CONFIDENTIAL CLINICAL TRIAL PROTOCOL

TITLE:	Neuroprotective goal directed hemodynamic optimization in post-cardiac arrest patients: a randomized controlled trial (the NEUROPROTECT post-CA trial)
INDICATION:	Post-Cardiac arrest patients
CLASSIFICATION	**Academic, investigator initiated trial**
PROTOCOL DATE	13 May 2015
PROTOCOL VERSION	2
STUDY INITIATION	1 July 2015
STUDY DURATION	2 years
STUDY SPONSOR *('opdrachtgever', as defined by Art. 2, 21° of the Belgian Law of 7 May 2004)*	University Hospitals Leuven (UZ Leuven) Herestraat 49, 3000 Leuven, Belgium
PRINCIPAL INVESTIGATORS	Stefan Janssens, MD, PhD Koen Ameloot, MD Joseph Dens, MD, PHD Cathy De Deyne, MD, PHD
FUNDING RESOURCES	Division of Clinical cardiology and IWT Brussels (application for IWT/TBM grant)
GCP:	These studies will be performed in compliance with good clinical practices (GCP) guidelines. All essential documents will be archived.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Below is a list of abbreviations that are used in this clinical report.

6MWD	6 Minute Walking Distance
ADC	Apparent Diffusion Coefficient
ADL	Activities Daily Life
AMI	Acute Myocardial Infarction
CA	Cardiac Arrest
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
DMC	Data Safety Monitoring Board
DW-MRI	Diffusion Weighted MRI
ECMO	Extracorporeal Membrane Oxygenation
EEG	Electro-encephalography
FIO2	Fraction of inspired oxygen
GCS	Glasgow Coma Scale
GCP	Good Clinical Practice
IABP	Intra-aortic Balloon Pump
ICU	Intensive Care Unit
IVRS	Interactive Voice Response System
IV	Intravenous
IEC	Independent Ethics Committee
LCC	Leuven Coordinating Centre
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
MRI	Magnetic Resonance Imaging
NSE	Neuron Specific Enolase
NSTEMI	Non-ST segment elevation myocardial infarction
OR	Odds Ratio
PAC	Pulmonary Artery Catheter
PCI	Percutaneous Coronary Intervention

PEEP	Positive End-expiratory Pressure
PPV	Pulse Pressure Variation
ROSC	Resume of Spontaneous Contractions
SSEP	Somatosensory Evoked Potential
STEMI	ST segment elevation myocardial infarction
SVO_2	Mixed Venous Oxygen Saturation
SVV	Stroke volume Variation
TIA	Transient ischemic attack

1. SYNOPSIS

Classification: Academic, Investigator Initiated Trial

Protocol Version and Date: Version 4, 20 Jan 2017

Title of Study: Neuroprotective goal directed hemodynamic optimization in post-cardiac arrest patients: a randomized controlled trial (the NEUROPROTECT post-CA trial)

Participating country: Belgium

Study Centers: 2 (UZ Leuven and ZOL Genk)

Study Period: 3 years
Anticipated start: July 2015
Anticipated completion: May 2018

Objectives:
The **primary objective** of the trial is to assess whether or not a new goal directed hemodynamic optimization strategy can reduce cerebral ischemia in post-cardiac arrest (CA) patients as quantified by diffusion weighted MRI (DW-MRI) to be performed at day 4-5 with quantification of the percentage of ischemic voxels with an apparent diffusion coefficient (ADC) below 0.650 mm2/s.

Secondary efficacy outcomes:

- Cerebral performance category 3-5 at discharge from the ICU CPC 1: return to normal cerebral function and normal living
  CPC 2: Disability but sufficient function for independent activities of daily life
  CPC 3: severe disability CPC 4: Coma
  CPC 5: Death
- Cerebral performance category 3-5 at 180 days post-CA (assessed by trial investigators that are unaware of the treatment assignment)
- SF36 questionnaire at 180 days post-CA (assessed by trial investigators that are unaware of the treatment assignment)
- Neurocognitive testing at discharge from the hospital
- Biomarkers: Neuron specific enolase (day 1-2-3-4-5)

- Functional testing: Activities Daily Life (ADL) and 6 minute walking distance (6MWD) at discharge from the hospital
- Renal function: creatinine day 1-2-3-4-5 and urinary output day 1-2- 3-4-5.
- Length of stay in the ICU
- Duration of mechanical ventilation
- Placement of tracheostomy

Safety outcomes:

- Incidence of life threatening arrhythmias during intervention period
- Incidence of new onset atrial fibrillation during intervention period
- Incidence of pulmonary congestion requiring diuretics during intervention period

Methodology: Prospective, multi-centre, interventional open label investigator driven randomized controlled trial. Randomisation will be stratified by the presence of an initial shockable rhythm.

Number of subjects planned: A total of 112 pts are planned for this study.

Anticipated duration of trial: 3 years from first patient entered to last patient randomized

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria:

- Out-of-hospital CA of presumed cardiac cause irrespective of the presenting rhythm
- Unconsciousness (Glasgow coma scale < 8) at hospital admission
- Age ≥ 18 years
- Sustained return of spontaneous circulation (ROSC) (=when chest compressions have not been required for 20 consecutive minutes)

Exclusion criteria:

- Suspected or confirmed intracranial bleeding or stroke
- Known limitations in therapy or Do Not Resuscitate-order
- Known disease compromising 180 day survival
- Known pre-CA cerebral performance category 3-4
- Previous stroke (TIA can be included)
- MRI incompatible cardiac or neurosurgical device

- Systolic blood pressure < 90 mmHg on norepinephrine > 1 mcg/kg/min).
- Open chest
- ECMO (extracorporeal membrane oxygenation)
- Pregnancy

Interventional hemodynamic optimization protocol: In patients randomized to receive the intervention, the target mixed venous oxygen saturation (SVO_2) will be between 65-75% and the target mean arterial pressure (MAP) is between 85-100mmHg. Fluid administration and hemodynamic support will be adjusted according to a flow chart in case SVO_2or MAP are below or above the suggested targets on an hourly basis.

Duration of treatment: The study protocol will start at admission in the intensive care unit (ICU) and will last 36 hours.

Reference therapies, dose and mode of administration: In patients randomized to receive current standard of care, hemodynamic support will be at the discretion of the treating physician with a target MAP of 65mmHg.

2. ETHICS

2.1. Independent Ethics Committee (IEC)

The protocols and local Informed Consent Forms must be reviewed and approved by each of the participating institution's Independent Ethics Committee (IEC) prior to the initiation of patient accrual. The IEC must be notified of all subsequent protocol amendments. In addition, progress reports will be submitted to the IEC by the investigator as indicated by IEC's guidelines. Each IEC must meet the applicable regulatory requirements for composition, documentation, and operational procedures.

2.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the principles that have their origins in the Declaration of Helsinki, as well as ICH GCP and applicable national and local regulatory requirements, including but not limited to the Belgian Laws of 7 May 2004 relating to experiments on the human person (LEH), of 22 August 2002 on Patients' Rights and of 8 December 1992 (as amended) regarding the Protection of Privacy in relation to the Processing of Personal Data. All essential documents will be archived.

2.3. Patient Information and Informed Consent

The informed consent will contain all elements required by ICH GCP. Written informed consent will be obtained from a next of kin prior to enrollment and participation of the study Subject. If a next of kin or another designated person is not available, a procedure for inclusion in the study in emergency situations will be applied. A definitive post hoc consent form will ultimately be obtained from patients who survived but had been initially treated on the basis of the emergency consent. Subjects or legally representatives will be informed of any significant new finding developed during the course of the research that may affect their decision to continue participation.

The Study Centers shall use the informed consent forms as approved by the appropriate ethics committee. The Study Centers further commit to conduct the study only on the basis of prior written consent by the Subjects or their legal representatives. The Study Centers shall retain such informed consent forms in accordance with the applicable regulatory requirements.

3. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

3.1. Investigators

Two sites (ZOL-Genk and UZ Leuven) will participate in the trial.

3.2. Steering Committee

The Steering Committee will be responsible for the overall design, conduct, and supervision of the trial, including the development of the protocol and any protocol amendments. The Steering Committee meets periodically to assess the progress of the study to ensure subject safety and study integrity. The Steering Committee is composed of designated academic leaders and clinical experts.

Prof. Dr. Stefan Janssens
Prof. Dr. Joseph Dens
Prof Dr. Peter Sinnaeve
Prof. Dr. Alexander Wilmer
Prof. Dr. Cathy DeDeyne
Dr. K. Ameloot
And others

The Steering Committee will prepare a manuscript(s) plan to ensure timely and high quality presentation and publication of the study results.

3.3. Study Coordinating Centre

The Leuven Coordinating Centre (LCC) will provide services with respect to the design and operation of the clinical trial. LCC will interact closely with the Principal Investigators and will have operative responsibility for different areas like regulatory submissions, randomization, data management and safety reporting.

3.4. Data Monitoring Committee (DMC)

A Safety and Data Monitoring Board will be established to provide independent oversight to this trial. The primary responsibility of the DSMB will be to review the progress and conduct of the trial in order to maintain scientific rigor and to ensure the well being of patients participating in the trial. Data will be provided to the DSMB after inclusion of the 60th patient. The DSMB consists of Fabio Taccone (MD, Chair), Niklas Nielsen (MD) and Karen Hirsch (MD).

4. INTRODUCTION

4.1. The clinical problem

There is absolutely no doubt that sudden cardiac death is a major problem in Belgium in terms of numbers of patients, medical impact and socio-economic impact. Each day, approximately 30 adults suffer from an unexpected out-of- hospital cardiac arrest in Belgium, a number exceeding the incidence of breast or prostate cancer with an estimated 25 new patients per day in Belgium. In addition, many cardiac arrest patients are young (mean age in our hospital 60±12 years, 56% of patients younger than 65 years) with a large economic potential for society. In the community, the occurrence of sudden death often takes center stage through highly mediatized cases of cardiac arrest in young sportsmen with or without a previously undiscovered cardiac anomaly. Apart from the traumatic experience of these dramatic sudden events, only 40% of patients that reach the hospital with spontaneous circulation survive without major neurological impairment or care dependency. An additional 5-10% of the cohort survives with major neurological impairment including a permanent vegetative state. These sobering outcome data and the large economic burden for society (estimated cost of a nursing home facility for these patients approximately 30-50000 €/year) mandate novel treatment strategies that could improve prognosis after cardiac arrest.

Apart from temperature management to avoid fever, no single in hospital randomized controlled intervention trial has improved outcome of these patients. In this way, there is absolutely no doubt that a positive result of the Neuroprotect post-CA trial would be a clear added value for this vulnerable and highly under- investigated patient group.

4.2. Current state of the art

Current hemodynamic post-CA guidelines state that "*Fluid administration as well as vasoactive (e.g. norepinephrine), inotropic (e.g. dobutamine) and inodilator (e.g. milrinone) agents should be titrated to optimize blood pressure, cardiac output and systemic perfusion (class I, level of evidence B). Although human studies have not established robust targets for blood pressure or blood oxygenation, a mean arterial pressure above 65mmHg is generally considered to be a reasonable goal*" (*Peberdy et al, Circulation 2010*).

It is important to emphasize that these recommendations are not based on mortality data in post-cardiac arrest patients. Nor has it been shown or even investigated that a blood pressure of 65mmHg would result in optimal brain perfusion in post-cardiac arrest patients. Instead, these guidelines are adapted from sepsis guidelines based on the unsubstantiated assumption that the post- cardiac arrest syndrome is a sepsis like syndrome. Moreover, the true value of goal direct therapy in sepsis has recently been questioned *(Peake et al, NEJM 2014).* All the above emphasize the need for objective and properly validated guidelines for hemodynamic support in the post-CA setting.

4.3. Observational studies on new hemodynamic targets

During intensive care unit stay after cardiac arrest, the optimal MAP and cardiac output should maintain optimal cerebral perfusion to avoid additional cerebral ischemic damage caused by cerebral hypo- and hyper perfusion.

In a first study, we showed that there is a large inaccuracy regarding cardiac output measurements by conventional continuous thermodilution in CA patients treated with therapeutic hypothermia. In contrast, cardiac output calculated by means of continuous SVO_2 using the Fick equation was shown to be a valuable alternative in patients treated with therapeutic hypothermia (*Ameloot et al, Resuscitation 2014)*.

In a second observational trial, we constructed a hemodynamic model to determine the optimal MAP and SVO_2 range associated with optimal cerebral oxygen saturation (*Ameloot et al, resuscitation 2015)*. It was previously shown that in a subset of post-CA patients (mainly these with chronic hypertension) the lower threshold of cerebral autoregulation is shifted rightward towards higher systemic blood pressures and these patients might benefit from resuscitation to higher MAP's to preserve adequate cerebral perfusion *(Sundgreen, Stroke 001).* In contrast, many post-CA patients have a reduced left ventricular function and might benefit from afterload reduction to maintain stroke volume and cerebral perfusion. Therefore, we hypothesized that the optimal MAP should maintain cerebral perfusion without exposing the damaged myocardium to excessive afterload. The relationship between MAP, SVO_2 and cerebral saturation is shown in the figure below (n=1 635 827 data points obtained in 41 patients during the first 24 hours after ICU admission). We found a strong linear relationship between MAP and cerebral saturation in the MAP range between 45 and 101mmHg (R^2

0.83). Mean arterial blood pressures above 101mmHg were associated with progressively decreasing cerebral saturations (R^2 0.72).
Additionally, MAP's above 101mmHg were also associated with progressively decreasing SVO2's suggesting that this excessive left ventricular afterload impairs cardiac output and by consequence cerebral perfusion. The currently recommended MAP of 65mmHg clearly resulted in a submaximal cerebral saturation. The lowest optimal MAP based on this hemodynamic model was determined to be 87mmHg since the cerebral saturation corresponding with this MAP of 87mmHg was 67.6% and almost equal to the average of all calculated cerebral saturations associated with higher MAP values (average 67.5%). Cerebral saturation is maximized at a MAP of 101mmHg. Therefore, the MAP range associated with optimal cerebral oxygenation was determined to be between 87-101mmHg. The corresponding SVO_2 range associated with optimal cerebral oxygenation was determined to be between 70-75%. Both the suggested MAP (87-101mmHg) and the SVO_2 range (70-75%) resulted in cerebral saturations between 67-69%.

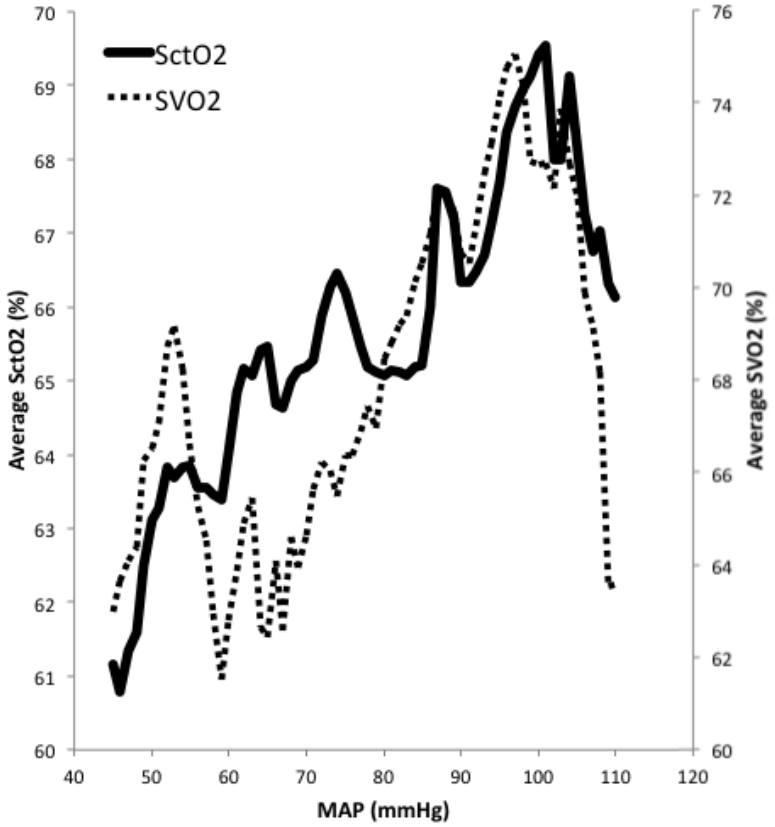


Figure 1: Relationship between mean arterial pressure (MAP), mixed venous oxygen saturation (SVO_2) and cerebral saturation ($SctO_2$).

In a third observational trial, we focussed on cerebral autoregulation. We confirmed the previous findings by Sundgreen et al (*Stroke 2001*) that cerebralutoregulation is shifted rightward in 35% of post-cardiac arrest patients.Phenotypically, a higher proportion of patients with disturbed autoregulation had pre-cardiac arrest hypertension (65±49 vs 31±47%, *P*=0.02) suggesting that right shifting of autoregulation is caused by chronic adaptation of cerebral blood flow to pre-existing higher blood pressures. In multivariate analysis, patients with preserved autoregulation had a significantly higher 180-days survival rate (odds ratio 4.62). Finally, we defined the optimal MAP range within the autoregulatory zone as defined by an index of autoregulation (COX). *COX was calculated as a linear correlation coefficient between 10 seconds averaged values of brain saturation and MAP, that is continuously changing and recorded over 5 minute time windows during the 24 hours study period*". In this way, COX is a continuous variable that ranges from -1 to +1 and that can be used as a robust surrogate marker of autoregulation at a specific time point. Intact autoregulation is indicated by negative or near-zero COX because

small MAP variations will not alter cerebral oxygenation when autoregulation is active. When autoregulation becomes impaired, COX becomes positive because MAP and SctO2 correlate indicative of MAP-dependency of cerebral saturation. We averaged all obtained COX values per 5mmHg MAP bins and generated bar graphs to identify the COX predicted optimal MAP range as the MAP bins with negative or near-zero COX values. When COX per 5 mmHg bar graphs were pooled and averaged over all 51 study patients, the overall COX predicted optimal MAP was between 85 and 105mmHg (see figure below).

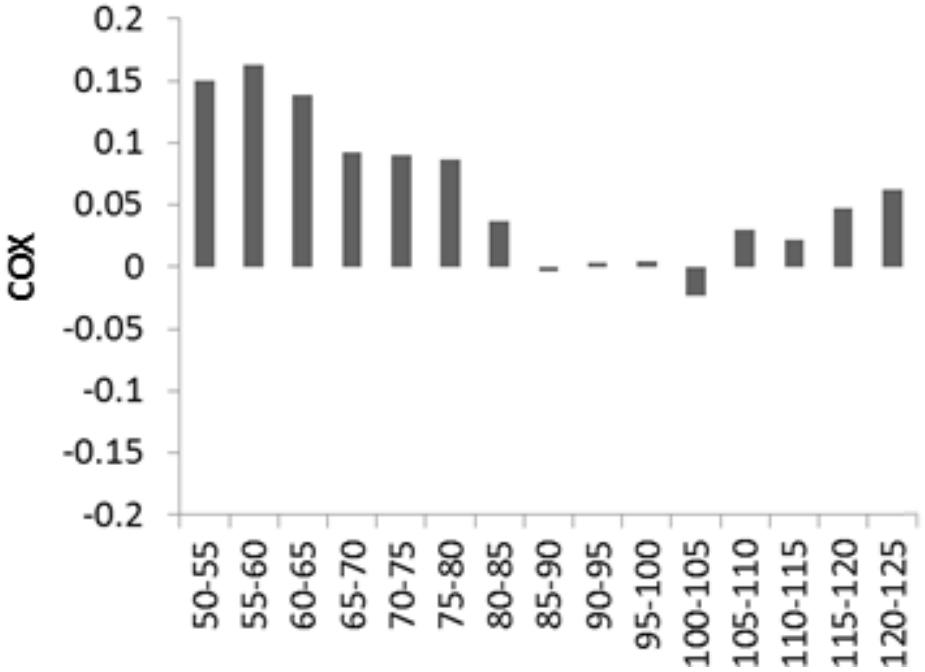


Figure 2: Pooled COX per 5 mmHg MAP plot. The MAP range associated with optimal autoregulation (negative COX values) was defined to be between 85-105mmHg.

In summary, we found that the MAP range associated with optimal cerebral perfusion corresponds with the MAP range within the autoregulatory zone (85- 100/105mmHg).

Is there any evidence from observational studies that a higher MAP would be associated with a better neurological outcome? In our own observational study *(Ameloot et al, resuscitation 2015),* we showed that the MAP range associated with the highest odds ratio for survival was 76-86 mmHg (OR 2.63, 95% CI [1.01; 6.88], p=0.04). The SVO_2 range associated with the highest odds ratio for survival was 67-72% (OR 8.23, 95% CI [2.07; 32.68], p=0.001). Logistic regression revealed that the probability of survival increased with increasing percentage of time within the optimal MAP (OR 1.04 per % in the optimal range, 95% CI [1.00; 1.07], p=0.001) and SVO_2

range (OR 1.03 per % in the optimal range, 95% CI [1.00; 1.05], p=0.04). An average MAP>65 mmHg or SVO_2>70% were not associated with increased survival highlighting marked limitations of current patient management recommendations. In two separate models using backward multiple logistic regression, a mean MAP in the optimal range (OR 3.72, 95% CI [1.11; 12.50], p=0.03) and a mean SVO_2 in the optimal range (OR 10.32, 95% CI [2.03; 52.60], p=0.001) remained independently associated with increased survival.

Our findings are in agreement with 2 retrospective and 1 prospective observational study on the positive association between higher MAP's during the first 6 hours post-ROSC and increased survival in post-cardiac arrest patients *(Beylin, ICM 2013;* Trzeciak, Crit Care Med. 2009; Kilgannon, Crit Care Med. 2014). In contrast with these observational trials, in the Neuroprotect post-CA trial the intervention strategy will be extended until 36 hours after admission. Is there any evidence from non-randomized controlled trials that forcing MAP or SVO_2 into the suggested range with additional pharmacological support would improve outcome? In a small study by Gaieski et al, 20 prospective post-cardiac arrest patients received early goal directed hemodynamic optimization with a target central venous saturation above 65% and MAP between 80-100mmHg. A trend toward better survival was observed in treated patients (50% survival) when compared with 18 historic controls (22% survival) (*Gaieski, Resuscitation 2009)*. This study, however, is limited by the small sample size and extremely low survival rates in the historic control group.

We have shown that the currently recommended MAP target of 65mmHg results in a suboptimal cerebral saturation beyond the autoregulatory range. Moreover, analysis of available patient data thus far indicates that an average MAP above 65mmHg is not associated with a greater likelihood to survive with good neurological outcome compared with an average MAP below 65mmHg. In contrast, both our hemodynamic model and our preliminary study on cerebral autoregulation suggest that optimal cerebral perfusion is maintained with markedly higher MAP's (85-100mmHg) and normal SVO_2's (70-75%). As shown above, 4 observational studies and one small prospective interventional with historic controls suggest that resuscitation to higher MAP's might confer better neurological outcome in post-cardiac arrest patients, which needs to be confirmed in adequately powered prospective randomized controlled studies. Here, we hypothesize that our proposed neuroprotective hemodynamic optimization strategy will reduce cerebral ischemia thereby improving

neurological outcome in post-cardiac arrest patients.

4.4. Innovative aspect of the Neuroprotect post-CA trial

The Neuroprotect post-CA trial will be the first randomized controlled trial to investigate whether forcing MAP and SVO_2 in the suggested range improves cerebral ischemia and neurological outcome in post-cardiac arrest patients. It has been shown that targeted temperature management to avoid the deleterious effects of fever, somewhat improves outcome of post-CA patients (*Nielsen, NEJM 2014*). Nevertheless, even with optimal targeted temperature management recovery with good functional outcome is limited to 40% of the post-CA patients. Apart from targeted temperature management, no single in hospital randomized controlled intervention trial has been able to improve outcome in these patients with a major unmet clinical need.

5. STUDY OBJECTIVES

The **primary objective** of the trial is to assess whether or not a new goal directed hemodynamic optimization strategy can reduce cerebral ischemia in post-CA patients as quantified by diffusion weighted MRI (DW-MRI) to be performed at day 4-5 with quantification of the percentage of ischemic voxels with an apparent diffusion coefficient (ADC) below 0.650 mm2/s.

Secondary efficacy outcomes:

- Cerebral performance category 3-5 at discharge from the ICU
  CPC 1: return to normal cerebral function and normal living
  CPC 2: Disability but sufficient function for independent activities of daily life
  CPC 3: severe disability
  CPC 4: Coma
  CPC 5: Death
- Cerebral performance category 3-5 at 180 days post-CA (assessed by trial investigators that are unaware of the treatment assignment)
- Neurocognitive testing at discharge from the hospital
- Biomarkers: Neuron specific enolase (day 1-2-3-4-5)
- Functional testing: Activities Daily Life (ADL) and 6 minute walking distance (6MWD) at discharge from the hospital

- Renal function: creatinine day 1-2-3-4-5 and urinary output day 1-2-3-4-5
- Length of stay in the ICU
- Duration of mechanical ventilation
- Placement of tracheostomy

Safety outcomes:

- Incidence of life threatening arrhythmias during intervention period
- Incidence of new onset atrial fibrillation during intervention period
- Incidence of pulmonary congestion requiring diuretics during intervention period

6. INVESTIGATIONAL PLAN

6.1. Study Plan and Design

Multicenter randomized controlled open label trial conducted in 2 tertiary care hospitals in Belgium (UZ Leuven, and ZOL-Genk). Eligible patients will be randomly assigned in a 1:1 ratio to goal directed hemodynamic optimization or standard care strategy. Randomization will be performed centrally at the Leuven Coordinating Centre for Clinical Trials with the use of a computer-generated assignment sequence and an interactive voice response system. Patients will be stratified according to the presence of an initial shockable rhythm. Health care professionals caring for the trial patients will be aware of the intervention assignments because of the inherent problems with blinding of MAP. Physicians performing neurologic prognostication, radiologist interpreting MRI's, study personnel assessing final outcomes and statisticians will be unaware of the intervention assignments. Unblinding of all data and the final analysis of all primary and secondary outcome parameters will be performed after inclusion of all study patients. Written informed consent will be obtained from a next of kin. If a next of kin or another designated person is not available, a procedure for inclusion in the study in emergency situations will be applied. A definitive post hoc consent form will ultimately be obtained from patients who survived but had been initially treated on the basis of the emergency consent. The ethical committees in the participating hospitals will approve the study protocol prior to enrolment of the first patient.

6.2. Discussion of Study Design

A multicentre study is necessary to recruit an appropriate number of patients and guarantee generalizability of the study results.

6.3. Selection of Study Population

All patients presenting or referred to the investigational site after being successfully resuscitated from out of hospital CA will be screened for enrolment. All patients will be expected to meet all inclusion and exclusion criteria before entering the study. Minor deviations to these criteria may be allowed with prior approval of the principle investigator of the study site.

6.3.1. Inclusion Criteria

The patient must meet the following criteria:

1. Out-of-hospital CA of presumed cardiac cause irrespective of the presenting rhythm
2. Unconsciousness (Glasgow coma scale < 8) at hospital admission
3. Age ≥ 18 years
4. Sustained return of spontaneous circulation (ROSC) (=when chest compressions have not been required for 20 consecutive minutes)

6.3.2. Exclusion Criteria

Exclusion Criteria:

1. Suspected or confirmed intracranial bleeding or stroke
2. Known limitations in therapy or Do Not Resuscitate-order
3. Known disease compromising 180 day survival
4. Known pre-CA cerebral performance category 3-4
5. Previous stroke (TIA can be included)
6. MRI incompatible cardiac or neurosurgical device
7. Systolic blood pressure < 90 mmHg on norepinephrine > 1 mcg/kg/min).
8. Open chest
9. ECMO (extracorporeal membrane oxygenation)
10. Pregnancy

6.3.3. Withdrawal of Patients from Therapy or crossover

In the intervention (“Neuroprotect post-CA”) group, a reduction in vasopressor doses to maintain a MAP of 65mmHg is recommended if any of the pre-specified serious adverse events that were potentially related to an increased rate of vasopressor infusion occurs. These events include: major ventricular arrhythmia requiring life support, electrical or pharmacological cardioversion, poorly tolerated supraventricular arrhythmia and peripheral limb ischemia.

Treatment may also be discontinued if the legal representative withdraws their consent.

All patients who are withdrawn from study treatment will have safety assessments completed during the entire course of the study.

6.3.4. Definition of Randomization and Completion

A patient will be considered 'randomized' when a randomization number has been assigned by the Interactive Voice Response System.

6.4. Baseline Characteristics to be collected

Baseline characteristics to be collected:

- Informed Consent
- Compliance with the inclusion/exclusion criteria will be documented
- Age
- Gender
- Medical history (chronic heart failure, previous AMI, previous cardiac surgery, previous arrhythmia, arterial hypertension, diabetes mellitus, COPD, chronic kidney disease, stroke)
- Chronic medication
- Arrest Characteristics (Public vs private place, bystander witnessed, bystander CPR performed, presenting rhythm, time to ROSC)
- Admission Characteristics (MAP, PaCO2, PaO2, Lactate, pupillary reflex, corneal reflex, FIO2, dose of norepinephrine and dobutamine)
- Cause of arrest (STEMI, NSTEMI, arrhythmogenic, hypoxic, unknown)
- Angiography performed (time in hospital, time in cathlab, time in ICU)
- PCI performed
- SOFA score

6.5. Study treatments

6.5.1. Treatments Administered

In patients assigned to the intervention group, placement of an IABP will be considered in the catheterization laboratory if the dose of norepinephrine necessary to achieve a MAP of 65mmHg exceeds 0.5 mcg/kg/min. In patients assigned to the intervention group, a new generation pulmonary artery catheter (CCOmbo, Edwards life sciences) will be inserted. Other trial interventions will start immediately after ICU admission and a summary flow chart guiding the targeted interventions is presented in the figure below. In patients randomized to receive the intervention, the target mixed venous oxygen saturation (SVO_2) is between 65-75% and the target MAP is between 85-100mmHg. Arterial blood

gas analysis will be performed on an hourly basis by treating nurses and physicians during the first 36 hours after ICU admission. Calibration of the continuous SVO_2 monitor will be performed per 4 hours by a central venous blood gass. In the treatment protocol, we will include specific recommendations for uniform and homogeneous interventions across centres in response to changing hemodynamic variables.

	MAP < 85 mmHg	MAP 85-100 mmHg	MAP > 100 mmHg
SVO_2 < 65 %	**Step1**: Fluid responsiveness? • Sinus: SVV > 12% • AF: Passive leg raising test 7 Plasmalyte 500 cc/u (max 3l/24u) **Step2**: Hemoglobin < 10 g/dl? 7 Transfusion 1 UPC **Step3**: Heartrate < 40 SPM 7 Consider Isuprel of Pacing **Step4**: Inotropics/vasopression • Dobutamine + 5 mcg/kg/min (max 20 mcg/kg/min) • Levophed + 0.05 mcg/kg/min per 10 minutes until MAP OK (max 1 mcg/kg/min)	**Step1**: Fluid responsiveness? • Sinus: SVV > 12% • AF: Passive leg raising test 7 Plasmalyte 500 cc/u (max 3l/24u) **Step2**: Hemoglobin < 10 g/dl? 7 Transfusion 1 UPC **Step3**: Heartrate < 40 SPM 7 Consider Isuprel of Pacing **Step4**: Inotropics/vasopression • Dobutamine + 5 mcg/kg/min (max 20 mcg/kg/min)	**Step1**: Fluid responsiveness? • Sinus: SVV > 12% • AF: Passive leg raising test 7 Plasmalyte 500 cc/u (max 3l/24u) **Step2**: Hemoglobin < 10 g/dl? 7 Transfusion 1 UPC **Step3**: Heartrate < 40 SPM 7 Consider Isuprel of Pacing **Step4**: Inotropics/vasopression • Dobutamine + 5 mcg/kg/min (max 20 mcg/kg/min)

SVO_2 65-75%	Levophed + 0.05 mcg/kg/min per 10 minutes until MAP OK (max 1 mcg/kg/min)	OK (recheck after 1hour)	Levophed - 0.05 mcg/kg/min per 10 minutes until MAP OK
SVO_2 > 75%	Levophed + 0.05 mcg/kg/min per 10 minutes until MAP OK (max 1 mcg/kg/min)	**Step1**: Inotropics • Dobutamine - 5 mcg/kg/min **Stap 2:** Seloken 5mg/5 min IV if HR > 90 SBM	**Step1**: Inotropics/Vasopressors • Dobutamine - 5 mcg/kg/min • Levophed - 0.05 mcg/kg/min per 10 minutes until MAP OK **Step 2:** Seloken 5mg/5 min IV if HR > 90 SBM

Table 1: Hemodynamic interventions

In case of below target SVO_2, fluid status will be optimized if fluid responsiveness is anticipated as indicated by stroke volume variation (if sinus rhythm, full sedation, normal TV ventilation) or passive leg raising test (step 1), anemia will be corrected to maintain a hemoglobin above 10 g/dl (step 2), treatment of excessive bradycardia (heart rate <40 BPM) will be considered (step 3) and dobutamine will be infused (step 4) according to the study protocol. Additional fluid challenge will be limited to 3 liters/24 hours.
In case of below target MAP but normal SVO_2, norepinephrine will be infused.

In case SVO_2 exceeds 75%, dobutamine infusion rate will be reduced (step 1) and seloken 5mg IV (1mg/min) will be infused if heart rate exceeds 90 BPM and MAP 100mmHg in the absence of inotropic or vasopressive support (step 2).
In case MAP is greater than 100mmHg, norepinephrine infusion rate will be reduced (step 1) and seloken 5mg IV (1mg/min) will be infused if heart rate exceeds 100 BPM and SVO_2 75% in the absence of inotropic or vasopressive support (step 2). In the intervention ("Neuroprotect post-CA") group, a reduction in vasopressor doses to maintain a MAP of 65mmHg is recommended if any of the pre-specified serious adverse events that were potentially related to an increased rate of vasopressor infusion occurs. These events include: major ventricular arrhythmia requiring life support, electrical or pharmacological cardioversion, poorly tolerated supraventricular arrhythmia and peripheral limb ischemia.

In patients randomized to receive current standard of care, hemodynamic support will be at the discretion of the treating physician with a target MAP of 65mmHg. All the drugs used in the study will be purchased from manufacturers not involved in the study.

6.5.2. Method of Assigning Patients to Treatment Groups

Randomization will be performed centrally via a centralized telephone Interactive Voice Response System (IVRS) at the Leuven Coordinating Centre for Clinical Trials with the use of a computer-generated assignment sequence. Patients will be stratified according to the presence of an initial shockable rhythm.

6.5.3. Prior and Concomitant Therapy

All patients will be treated according to the current American heart association guidelines (*Peberdy et al, Circulation 2010).* All patients should be intubated, mechanically ventilated and sedated with propofol and remifentanil if hemodynamically tolerated. Cisatracurium should be administrated in case of shivering during hypothermia and continued until the end of the 36 hours study period once started. Doses of sedative and analgetic drugs or muscle relaxants will be reassessed at least once every eight hours to achieve values ranging from -3 to 0 on the Richmond Agitation-Sedation scale (which ranges from -5 to 4 with lower scores indicating deeper sedation and higher scores indicating increasing agitation). Unless an obvious non-cardiac cause can be identified, all patients should be referred for urgent coronary angiography for prompt revascularization of severe culprit coronary lesions. Basic infusions will include glucose 5% (40 ml/hr) and balanced crystalloids (40ml/hr).

Therapeutic hypothermia will be induced in all patients by endovascular (Icy-catheter, CoolGard® 3000, Alsius, Irvine, CA, USA) or surface (ArcticGelTM pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling systems at 33°C for 24-hours as per existing ESC/AHA guidelines. After rewarming (0.3°C/hr) until 36°C, further targeted temperature management to avoid fever will be applied for 36 hours by antipyretic drugs and mechanical cooling devices.

Mechanical ventilation will be adjusted guided by hourly blood gas analysis to target a $PaCO_2$ between 35-45mmHg and a PaO_2 between 70-150mmHg. In principle, extreme low-tidal volume will be avoided to exclude interference with stroke volume variation measurements. Sedation will be titrated towards patient's comfort. Patients will be extubated after sufficient neurological (GCS>8/15), respiratory (successful spontaneous breathing trial) and hemodynamic recovery. A uniform and detailed protocol for mandatory testing of these parameters will be implemented at both recruiting sites.

6.5.4. Treatment Compliance

It is the principal investigators responsibility to ensure that the treatment, as detailed in the approved protocol, is administered to each enrolled subject. All patients will be treated under the principal investigator's (or responsible sub-investigator) direct supervision. All drug used in the study must be accounted for and documented in a usage log.

6.6. Recordings during treatment period

6.6.1. Continuous automatic recordings

- **All patients:**
    - Continuous invasive arterial blood pressure (MAP, systolic, diastolic)
    - Heart rate
    - Oxygen saturation
    - Cerebral saturation monitoring (FORE-SIGHT^{TM} technology (CAS Medical systems, Branford, CT, USA). This information will be blinded to the treating physicians.
- **Intervention group:**
    - Continuous Cardiac output (CCO) by Pulmonary Artery Catheter (PAC) (Edwards®, Irvine, California, USA)
    - Continuous SVO_2 monitoring
    - Continuous stroke volume variation (SVV) by radial artery vigileo
    - Continuous Pulse pressure variation (PPV) by radial artery vigileo

6.6.2. Hourly automatic recordings

- **All patients:**
    - Dose of norepinephrine
    - Dose of dobutamine
    - Dose of Isuprel (if applicable)
    - Ventilator settings: FIO2, PEEP, Tidal volume, respiratory frequency

6.6.3. Hourly manual recordings

- **All patients:**
    - Blood gas analysis with determination of pH, p_aCO_2, p_aO_2, hemoglobin and lactate
    - Adverse events:
        - Incidence of life threatening arrhythmias
        - Incidence of new onset atrial fibrillation
        - Incidence of pulmonary congestion requiring diuretics
        - Presence of limb ischemia
    - If applicable
        - IABP ratio
        - Temporary pacing (Beats per minute)
- **Intervention group:**
    - SVO_2 by blood gas per 4 hours to calibrate the continuous SVO_2 monitor

6.6.4. Daily recordings (day 0-5)

- **Clinical examination**
    - Glasgow Coma Scale
    - Pupil and cornea reflex
- **ECG**
- **Chest X-ray (pulmonary edema?)**
- **Urinary output**
- **Biochemistry**
    - RBC count
    - WBC count
    - Hemoglobin
    - Hematocrit
    - INR
    - Creatinine
    - Urea
    - Liver function
    - Troponin
    - Creatinine Kinase / (MB)

- C reactive protein
- Neuron specific enolase
- S-100B

Serum samples: All blood specimens will be collected, prepared and handled according to the guidelines provided by Gasthuisberg University Clinical Laboratory, the central blood chemistry laboratory or the laboratory for Experimental Cardiology.

6.6.5. Other recordings

- Day 1: Cardiac ultrasound with determination of the left ventricular ejection fraction (LVEF)
- Day 4: neurologic examination including EEG, SSEP
- Day 4-5: MRI with DWI
- Transcranial Doppler at 3,6,12,24, 36 and 48 hours in a subset of patients
- At ICU discharge: Cerebral performance category score
- At discharge from the hospital: Neurocognitive testing.
    - Wechsler memory scale (version IV)
    - Montreal cognitive assessment (version 7.2)
    - Wechsler adult intelligence scale
- At discharge from the hospital: Functional testing: Activities Daily Life (ADL) and 6 minute walking distance (6MWD)
- Length of stay in the ICU
- Duration of mechanical ventilation
- PGF2 alfa (as a marker of reactive oxygen species) will be measured on stored serum samples to be collected at baseline and after 24 hours

6.7. Neurologic prognostication

All patients will receive full ICU treatment until minimum 5 days after admission. At this point, a neurologist who is unaware of the intervention assignment will perform a standardized full neurologic evaluation and issue a recommendation for the continuation or withdrawal of therapy. The neurologic evaluation will be based on clinical signs (including GCS, pupillary and corneal reflexes), SSEP and EEG. Findings allowing for earlier discontinuation of active intensive care will be (1) patients with myoclonus

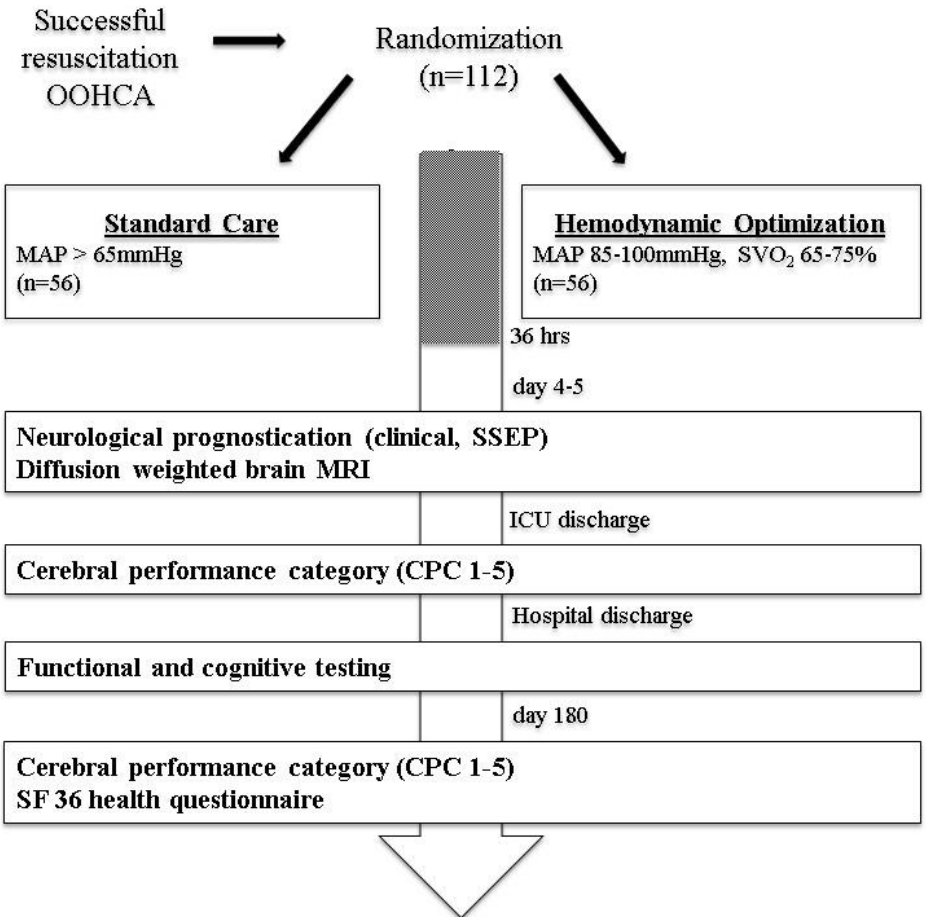
status during the first 24 hours after admission and a bilateral absence of N20-peak on SSEP and (2) patients who become brain death due to cerebral herniation. All clinical decisions will remain at the discretion of the treating team.

6.8. Efficacy and Safety Variables

6.8.1. Duration of Participation

It is expected that patients will participate in this study for 180 days, including 36 hours of treatment with study drug, cardiac MRI at day 4-5 and clinical follow-up until 180 days after CA.

Adverse events will be recorded during the period of study drug administration.



Visit schedule overview:

- At ICU discharge:
    - Cerebral performance category score
    - Length of ICU stay
    - Length of mechanical ventilation
    - Tracheostomy (yes/no)

- At hospital discharge
    - Cognitive testing
    - ADL
    - 6 MWD
    - Cerebral performance category score
- At 180 days post-CA
    - Cerebral performance category score
    - SF36

6.8.2. Assessment of outcome

- **Primary efficacy outcome**:

  The primary outcome is the extent of cerebral ischemia as quantified by diffusion weighted MRI (DW-MRI) to be performed at day 4-5 with quantification of the percentage of ischemic voxels with an apparent diffusion coefficient (ADC) below 0.650 mm^2/s.

- **Secondary efficacy outcomes:**
    - Cerebral performance category 3-5 at discharge from the ICU

      CPC 1: return to normal cerebral function and normal living

      CPC 2: Disability but sufficient function for independent activities of daily life

      CPC 3: severe disability

      CPC 4: Coma

      CPC 5: Death
    - Cerebral performance category 3-5 at 180 days post-CA (assessed by trial investigators that are unaware of the treatment assignment)
    - SF36 questionnaire at 180 days post-CA (assessed by trial investigators that are unaware of the treatment assignment)
    - Neurocognitive testing at discharge from the hospital
    - Biomarkers: Neuron specific enolase (day 1-2-3-4-5)
    - Functional testing: Activities Daily Life (ADL) and 6 minute walking distance (6MWD) at discharge from the hospital
    - Renal function: creatinine day 1-2-3-4-5 and urinary output day 1-2-3-4-5.
    - Length of stay in the ICU
    - Duration of mechanical ventilation
    - Placement of tracheostomy

- **Safety outcomes:**
    - Incidence of life threatening arrhythmias during intervention period
    - Incidence of new onset atrial fibrillation during intervention period
    - Incidence of pulmonary congestion requiring diuretics during intervention period

6.9. Statistical Methods Planned

6.9.1. Sample size

Based on the results of a pilot study at Stanford University in which the standard deviation of the percentage ADC < 0.650 mm^2/s in comparable post-CA patients was 8.9%, we estimated that 56 patients would be necessary in each study group to show a 40% reduction in the extent of cerebral ischemia with a power of 80% at a two-sided alpha level of 0.05.

6.9.2. Interim Analyses

Given the relative small sample size, we will not perform interim analysis.

6.9.3. General statistics

All data will be managed by the LCC in conjunction with the Steering Committee. Data will be entered and reviewed on an ongoing basis. Key listings and tables will be defined by the Steering Committee. Tables, listings and raw data (as SAS transport files) will be made available to the members of the Steering Committee upon request.

The statistical analysis of the primary and all secondary efficacy endpoints will be performed in the modified Full Analysis Set (FAS), defined as all randomly assigned patients except those withdrawing informed consent for use of all trial data and in case many protocol violations are observed throughout the study, a Per Protocol Set (PPS) will be defined and all efficacy analyses will be repeated on the PPS.

All continuous data will be presented by treatment group using the number of non-missing observations, mean, standard devation, median and (Q1,Q3). Categorical data will be presented by treatment group using the observed frequencies and percentages for each category.

The primary endpoint (% voxels with ADC < 0.650 mm^2/s) will be analyzed by means of an analysis of variance (ANOVA) that includes randomized group and initial shockable rhythm as factors. The treatment effect will be estimated by the difference between treatment groups and presented along with its corresponding 95% confidence interval. Missing values for patients who die prior to the DW-MRI will be imputed on the basis of age, gender, presence of basic life support, presence of initial shockable rhythm, duration of advanced life support, neuron specific enolase, presence of a malign EEG pattern on day 1, final outcome at ICU discharge and allocated treatment arm.

Continuous and normally distributed secondary endpoints will be analyzed by means of an ANOVA including randomized treatment and initial shockable rhythm as factors in the model. Estimated treatment differences will be presented with their 95% confidence interval. Continuous secondary endpoints that show serious deviations from a normal distribution will be analyzed by means of a Van Elteren that includes the initial shockable rhythm as stratification factor. Binary secondary endpoints will be analyzed by means of a stratified Chi-squared test. Treatment differences will be expressed as risk ratios and presented along with their corresponding 95% confidence intervals.
Censored outcomes will be presented using Kaplan-Meier curves analyzed using a stratified long-rank test. The treatment effect will be expressed as a hazard ratio.

Prespecified subgroup analysis

Prespecified subgroup analysis will be performed for the primary endpoint according to age (> or <65 years), gender, time-to-ROSC (> or < 25 min), Initial rhythm (shockable or non-shockable), presence of bystander CPR (yes/no), presence of chronic hypertension (yes/no) and treatment center.

The interaction will be assessed using an analysis of variance.

The full statistical methods planned for this trial will be written as a separate document (Statistical Analysis Plan) prior to the completion of the study.

6.10. Changes in Conduct of the Study or Planned Analyses

Any change in the conduct of the study or planned analyses instituted after the start of the study will be documented. The date, time and reason for the change, the procedure used to decide on the change, the person or group responsible for the change and the nature and content of the data available when the change is made will be documented whether or not the change was documented as a formal protocol amendment.

7. MISCELLANEOUS

7.1. Case Report Forms

All case report forms will be electronic using Open Clinica, a web-based tool, provided by LCC. The site staff will enter and edit the data via a secure network, with secure access. An electronic audit trail will be maintained. The investigator will confirm the accuracy of the data by using an electronic signature. ZOL as a Study Center shall only provide coded or de-identified study data to the Sponsor.

7.2. Investigator Requirements

All investigators must be qualified by training and experience to undertake the proposed clinical trial, and assume responsibility for all aspects of the trial conducted at their investigative site.

Prior to study initiation, the investigator will complete and submit to LCC all documents required by ICH (E6) section 8.0. Additionally, each investigator must assure the following:

7.2.1. Study Staff Training

The study staff is qualified by training and experienced to assist with the proposed research. This training must be documented and maintained at the study site.

7.2.2. IEC Requirements

An IEC that complies with the requirements set forth in ICH (E6) section 3.0 will be responsible for the initial and continuing review and approval of the proposed clinical study.

7.2.3. IEC Reporting of Issues

Prompt reporting to the IEC all changes in research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research until the IEC has approved the changes.

7.2.4. IEC Approvals

Reporting to IEC as required on the progress of the investigation and within three months after completion, termination or discontinuation of the study.

7.3. Recording of Adverse Events

Each patient/subject will be assessed for any new or continuing adverse events by the clinical investigator and the study coordinator during the intervention period. An adverse event is defined as any untoward medical occurrence in a patient/subject during the clinical trial. The event need not have a causal relationship with the treatment. This includes any events that are not seen at baseline or, if present at baseline, have worsened in severity. Any adverse event reported by the caregiver or noted by the investigator or study coordinator will be recorded on the Adverse Event pages on the case report form. The severity and drug relationship will be determined, and any management required will be recorded. The investigator will review the clinical laboratory test results in a timely fashion. Only those results qualifying as adverse events, as defined above, will be recorded on the Adverse Event section of the case report form. An effort will be made to determine the final outcome/resolution of adverse events that persist at the time of study completion.

7.3.1. Study treatment Relationship

The investigator is responsible for assessing the causal relationship between any events and the study treatment. Additionally, the investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The clinical investigator should determine the relationship between the adverse event and the treatment using the following explanations:

Not Related

The event is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject.

Unlikely

The event was most likely produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject, and does not follow a known response pattern to the study treatment.

Possible

The event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study treatment, but could have been produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Probable

The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study treatment and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Definitely

The event follows a reasonable temporal sequence from the time of treatment administration and follows a known response pattern to the study treatment and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject and either occurs immediately following study drug administration, or improves on stopping the treatment.

Temporal sequence is defined as an association between the suspect treatment and the observed reaction or event in which the suspect treatment was started prior to the reaction or event as defined by history or blood level of drug.
Study drug(s) includes the drug(s) under evaluation, the reference drug(s), placebo, or any other drug(s) required by the protocol.
Severity of an adverse event will be defined from the qualitative assessment of the degree of intensity of the event as determined by the investigator or as reported to him/her by the patient/subject. The assessment of severity is made irrespective of treatment or seriousness of the event and should be evaluated according to the following scales:

1 = **Mild** - awareness of the symptom but easily tolerated
2 = **Moderate** - discomfort enough to interfere with normal activities
3 = **Severe** - Incapacitating with the inability to perform normal activities

7.3.2. Serious Adverse Events

A serious adverse event is defined as any event that at any dose: results in death, is life-threatening, results in persistent or significant disability / incapacity, requires or prolongs inpatient hospitalization, or is a congenital anomaly. Important medical events that without medical or surgical intervention would also have resulted in one of the outcomes listed above are also considered a serious adverse event. Any serious adverse event must be reported on a Serious Adverse Event form to LCC within 24 hours of investigator becoming aware of the event by fax to:

Leuven Coordinating Centre
Fax to: (32) 16 342100

The patient/subject must be monitored carefully until the condition disappears, reaches a clinically stable endpoint, and/or the etiology is identified. The initial telephone contact will be followed by detailed descriptions of the event and supported as needed with written copies of hospital case reports, autopsy reports, and other appropriate documents.
Follow-up information (including information requested by the Sponsor) should be reported within 24-hours. All serious, related and unexpected adverse events will be sent from LCC to the principal investigator (blind maintained), who will forward these reports to their IEC. All serious adverse events will also be

distributed to the Data Safety and Monitoring Board and other investigative sites. Serious adverse events will be recorded during the period of study drug administration.

7.3.3. Unexpected Adverse Events

An unexpected adverse event is any event that is not identified in nature, severity or frequency in the current study protocol.

7.4. Records Retention

In compliance with GCPs and ICH Guidelines, copies of all records (e.g., informed consent documents, laboratory data slips, source documents, IND safety reports, test article dispensing records, etc.) which support case report forms of this study, must be retained in the files of the responsible investigator for a minimum of two years following notification by LCC that all investigations at all sites are completed, terminated, or discontinued. If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. LCC must be notified in writing of the name and address of the new custodian.

7.5. Monitoring

The study will be periodically monitored by a CRA. It is the responsibility of the principal investigator to provide all study records, including case report forms, source documentation, etc., to the monitor at their visit.

7.6. Amendments to the Protocol

Neither the investigator nor the Steering Committee will amend or modify the protocol without written notification of the other. All amendments must be approved by the Steering Committee prior to implementation. All amendments must be submitted to the IEC as required. The IEC must approve major amendments prior to implementation at the study site.

7.7. Termination of Trial

It is agreed that, for reasonable cause, either the investigator or the Steering Committee may terminate this study, provided written notice is submitted at a reasonable time in advance of intended termination.

7.8. Insurance

In accordance with the LEH Sponsor shall assume, even without fault, the responsibility of any damages incurred by a study Subject and linked directly or indirectly to the participation to the study, and shall provide compensation therefore through its insurance.

7.9. Intellectual Property

Unless arranged for otherwise in the IWT grant agreement, Study Centers expressly agree that each Study Center shall remain the owner of its source data and results it generates pursuant to the study. In the event of joint results the Study Centers shall have joint property thereof

APPENDIX 1. INVESTIGATOR AGREEMENT

Protocol Neuroprotect
Version: PROTOCOL version 4, 20 Jan 2017

I have read the protocol, *"Neuroprotective goal directed hemodynamic optimization in post-cardiac arrest patients: a randomized controlled trial (the NEUROPROTECT post- CA trial)"*, and agree to conduct the study as outlined therein. I will make a reasonable effort to conduct the study in a timely and efficient manner and will ensure that all participating staff members are adequately trained to carry out the tasks for which they have been assigned.

I will submit this protocol and all other pertinent information to my EC for approval.

_____ _____
Principal Investigator's Signature Date

_____
Name of investigator (printed)