplementary Appendix).

**Neuromonitoring sub-studies**

We will conduct a series of observational sub-studies outlined below, additional neuromonitors may be evaluated at sites where they form part of usual care. Sites with the capacity and capability to deliver multimodal neuromonitoring will be eligible to participate in the neuromonitoring sub-studies. Patients in whom neuromonitoring is not technically feasible will be excluded from individual sub-studies. Patients with absent acoustic windows will be excluded from the TCD sub-study. Patients with cataracts will be excluded from the pupillometry sub-study. No additional monitoring or adverse event reporting will be undertaken as part of the neuromonitoring sub-studies. The neuromonitoring sub-study writing committee will be presented with aggregate data after the follow-up of the last recruited patient.

**Primary Outcome Measure**

We will explore the effect of sedation, temperature management and blood pressure targets on neuromonitoring modalities.

**Cerebral oximetry sub-study:** We will measure rScO2 continuously for up to 72 hours post randomisation using any CE marked near infrared spectroscopy device. The primary outcome measure will be rScO2 at 72 hours.

**Transcranial doppler sub-study:** We will use ultrasound to measure Middle Cerebral Artery (MCA) mean flow velocity (mFV), peak systolic flow velocity (sFV), end diastolic flow velocity (dFV). Values will be averaged over at least 5 cardiac cycles. [13] Paired blood pressure (systolic, diastolic and mean arterial pressure) will be recorded. The primary outcome measure will be Pulsatility Index defined (sFV- dFV)/mFV at 72 hours.

**Optic nerve sheath diameter sub-study:** We will measure ONSD using ultrasound in the 30o head up position. Measurements will be obtained 3 mm behind the retina. Two sets of axial and sagittal measurements will be performed, and the mean of these four values will be taken for each eye. The primary outcome measure will be ONSD at 72 hours.

**Automated pupillometry:** We will assess quantitative pupillary response using any CE marked pupillometer. Two measurements will be taken, and the lowest value recorded in keeping with previous studies. [14] q-PLR defined as percentage reduction in pupillary size at 72 hours.

All measurements will be taken bilaterally. The observation period will commence immediately after randomisation until 72 hours post randomisation. However, this may be delayed until the patient has completed the required diagnostic work-up and is admitted to ICU. Measurements will be performed at baseline, 24, 48 and 72 hours post randomisation (±8 hours). Measurements will be discontinued in cases of withdrawal of life sustaining therapy, diagnosis of death using neurological criteria, or where patients are extubated before 72-hour intervention period. Where interventions are reinstituted in the event of re-intubation/re-sedation within 72 hours, measurements will resume.

**Secondary Outcome Measures**

Secondary outcome measures are presented in Table 2.

**Transcranial doppler sub-study:** we will record rates of pathologically low or high MCA flow velocities (Table 1). We will use two methods to provide non-invasive estimates of ICP and cerebral perfusion pressure (CPP) (Table 3). [15,16]

**Optic nerve sheath diameter sub-study:** we will calculate non-invasive estimates of ICP and CPP (Table 3). [17]

**Automated pupillometry sub-study:** In centres using NPi automated pupillometers (NeurOptics®, Irvine, CA, USA) we will record Neurological Pupil index (NPi). NPi is a dimensionless index derived from a propriety algorithm using pupil size and response times. In centres using NeuroLightAlgiscan automated pupillometers (NeuroLight®, IDMed, Marseille, France) we will record Quantitative Pupillometry Index (QPi). QPi is derived from q-PLR. Values for both NPi and QPi range from 0 (no pupillary response) to 5 (full pupillary response), with values < 3 (sluggish) considered abnormal. [18]

**Mortality and functional outcome**

We will examine the association between rScO2, Pulsatility Index, ONSD, non-invasive estimates of ICP and q-PLR and mortality and functional outcome at 6 months.

**Statistical methods**

Data will be analysed after follow-up is complete for the last recruited patient. Categorical data will be presented as frequency (%). Normally distributed data will be presented as mean (standard deviation, SD), non-normally distributed data as median (interquartile range, IQR). Both normal and non-normal distribution has been reported for rScO2 [19,20], ONSD [21,22], TCD flow velocities [23,24] and quantitative pupillometry results [18,25].Therefore, variables will be tested for normal distribution using Kolmogorov-Smirnov test. Between group comparisons will be made using Mann-Whitney U test for non-normally distributed continuous data, t-test for normally distributed continuous data and chi-square for categorical data. P-values < 0.05 (two-sided) will be considered statistically significant. Secondary outcomes will be considered hypothesis generating and no adjustment will be made for multiplicity.

**Prediction of mortality and functional outcome**

We will employ an interaction model to test whether treatment group allocation moderates the relationship between neuromonitoring values and mortality and functional outcomes. If the interaction is significant (P-values < 0.05), we will report prognostic accuracies separately for each intervention group. If the interaction effect is not statistically significant, we will pool data to explore the association between rScO2, Pulsatility Index, ONSD, non-invasive estimates of ICP and q-PLR and mortality and functional outcomes at 6 months.

The relationship between the neuromonitoring values and mortality and functional outcome at 6 months will be modelled using regression analysis. Functional outcome will be modelled as both a binary and categorical outcome. In addition, neuromonitoring values for each time point will be split into tertials and Kaplan-Meier curves created presenting survival up to 180 days with 95% confidence intervals. P-values will be calculated using a log-rank test. We may undertake additional exploratory analyses examining the association between other neuromonitoring measures and mortality or poor functional outcome to establish thresholds to predict outcome.

**Sample size**

The STEPCARE trial plans to recruit 3500 patients, with sub-studies open to recruitment after the first 1000 patients have been enrolled in the main trial. For the neuromonitoring sub-studies a sample of convenience from capable participating sites will be taken. In relation to the prediction of mortality and functional outcome, power calculations are presented below.

**Cerebral oximetry sub-study:** Previous studies have demonstrated mean (SD) rScO2 of 61% (±10%) in those with good functional outcome and 54% (±14%) in those with poor outcome. [19] A 7% difference in rScO2 between survivors and non-survivors has also previously been reported. [26] Based on a conservative estimate of mean (SD) rScO2 of 60% (±10%) in survivors and 55% (±10%) in non-survivors, 168 patients are needed to achieve a power of 0.9 with a significance level of 0.05 (two sided). This will be inflated to 200 patients to account for a 4% drop out and 14.5% mortality prior to 72 hours.

**Transcranial doppler sub-study:** A mean (SD) Pulsatility Index of 1.2 cm/s (±0.2cm/s) and 1.4 cm/s (±0.4 cm/s) has previously been observed in survivors and non-survivors. [23] Based on these values (assuming SD ±0.4 in both groups), 168 patients are needed to achieve a power of 0.9 with a significance level of 0.05 (two sided). This will be inflated to 200 to account for drop out and mortality.

**Optic nerve sheath diameter sub-study:** Previous studies have reported a mean (SD) ONSD of 5.6mm (±0.6mm) in survivors and 6.0mm (±0.4mm) in non-survivors. [27] Based on these values, 94 patients are needed to achieve a power of 0.9 with a significance level of 0.05 (two-sided). This will be inflated to 112 to account for drop out and mortality.

**Automated pupillometry sub-study:** Previous studies have reported a median (range) q-PLR of 20% (13-41%) in survivors and 11% (0-55%) in non-survivors. [28] Based on a conservative estimate of mean (SD) 16% (±6%) in survivors and 12% (±6%) in non-survivors, 94 patients are needed to achieve a power of 0.9 with a significance level of 0.05 (two-sided). This will be inflated to 112 to account for drop out and mortality.

**Missing data**

Trial management includes onsite and remote monitoring to ensure data completeness, reducing the risk of substantial missingness. Missingness will be managed in accordance with recommendations for the handling of missing data by Jakobsen and colleagues. [29] Where missingness is ≤5% complete case analysis will be conducted. We will perform sensitivity analyses using “best-worst” and “worst-best” scenarios replacing missing variables with values 2 SD above and below the mean. Where missingness is > 5%, we will use multiple imputation using chained equations or Markov chain Monte Carlo method.

**Reporting**

We will report our findings in a peer reviewed journal. The association between neuromonitoring values and mortality and functional outcome will be reported in accordance with the Standards for Reporting Diagnostic accuracy studies (STARD).

**Discussion**

In the prospective, international, multicenter randomised controlled STEPCARE trial, comatose survivors of OHCA will be randomised to sedation, temperature management and blood pressure targets. We will conduct a series of neuromonitoring sub-studies examining the effect of these interventions on cerebral oximetry, Pulsatility Index, ONSD, non-invasive estimates of ICP and q-PLR. These will provide important mechanistic insights. Derangements in cerebral blood flow [30], cerebral metabolic rate [31], cerebral oxygenation and ICP are common in the first 72 hours following cardiac arrest providing a window for therapeutic intervention. [32] In addition, we will examine the ability of neuromonitoring to predict mortality and functional outcome at six months.

**Cerebral oximetry**

Cerebral oximetry utilises near infrared spectroscopy to measure the ratio of oxygenated hemoglobin to total hemoglobin [33] in the first 2-3cm of cerebral tissue in frontal regions. As the frontal cortex is prone to hypoxaemia, rScO2 provides a useful non-invasive measure of cerebral ischaemia. [30] rScO2 correlates with MAP in non-survivors of cardiac arrest. [34] Previous studies have demonstrated higher rScO2 in survivors and those with good neurological outcome following cardiac arrest [19,20], whereas other studies have not. [6] However, studies are typically underpowered, limiting confidence in the findings. [6,19,20] Therefore, the value of rScO2 in post resuscitation care is uncertain leading to calls for further research. [9]

**TCD**

Transcranial doppler can measure velocity in the middle cerebral artery (MCA) to provide a surrogate for cerebral blood flow. Interpreting flow velocities may be challenging in comatose survivors of cardiac arrest. Pathological increases in cerebral vascular resistance results in higher sFV and mFV, but lower dFV as patients progress to diastolic flow arrest. In contrast, an increase in mFV over time may represent a transition from pathologically low to normal flow velocities [13,37]. As a result, sFV or mFV have been reported to be lower [38], not different [13,24,38] or higher [23] in non-survivors. Pulsatility Index [(sFV- dFV)/mFV], which increases with both elevated systolic flow velocity or decreased diastolic flow velocity, may be a useful predicter of mortality or functional outcome. [23,24,38] However, this remains poorly studied.

**ONSD**

The optic nerve is surrounded by a sheath filled with cerebrospinal fluid (CSF) in direct connection with the subarachnoid space. [35] With raised intracranial pressure, the optic nerve sheath distends due to passage of CSF into this space. Therefore, ONSD provides a surrogate measure for ICP [36] with an excellent ability to predict intracranial hypertension. [17,35] However, in a systematic review, the threshold ONSD to identify intracranial hypertension ranged from 4.8 to 6.3mm with the quality of evidence assessed as very low. [35]A ONSD of ≥ 5.75mm has previously been suggested as a threshold to predict mortality following cardiac arrest. [27] However, a near linear relationship between ONSD and mortality without a threshold to predicted mortality has subsequently been described. [22] Furthermore, subsequent observational studies have reported higher ONSD of 6.5mm [22] and 7.1 mm [21] in survivors. Therefore, the role of ONSD in predicting outcome remains unclear.

**Pupillometry**

Assessment of pupillary response is a key component of determining prognosis following OHCA. Pupillary response can be assessed qualitatively using a pen torch. Automated pupillometry provides a fixed, reproducible stimulus and an objective measure of pupillary response. The 2021 European Resuscitation Council guidelines suggest using automated pupillometry where available (weak recommendation based on very-low-certainty evidence). [11] Low q-PLR [28,39] and NPi [14,18] have been associated with mortality and poor functional outcome. In a sub-study of the Blood Pressure and Oxygenations Targets After Cardiac Arrest (BOX)-trial, q-PLR < 4% and NPi ≤ 2 both predicted mortality, or poor functional outcome with zero false positives. [14] However, in a large study of patients with traumatic brain injury, sub-arachnoid haemorrhage or intracranial haemorrhage, 15% of survivors had a NPi of zero (denoting unreactive pupils) in the first 7 days. [40] Therefore, automated pupillometry requires further validation before implementation in clinical practice.

**Strengths and limitations**

These planned sub-studies have several strengths. They will be conducted as part of a large, international, multicentre study which includes standardised blinded neuroprognostication. Mortality and neurological outcome assessors will be blinded.

Several challenges are anticipated. We plan to report neuromonitoring values at discrete not continuous time points, this will be offset by our large sample size. Different brands of cerebral oximeters and pupillometers exhibit variation in readings. [41,14] To counter this we will record monitor brand and report change from baseline. Low ultrasound resolution may make identification of optic nerve sheath boarders difficult. [42] The ONSD threshold of ≥ 5.75mm to predict mortality results in a small margin for error which may diminish accuracy. [16] The intra-class correlation of 0.60 (95% CI: 0.37–0.83) for ONSD measurements indicates only moderate reliability. [17] We will take the mean of four readings bilaterally to limit inaccuracies. The absence of acoustic window in 5-30% of patients provides a barrier to TCD measurement. [16,43] However, we will only enrol those with acoustic windows. An angle of insonation > 10-15o will result in underestimation of flow velocities. [16] However, we will record Pulsatility Index which is unaffected by angle of insonation.

**Conclusions**

In response to recent calls by the American Heart Association, we will conduct a series of neuromonitoring sub-studies as part of the STEPCARE trial. These will provide important mechanistic insights into the effect of sedation, temperature management, and blood pressure targets on rScO2, PI, ONSD, non-invasive estimates of ICP and q-PLR. In addition, we will examine the association between neuromonitoring values and mortality and functional outcome at 6 months.

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**Tables**

**Table 1. STEPCARE inclusion and exclusion criteria**

|  |  |
| --- | --- |
| Inclusion Criteria | Exclusion Criteria |
| OHCA of non-traumatic origin | On extracorporeal membrane oxygenation (ECMO) prior to randomisation |
| A minimum of 20 minutes without chest compressions | Pregnancy |
| 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 | Suspected or confirmed intracranial hemorrhage |
| Eligible for intensive care without restrictions or limitations | Previously randomised in the STEPCARE trial |
| Inclusion within 4 hours of ROSC |  |

**Table 2. Secondary outcome measures**

|  |
| --- |
| Cerebral Oximetry sub-study secondary outcome measures |
| rScO2 at 24 and 48 hours |
| Change in rScO2 between baseline and 24, 48 and 72 hours |
| ONSD sub-study secondary outcome measures |
| ONSD at 24 and 48 hours |
| Change in ONSD between baseline and 24, 48 and 72 hours |
| Incidence of ONSD > 5.8 mm denoting intracranial hypertension at 24, 48 and 72 hours |
| ICPONSD at 24, 48 and 72 hours |
| CPPONSD at 24, 48 and 72 hours |
| Optic disc elevation at 24, 48 and 72 hours\* |
| TCD sub-study secondary outcome measure |
| MCA mFV at 24, 48 and 72 hours |
| Incidence of abnormal MCA mFV (outside 50-80cm/s range) at 24, 48 and 72 hours |
| Incidence of severely abnormal MCA mFV (> 200cm/s) at 24, 48 and 72 hours |
| Incidence of change in MCA mFV > 50cm/s between serial measurements |
| MCA sFV at 24, 48 and 72 hours |
| MCA dFV at 24, 48 and 72 hours |
| Incidence of severely abnormal MCA dFV (< 20cm/s) at 24, 48 and 72 hours |
| Incidence of Pulsatility Index > 1.4 (denoting ICP > 20 mmHg)at 24, 48 and 72 hours |
| Incidence of Pulsatility Index < 1.2 (denoting ICP < 12 mmHg)at 24, 48 and 72 hours |
| ICPFV at 24, 48 and 72 hours |
| CPPFV at 24, 48 and 72 hours |
| ICPPI at 24, 48 and 72 hours |
| CPPI at 24, 48 and 72 hours |
| Pupillometry sub-study secondary outcome measure |
| q-PLR at 24, 48 and 72 hours |
| NPi where NeurOptics® (Irvine, CA, USA) pupillometer used at 24, 48 and 72 hours |
| QPi where NeuroLight® (IDMed, Marseille, France) pupillometer used at 24, 48 and 72 hours |
| Maximum constriction velocity (mm/s) at 24, 48 and 72 hours |
| Average constriction velocity (mm/s) at 24, 48 and 72 hours |
| Average dilation velocity (mm/s) at 24, 48 and 72 hours |
| Latency, time for light stimulation to the start of light reflex (s) at 24, 48 and 72 hours |
| Change in q-PLR between baseline and 24, 48 and 72 hours |
| Change in NPi between baseline and 24, 48 and 72 hours |
| Change in QPi between baseline and 24, 48 and 72 hours |

\*Capable sites only

CPPFV: cerebral perfusion pressure calculated as mean arterial pressure minus non-invasive estimate of ICP derived from transcranial doppler flow velocity measurements; CPPONSD: cerebral perfusion pressure calculated as mean arterial pressure minus non-invasive estimate of ICP derived from optic nerve sheath diameter measurements; CPPPI: cerebral perfusion pressure calculated as mean arterial pressure minus non-invasive estimate of ICP derived from transcranial doppler Pulsatility Index; dFV: end diastolic flow velocity; ICP: intracranial pressure; ICPFV: non-invasive estimate of ICP derived from transcranial doppler flow velocity measurements; ICPONSD: non-invasive estimate of ICP derived from optic nerve sheath diameter measurements; ICPPI: non-invasive estimate of ICP derived from transcranial doppler Pulsatility Index; MCA: middle cerebral artery; mFV: mean flow velocity; NPi: neurological pupil index; ONSD: optic nerve sheath diameter; q-PLR: quantitative pupillary light reflex; QPi: quantitative Pupillometry Index; rScO2: regional cerebral oximetry; sFV: peak systolic flow velocity

**Table 3. Formulae for estimating ICP and CPP**

|  |  |
| --- | --- |
| Measure | Formulae |
| ICPFV | MAP x (1 – dFV/mFV) – 14mmHg |
| CPPFV | (MAP\*dFV/mFV) + 14mmHg. |
| ICPPI | (10.93 x Pulsatility Index) - 1.28 |
| CPPPI | MAP – ICPPI |
| ICPONSD | (5xONSD) – 13.92mmHg |
| CPPONSD | MAP – ICPONSD. |

CPPFV: cerebral perfusion pressure calculated as mean arterial pressure minus non-invasive estimate of ICP derived from transcranial doppler flow velocity measurements; CPPONSD: cerebral perfusion pressure calculated as mean arterial pressure minus non-invasive estimate of ICP derived from optic nerve sheath diameter measurements; CPPPI: cerebral perfusion pressure calculated as mean arterial pressure minus non-invasive estimate of ICP derived from transcranial doppler Pulsatility Index; dFV: end diastolic flow velocity; ICP: intracranial pressure; ICPFV: non-invasive estimate of ICP derived from transcranial doppler flow velocity measurements; ICPONSD: non-invasive estimate of ICP derived from optic nerve sheath diameter measurements; ICPPI: non-invasive estimate of ICP derived from transcranial doppler Pulsatility Index; mFV: mean flow velocity; ONSD: optic nerve sheath diameter; sFV: peak systolic flow velocity

**Supplementary Appendix.**

**Functional outcome assessment**

Functional outcome will be assessed using modified Rankin Scale (mRS), dichotomised as good (mRS 0-3) or poor (mRS 4-6). Assessments will be performed face-to-face or by telephone/video. Where face-to-face or telephone/video assessment is not possible, functional outcome will be assessed using medical records, information from a family member, a primary care provider, or other sources. The dichotomization will be based on whether the participant is independent for basic activities of daily living (moving indoors, eating, dressing, personal hygiene).

**modified Rankin Scale (mRS)**

1. No symptoms.
2. No significant disability despite symptoms. Able to carry out all usual activities, despite some symptoms.
3. Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
4. Moderate disability. Requires some help, but able to walk unassisted.
5. Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
6. Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
7. Dead.