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Mean arterial pressure after out-of-hospital cardiac arrest: a study protocol for a multicentre randomised controlled trial with blinded primary outcome assessor (METAPHORE)

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Mean arterial pressure after out-of-hospital cardiac arrest: a study protocol for a multicentre controlled trial with blinded primary outcome assessor (METAPHORE)

ABSTRACT

Introduction: Out-of-hospital cardiac arrest is a public health concern with a high mortality rate. Hypoxic ischemic brain injury is the primary cause of death in patients admitted to intensive care unit (ICU) after return of spontaneous circulation (ROSC). Several systemic factors, such as hypotension, can exacerbate brain injuries. International guidelines recommend targeting mean arterial pressure (MAP) of at least 65 mmHg. Several observational studies suggest that a higher MAP may be associated with better outcomes but no randomised trials have shown an effect of higher MAP. The ongoing "Mean arterial pressure after out-of-hospital cardiac arrest" (METAPHORE) trial aims to compare a standard MAP threshold (MAP ≥ 65 mmHg) with a high MAP threshold (MAP ≥ 90 mmHg) to evaluate whether implementing a higher MAP threshold can improve neurological outcome in patients admitted to ICU after cardiac arrest.

Methods and analysis: METAPHORE is a randomised, controlled, multicentre, open-label with blinded primary outcome assessor, comparing two parallel groups of patients 18 years of age or older, receiving invasive mechanical ventilation for coma defined by a Glasgow Coma Score ≤ 8/15 after out-of-hospital cardiac arrest and sustained ROSC. The MAP target threshold is 65 mmHg or more in the control group throughout

the ICU stay and 90 mmHg or more in the intervention group within the first 24 hours after randomisation followed by 65 mmHg or more for the remainder of the ICU stay. Both groups receive the same general care concerning post-cardiac arrest syndrome management according to international guidelines. The primary endpoint is the proportion of patients with a favorable neurological outcome as defined by a modified Rankin scale (mRS) of 0 to 3 measured on day 180 after randomisation by a psychologist blinded to the allocation of the intervention. Secondary outcomes include proportion of patients alive at ICU and hospital discharge, at day 28 and day 180; proportion of patients alive at ICU discharge with a mRS of 0 to 3; the EuroQOL-5D-5Q at day 180; the Clinical Frailty scale at day 180; the duration of organ support; the proportion of patients with acute kidney injury stage 3 and need for renal replacement therapy within ICU stay and proportion of patients with persistent need for renal replacement therapy at ICU discharge; and safety outcomes (cardiovascular, neurological, cutaneous, digestive and hemorrhagic complications within 7 days after randomisation). Subgroup analysis are planned according to initial cardiac arrest rhythm (shockable or non-shockable), chronic hypertension and cardiac arrest hospital prognosis (CAHP) score. Outcomes will be analyzed on an intention-to-treat basis. Recruitment started in October 2024 in 27 French ICU's and a sample of 1380 patients is expected by October 2027.

Ethics and dissemination: The study received approval from the national ethics review board on 8 February 2024 (Comité de Protection des Personnes Sud-Est V – 2023-

A00257-38). Patients are included after informed consent is obtained either from a proxy or through an emergency procedure. Results will be submitted for publication in peer-reviewed journals.

Trial registration: www.clinicaltrials.gov NCT05486884

Keywords:

Out-of-hospital cardiac arrest; arterial pressure; brain injury

STRENGHT AND LIMITATIONS

- This is a pragmatic randomised multicentre study comparing two MAP thresholds in patients who are comatose after out-of-hospital cardiac arrest resuscitation.
- The primary endpoint is the proportion of patients with good neurological outcome assessed by the modified Rankin scale measured 180 days after randomisation. The primary endpoint is evaluated by an independent psychologist blinded to the allocation of the intervention with a semi-structured interview.
- Safety outcomes are assessed through cardiovascular, neurological, cutaneous, digestive and major bleeding complications.
- A limitation is that blinding of the healthcare staff to MAP targets is not possible without a specific device.

INTRODUCTION

Background and rationale

Out-of-hospital cardiac arrest (OHCA) is a significant public health concern associated with high mortality rates and severe disability in survivors [1,2]. The primary cause of death in patients admitted in ICU after return of spontaneous circulation (ROSC) is brain injury [3,4]. Hypoxic-ischemic brain injury (HIBI) is the consequence of circulatory arrest and reperfusion. Several factors can exacerbate HIBI after ROSC such as arterial hypotension. In patients resuscitated from OHCA, cerebral autoregulation is often impaired, rendering brain vulnerable to ischemia and secondary injuries [5,6]. International guidelines suggest maintaining a mean arterial pressure (MAP) of 65 or 70 mmHg [7]. Several observational studies support that a higher MAP target is associated with better survival and neurological outcomes [8]. However, evidence supporting this strategy remains limited. Three interventional studies have shown no effect of higher MAP in OHCA patients [9-11]. However, two of these studies are pilot feasibility studies, lacking the power to show statistical differences in clinical outcomes [9,10]. The most recent study included 800 patients randomised in two arms regarding MAP: a low blood pressure target of 63 mmHg and a high blood pressure target of 77 mmHg [11]. Clinicians were blinded to the intervention through the use of a monitoring device that was randomly offset to display 10% lower or 10% higher blood pressure values while the treating physicians aimed for a common target of 70 mmHg in all patients. Limitations of this trial included a selected study population, a high MAP target lower than cerebral autoregulation threshold [12] and minimal differences in MAP

values between the two groups [13]. These limitations do not allow to conclude that there is no effect of a higher level of MAP after cardiac arrest.

In collaboration with the After ROSC network and the CRICS-TRIGGERSEP-F-CRIN network, we designed the MEan arTeriAl Pressure after out-of-HOspital cardiac arREst (METAPHORE) trial.

Herein, we report the trial protocol according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. This trial is registered at ClinicalTrials.gov and this manuscript was written in accordance with SPIRIT guidelines (www.spirit-statement.org/spirit-statement/).

Objectives

The study hypothesis is that a strategy targeting a MAP threshold ≥ 90 mmHg within 24 hours after ROSC will significantly reduce the proportion of patients with poor neurological outcomes on day 180 after randomisation compared with standard care (MAP ≥ 65 mmHg).

The main objective of the study is to demonstrate the efficacy of a high MAP threshold (MAP ≥ 90 mmHg) on neurological prognosis at six months in patients resuscitated from out-of-hospital cardiac arrest relative to the standard threshold (MAP ≥ 65 mmHg).

The secondary objectives of the study are:

- To demonstrate the superiority of a high MAP threshold (MAP ≥ 90 mmHg) compared to the standard threshold (MAP ≥ 65 mmHg) in terms of survival at ICU discharge, at hospital discharge, at day 28 and six months,

- To demonstrate the superiority of a high MAP threshold compared to the standard MAP threshold in terms of neurofunctional prognosis at ICU discharge, quality of life at six months, length of stay in the ICU, duration of organ support and organ failure.
- To demonstrate the safety of a high MAP threshold compared to the standard threshold in terms of global and specific complications within 7 days of inclusion.

Subgroup analysis will be performed:

- Neurofunctional prognosis at six months according to initial cardiac arrest rhythm (shockable or non-shockable);
- Neurofunctional prognosis at six months according to presence or absence of chronic arterial hypertension;
- Neurofunctional prognosis at six months according to Cardiac Arrest Hospital Prognosis score (CAHP score) at admission.

Trial design

The METAPHORE study is designed as a pragmatic, randomised, controlled, open-label, multicentre, superiority trial with two parallel groups, a 1:1 allocation and blinded primary outcome assessor.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The study is being conducted in 27 ICUs across France. Sites characteristics are listed in supplementary files. All ICU staff participating in the study receive mandatory training on the study procedures before the study begins.

Eligibility criteria

The trial includes adults (age ≥ 18 years) admitted in a participating ICU after resuscitated out-of-hospital cardiac arrest with initially shockable or non-shockable rhythm, with a sustained ROSC (defined as 20 minutes with signs of circulation without the need for chest compressions) and who need mechanical ventilation for coma (defined by a Glasgow Coma Scale ≤ 8). Patients are excluded from the study if they meet any of the following criteria:

- In-hospital cardiac arrest (first cardiac arrest in case of several ones)
- Unwitnessed cardiac arrest with initial rhythm of asystole
- Time between ROSC and inclusion > 6 hours
- Cardiac arrest in context of multiple trauma
- Cardiac arrest in context of hemorrhagic shock or severe hemorrhage necessitating hemostasis (by surgery,radiological procedure or endoscopic procedure)
- Cardiac arrest secondary to an acute brain disease (ischemic or hemorrhagic stroke, subarachnoid hemorrhage, severe traumatic brain injury)

- Refractory shock defined as a MAP < 65 mmHg for more than one hour on norepinephrine or epinephrine at a dose > 1 μg/kg/min despite adequate fluid resuscitation
- Extracorporeal circulatory support prior to inclusion
- Known allergy to norepinephrine or any of its excipients
- Decision to limit care before inclusion
- Modified Rankin scale (mRS) of 4 or 5 before cardiac arrest
- Inclusion in another interventional study in which the primary endpoint is neurological prognosis
- Pregnancy or breast feeding
- Patients in detention by judicial or administrative decision, under forced psychiatric care or under legal protection (guardianship or curatorship)
- Non-French speaking
- Patient already included in this trial
- Lack of social security coverage.

Interventions

High MAP threshold

For patients who are assigned to the high MAP threshold group, norepinephrine is titrated to maintain MAP ≥ 90 mmHg. This threshold is maintained for the first 24 hours following randomisation by the infusion of norepinephrine at an appropriate dose. The minimum dose of norepinephrine required to maintain MAP above the threshold is

sought. The vasopressor infusion rate is decreased in increments of 0.05 µg/kg/min at least every hour. Thus, if MAP falls below 90 mmHg, the dose of norepinephrine is increased by 0.05 µg/kg/min every ten minutes. No maximum threshold of MAP is defined. Lowering MAP is not recommended within 24 hours after randomisation except if the intervention is suspected to cause severe adverse events. This decision is left to the discretion of the clinician and drugs used are documented in the case report form. Norepinephrine dose will be reported as base equivalence.

From 24 hours after randomisation until ICU discharge, a MAP ≥ 65 mmHg is targeted. The management of vasopressor therapy, sedation/analgesia and antihypertensive agents after 24 hours is left to the discretion of the clinician.

Standard MAP threshold

For patients who are assigned to the standard MAP threshold group, norepinephrine is titrated to maintain MAP ≥ 65 mmHg during all the ICU stay. No maximum threshold of MAP is defined, and lowering MAP is not recommended within 24 hours after inclusion except in case of severe adverse events. This decision is left to the discretion of the clinician and drugs used are documented in the case report form. Norepinephrine dose will be reported as base equivalence.

Discontinuing or modifying allocated interventions

The investigator is allowed to temporarily or permanently discontinue a patient's participation in the study for any reason that would best serve the interests of the

subject, particularly in the case of serious adverse events suspected to be associated with the strategy used.

Other interventions in both groups

Because of the risk of increased cardiac afterload due to the use of vasopressors and high levels of MAP, the scientific board recommends that clinicians monitor cardiac function and use inotropic agents if appropriate. Monitoring method (echocardiography or invasive hemodynamic monitoring) is left to the discretion of the physician.

General ICU care, including respiratory management, sedation, glycemic control and transfusion, is delivered similarly in both allocation groups according to international guidelines [7]. Fever is actively prevented by targeting a temperature ≤ 37.8°C for at least 72 hours in patients who remain comatose [14].

Central line and arterial catheter insertion are left to the discretion of the physician.

In both groups, decisions regarding limitation or withdrawal of treatment follow European guidelines and neuroprognostication algorithm [7]. Decisions to withhold or withdraw active treatment are reported in the case report form.

Outcomes

The primary outcome is the proportion of patients with a good neurological outcome 180 days after randomisation. Good neurological outcome is defined by a mRS of 0 to 3. This scale is a global evaluation scale of disability, with seven levels (0 = no symptoms; 6 = patient dead). This score is commonly used to assess neurological

prognosis after CA [15,16]. mRS is measured by a psychologist (blinded to the randomisation arm) during a semi-structured telephone interview.

The secondary outcomes are:

- Proportion of patients alive at ICU discharge, at hospital discharge, at day 28 (D28) and six months (D180) after randomisation ;
- Proportion of patients alive at ICU discharge with a modified Rankin scale of 0 to 3;
- The EuroQol-5D-5L six months after randomisation. EuroQol-5D-5L is a measure of health-related quality of life and comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression);
- The Clinical Frailty Scale (CFS) six months after inclusion. CFS summarizes the overall level of fitness or frailty of a patient with a score from 1 (very fit) to 9 (terminally ill);
- Number of ICU-free days calculated from the number of days alive outside the ICU by D28;
- Number of ventilator-free days, number of catecholamine-free days and number of renal replacement therapy-free days calculated from the number of days alive without invasive mechanical ventilation, catecholamine infusion or renal replacement therapy by D28;

- The proportion of patients with acute kidney injury stage 3 according to the Kidney Disease Improving Global Outcomes (KDIGO) classification and need for renal replacement therapy (RRT) (for patients without renal replacement therapy before cardiac arrest) within ICU stay and persistent need for RRT at ICU discharge. Acute kidney injury stage 3 is defined by at least one of the following criteria: serum creatinine concentration of more than 4 mg/dl (354 µmol/liter) or greater than 3 times the baseline creatinine level, anuria (urine output of 100 mL/day or less) for more than 12 hours, oliguria (urine output below 0.3 ml/kg/h or below 500 mL/day) for more than 24 hours.

The safety outcomes are:

- **Cardiovascular complications** assessed by determining the number of patients presenting a severe cardiovascular complication within 7 days of randomisation. A severe cardiovascular complication is defined by at least one of the following criteria:
  - newly occurring or recurrent ventricular fibrillation or ventricular tachycardia requiring antiarrhythmic drugs and/or electrical cardioversion and/or resuscitation due to hemodynamic instability or cardiac arrest; or
  - severe atrial flutter or atrial fibrillation, requiring treatment (antiarrhythmic drugs or rate slowing medication) and/or electrical cardioversion due to

hemodynamic instability (a patient with chronic atrial flutter or atrial fibrillation but not requiring urgent treatment for hemodynamic instability will be not concerned); or

- bradycardia (<40 beats per minute) requiring pacing or resuscitation due to hemodynamic instability or cardiac arrest; or
- newly occurring or recurrent ST-Elevation Myocardial Infarction (STEMI) diagnosed using an electrocardiogram and confirmed by coronary angiography; or
- need for extracorporeal life support (ExtraCorporeal Membrane Oxygenation or Impella) for refractory cardiogenic shock; or
- unexpected recurrent cardiac arrest (cardiac arrest due to discontinuation of treatments will not be concerned);

- **Neurological complications** assessed by determining the number of patients presenting with stroke (ischemic stroke, subarachnoid hemorrhage or cerebral hematoma), confirmed by imaging (CT-scan or MRI) within 7 days of randomisation (systematic cerebral imaging is not required by the protocol but only in case of clinical suspicion of stroke or for neuroprognostication);
- **Cutaneous complications** assessed by determining the number of patients presenting ischemia or necrosis of the extremities within 7 days of randomisation;

- **Digestive complications**, assessed by determining the number of patients presenting a clinical suspicion of digestive ischemia, confirmed by imaging (CT-scan), endoscopy or exploratory laparotomy, within 7 days of randomisation;

- **Major bleeding** assessed by determining the number of patients presenting one of the International Society on Thrombosis and Haemostasis (ISTH) criteria within 7 days of randomisation (fatal bleeding and/or symptomatic bleeding in a critical area or in an organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 20 g.L-1 or more or leading to transfusion of two or more units of red cells) ;

- **Global complications** defined by the proportion of patients with at least one complication (cardiovascular, neurological, cutaneous, digestive or hemorrhagic) within 7 days of randomisation;

Subgroup analysis

Patients are analyzed by subgroups concerning neurological outcome at six months. Three subgroups are defined for this analysis:

- Subgroups of patients with and without confirmed chronic hypertension (defined as the need for chronic treatment);
- Subgroups of patients with an initial non-shockable rhythm and an initial shockable rhythm;

- Subgroup of patients with CAHP score < 150, CAHP score 150-200 and CAHP score > 200. The CAHP score represents a simple tool for early risk stratification of patients admitted in ICU after OHCA, using seven variables (age, rhythm, time from collapse to basic life support, time from basic life support to ROSC, location of cardiac arrest, epinephrine dose and arterial pH) [17].

Participant timeline

Figure 1 shows the Consort diagram of the METAPHORE trial and Table 1 assessments and visits for participants.

Data	Inclusion Day 0	H0 to H24	H24 to H72	D1	D2	D3	D4	ICU discharge	Hospital discharge	D28	D180
Eligibility screen	X										
Informed consent signed or emergency procedure	X										
Demographic data	X										
Comorbidities	X										
Modified Rankin Scale	X (before CA)							X			X
Clinical Frailty Scale	X (before CA)										X
Characteristics of CA	X										
Hemodynamic and clinical data	X	X	X								
Neurological examination	X										

Laboratory tests (at the discretion of the physician)	X			X	X	X	X				
Electrocardiogram	X			X	X	X					
SOFA score	X										
Cardiac function evaluation or invasive hemodynamic monitoring (at the discretion of the physician)	X			X	X	X					
Complications (between inclusion and D7)								X			
SAPS II				X							
Catecholamines		X	X								
Sedation and analgesia		X	X	X	X	X	X				
Vital status				X	X	X	X	X	X	X	X
Glasgow score	X										
FOUR Score	X										
Characteristics of ICU stay								X			
Characteristics of organ support								X		X	
Neuroprognostication							X	X			
Telephone interview											X
Living situation											X
EuroQol-5D-5L	X (before CA)										X
Patient consent (as soon as possible)								X	X	X	X

Table 1: Flowchart of timing in collection of different variables. CA, cardiac arrest; SOFA, Sequential organ failure assessment; SAPS II, Simplified acute physiology score II; FOUR score, Full outline of unresponsiveness score; ICU, intensive care unit.

Sample size estimation

The required number of subjects is based on an anticipated difference in proportion of patients with mRS 0 to 3 at D180 between the two groups. Based on previous studies and After ROSC registry [18], we estimate that 30% of the patients included in the standard group will have a good neurological outcome (mRS 0 to 3) at six months. By expecting 38% of patients with good neurological outcome at six months in the experimental group, 550 patients are required in each group (power of 80% and alpha risk of 5%). The sample size calculation corresponds to a relative risk reduction of 11.4% concerning worse neurological outcome and an absolute risk reduction of 8%. The number requiring treatment is 12.5. Assuming 20% of patients included in the standard group will have a spontaneous MAP over 90 mmHg during the first 24 hours after inclusion (personal data not published), 690 patients will be included in each arm (total = 1380 patients). Patients lost to follow-up will be considered deceased (mRS 6).

Recruitment

All patients admitted in participating ICU after out-of-hospital cardiac arrest during the study period are screened for eligibility. A log of patients considered for study participation will be maintained, including the reasons for non-inclusion.

All the participating centers currently manage patients after cardiac arrest. All the participating centers have already participated in clinical trials and the trial is supported by two clinical research networks:

- AfterROSC network, associating physicians from several intensive care units in France and Belgium aiming to promote and develop research and teaching in post cardiac arrest management;
- CRICS-TRIGGERSEP F-CRIN network, a national network for research on sepsis bringing together leaders in the field from fundamental and translational research, biostatistics research and clinical investigations.

METHODS: ASSIGNMENT OF INTERVENTIONS

Randomisation and treatment allocation

Using a web-based system (Ennov Clinical® Software), patients are randomised in a 1:1 ratio within 6 hours after ROSC to a high MAP threshold (MAP target ≥ 90 mmHg within 24 hours) or a standard MAP threshold (MAP target ≥ 65 mmHg). A minimization algorithm based on presumed chronic hypertension, initial cardiac arrest rhythm (shockable or not shockable) and participating center is used for the randomisation process. After enrolment and randomisation, patients, treating clinicians and study personnel are not blinded to study group assignment. Only the primary outcome assessor is blinded to study group allocation. The day of randomisation is defined as D0, and the time of randomisation is defined as H0. The designated strategy is initiated immediately after randomisation.

Blinding

The clinical team responsible for the participants (physicians, nurses and others) and involved with direct patient care will not be blinded to allocation group due to the inherent difficulty in blinding the intervention. Health personnel responsible for outcome assessment at follow-up will be blinded to the allocation of the intervention. Potential bias will be mitigated by using conservative and strict protocols for neuroprognostication and related decision making (i.e., regarding limitations in level of care). The same neuroprognostication algorithm, based on European Resuscitation

Council and European Society of Intensive Care Medicine guidelines [7], will be used for all patients included in the study.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection

Data collection for this study is described in supplementary files and can be found in the protocol version 1.1 dated 2024/01/24.

Data management

An internet-based data collection tool will be used for this study to store the data of all participants. This electronic case report form (eCRF) is a secure, interactive, web response system available at each study center. The data manager of the Clinical Research Unit of Le Mans Hospital will monitor collected data and screening forms in each participating center. A blind review of the data will be performed before the database is locked. The database will be locked according to standard operating procedures in force at the DRCI, and the data will be extracted for statistical analyses.

Statistical methods

The main analysis will be conducted on an intention-to-treat basis: all patients included in the study will be analyzed according to their group assigned by randomisation. A statistical analysis report will be prepared following the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) Statement (http://www.consort-statement.org/). Any modification of the presented statistical analysis strategy will be indicated in the final publication.

Descriptive statistics

Descriptive statistics will be used to summarize the characteristics of the control and experimental groups. Continuous variables will be presented as mean and SD if they follow a normal distribution or as median and IQR as appropriate. Categorical variables will be described using exact numbers and percentages.

Analysis of the primary endpoint

The primary endpoint will be the proportion of patients in each arm with good neurofunctional prognosis evaluated 180 days after inclusion by the modified Rankin scale (mRS). A mRS of 0 to 3 will be considered as a good neurological outcome, whereas a mRS of 4 to 6 will be considered as a poor one. The proportion of patients with a good neurofunctional outcome at D180 will be compared between the two arms in a chi-squared test or Fisher's exact test as appropriate.

Analysis of secondary endpoints

Survival analysis at ICU discharge, at hospital discharge, at D28 and 6 months will be characterized by Kaplan Meier curves (or actuarial according to the type of temporal distribution of the events of interest) to determine the median of survival with its 95% confidence interval. If the realization conditions are favorable, they will be compared by a log-rank test.

All the other secondary endpoints will be analyzed using standard descriptive statistics tools, diagrams, histograms for qualitative variables, box plots or bar charts for quantitative variables. If the comparative conditions are respected, the appropriate

statistical tests will be implemented (Chi 2 or Fisher's exact test, Student's t or Mann-Whitney test).

Level of statistical significance

A two-sided p-value of 0.05 or less will be considered statistically significant.

Handling of missing data

Due to the primary endpoint being evaluated remotely from inclusion and outside of ICUs, it is possible that some patients may be lost to follow-up. These patients will be considered as mRS 6 (deceased). Missing data are not imputed for the outcomes analysis.

METHODS: MONITORING

Data monitoring

The Data Monitoring Committee (DMC) comprises three clinicians with experience in the conduct, monitoring and analysis of RCTs. None of the members are directly involved in the study. Each member has signed a conflict-of-interest form. The DMC has approved the study protocol and the operating charter.

Two interim analyses are planned, after the inclusion of 400 and 800 patients. We will apply the Peto and Haybittle rule:

- Significance threshold for the first analysis: 0.01;

- significance threshold for the second analysis: 0.01;

The significance threshold for the final analysis will be 0.049.

Alternative endpoints will be used for interim analyses: death of any cause at day 28 and global complications within 7 days after randomisation (safety outcomes).

At interim analysis, the committee will monitor the rate of inclusion and record expected adverse effects (complications such as secondary endpoints of the study) and will make the final decision to continue the study or not. Results of interim analysis on day 28 mortality will be provided as well as the proportion of expected adverse events. Patients' characteristics recorded at randomisation will be also provided. Early stop for safety reasons will be left at the discretion of the DMC.

Monitoring of AEs

Post cardiac arrest patients are at high risk for developing complications no matter the strategy of MAP management. Several expected AEs will not be recorded as an entity (only such as complications in the CRF, secondary endpoints of the study). A list of serious AEs requiring an immediate declaration is established.

ETHICS AND DISSEMINATION

Research ethics approval

The METAPHORE trial received approval from the national ethics review board on 8 February 2024 (Comité de Protection des Personnes Sud-Est V, registration number 2023-A00257-38).

Consent to participate

Only patients who are comatose after resuscitation from OHCA are included in the trial, and the intervention should be implemented the earliest after ROSC in patients who are comatose. Consequently, it is anticipated that eligible patients will be unable to provide consent due to impaired consciousness and information about the study will be provided to their next of kin. Informed written consent will be obtained from the relative by the investigator or by a doctor representing the investigator before definitive inclusion in the study. A copy of the information form and the consent form signed by the two parties will be delivered to the relative.

In cases where no relative is available to consent within 6 hours after ROSC, an emergency consent form completed by the physician allows inclusion according to French law.

Patients who regain their decision-making capacity will be asked to confirm their willingness to participate in the trial. Patients' data of patients without relatives who die without previously recovering consciousness will be included in the statistical analysis.

If the patient at ICU discharge is not able to receive the information and give his consent, this will be collected in the medical file of the patient. The investigator will make every effort to obtain consent, as soon as the patient's health permits.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

The publication policy will follow international recommendations (N Engl J Med 1997; 336:309-315) and the CONSORT statement (http://www.consort-statement.org). Findings will be published in peer-reviewed journals and presented at national and international scientific meetings. The study coordinator (NC) will be responsible for communications and scientific reports, ensuring approval from the other investigators. Data will be shared on reasonable request from the principal investigator.

Patient and public involvement

We plan to engage patient representatives to determine exploratory analysis objectives (patient centered outcome), as well as for communication or dissemination of results.

Trial status

Inclusions started in October 2024. Data collection is ongoing, and inclusions are expected to reach completion in October 2027.

FULL REFERENCES

1. Grubb NR, Elton RA, Fox KA. In-hospital mortality after out-of-hospital cardiac arrest. Lancet Lond Engl. 1995 Aug 12;346(8972):417–21.
2. Bunch TJ, White RD, Gersh BJ, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. N Engl J Med. 2003 Jun 26;348(26):2626–33.
3. Laver S, Farrow C, Turner D, et al. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004 Nov;30(11):2126–8.
4. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013 Nov;39(11):1972–80.
5. Sundgreen C, Larsen FS, Herzog TM, et al. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke. 2001 Jan;32(1):128–32.
6. Ameloot K, Genbrugge C, Meex I, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop “one-size-fits-all” hemodynamic targets? Resuscitation. 2015 May;90:121–6.
7. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med. 2021 Apr;47(4):369–421.
8. Roberts BW, Kilgannon JH, Hunter BR, et al. Association Between Elevated Mean Arterial Blood Pressure and Neurologic Outcome After Resuscitation From

Cardiac Arrest: Results From a Multicenter Prospective Cohort Study. Crit Care Med. 2019 Jan;47(1):93–100.

9. Jakkula P, Pettilä V, Skrifvars MB, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med. 2018 Dec;44(12):2091–101.

10. Ameloot K, De Deyne C, Eertmans W, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. Eur Heart J. 2019 Jun 7;40(22):1804–14.

11. Kjaergaard J, Møller JE, Schmidt H, et al. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022 Oct 20;387(16):1456–66.

12. Ameloot K, Meex I, Genbrugge C, et al. Hemodynamic targets during therapeutic hypothermia after cardiac arrest: A prospective observational study. Resuscitation. 2015 Jun;91:56–62.

13. Chudeau N, Guitton C, Cariou A. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2023 Jan 19;388(3):284.

14. Sandroni C, Nolan JP, Andersen LW, et al. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Intensive Care Med. 2022 Mar;48(3):261-269.

15. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May;19(5):604–7.

16. Iqbal MB, Al-Hussaini A, Rosser G, et al. Predictors of survival and favorable functional outcomes after an out-of-hospital cardiac arrest in patients systematically brought to a dedicated heart attack center (from the Harefield Cardiac Arrest Study). Am J Cardiol. 2015 Mar 15;115(6):730–7.

17. Maupain C, Bougouin W, Lamhaut L, et al. The CAHP (Cardiac Arrest Hospital Prognosis) score: a tool for risk stratification after out-of-hospital cardiac arrest. Eur Heart J. 2016 Nov 7;37(42):3222–8.

18. Lascarrou JB, Bougouin W, Chelly J, et al. Prospective comparison of prognostic scores for prediction of outcome after out-of-hospital cardiac arrest: results of the AfterROSC1 multicentric study. Ann Intensive Care. 2023 Oct 11;13(1):100.

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DECLARATION OF INTERESTS

The METAPHORE study is an investigator-initiated trial funded by the French Ministry of Health obtained in 2021 from a national hospital clinical research program (Programme Hospitalier de Recherche Clinique National, PHRC-21-0056). A scientific committee including NC, JBL, AC and CG conceived, drafted and wrote the project. All authors reviewed the manuscript for important intellectual content and approved the final version submitted. The research networks AfterROSC and CRICS-TRIGGERSEP have endorsed the study project. The study is promoted by Le Mans Hospital.

None of the authors has declared competing of interests.

AUTHORS' CONTRIBUTIONS

NC conceived the study. JBL, AC and CG helped with implementation. PS and EPS provided statistical and methodological expertise in clinical trial design. All authors contributed to refinement of the study protocol and approved the final manuscript.

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FIGURES

Figure 1: Study flowchart

SUPPLEMENTARY MATERIALS

Supplementary material 1.docx: Participating ICU list

Supplementary material 2.docx: Data collection

Supplementary material 3.docx: SPIRIT 2013 Checklist

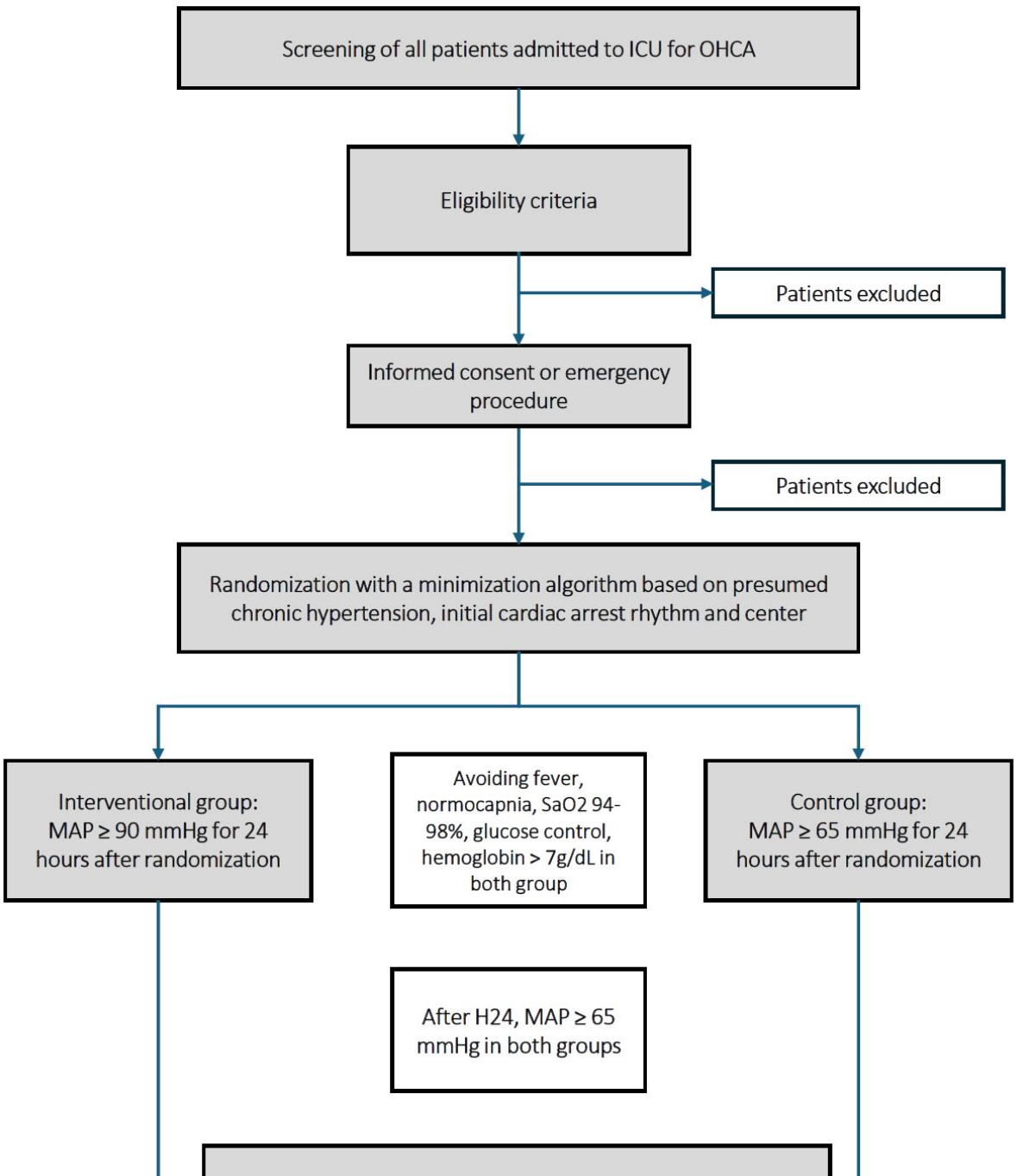

Figure 1: Flow chart. ICU, Intensive Care Unit; OHCA, Out-of-Hospital Cardiac Arrest; MAP, Mean arterial pressure

SUPPLEMENTARY MATERIAL 1 : PARTICIPATING ICU LIST

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SUPPLEMENTARY MATERIAL 2: DATA COLLECTION

Data at day 0 (day 0 starts at inclusion and ends at 11.59 pm the same day):

- Sex
- Weight and height
- Principal comorbid conditions (Charlson index)
- Confirmed chronic hypertension requiring treatment
- Chronic atrial fibrillation or atrial flutter
- Modified Rankin score before cardiac arrest obtained from a relative
- Clinical Frailty Scale before cardiac arrest obtained from a relative
- EuroQol-5D-5L questionnaire before cardiac arrest obtained from a relative
- Date and time of hospital admission and ICU admission
- Characteristics of the cardiac arrest (CA) and prehospital resuscitation: initial rhythm, ,CA localization (home, public place, nursing facility, work, or other), witnessed arrest, bystander cardiopulmonary resuscitation or defibrillation performed, duration of no flow (time from CA to the start of cardiopulmonary resuscitation (CPR)), duration of low flow (time between the start of CPR and return of spontaneous circulation ROSC), time from arrest to advanced life support, specific characteristics of CPR (number of external electric shocks, total dose of epinephrine)
- Glasgow Coma Scale following ROSC before sedation
- Hemodynamic data at the time of inclusion: systolic, diastolic and mean arterial pressure, heart rate, shock, doses of vasopressors and inotropes, fluid resuscitation volume between ROSC and inclusion
- Other clinical data: body temperature and temperature management, pupil examination, cerebral trunk reflexes and FOUR score (Full Outline of UnResponsiveness Score),

presence or absence of status myoclonus, presence of diarrhea, presence of gastrointestinal bleeding

- EKG at inclusion
- Presumed mechanism of CA (acute coronary syndrome, non-ischemic cardiac cause, pulmonary embolism, hypoxemia, shock, accidental hypothermia, metabolic cause, toxic cause, anaphylaxis or other origin)

Laboratory tests and other data analyzed will not be specific to the study and will be collected during routine care in the framework of the management of patients after CA. All biological tests will be performed by the laboratories at the investigating centers.

- Lactatemia
- Arterial blood gases (pH, PaO_2, $PaCO_2$, bicarbonates)
- Blood formula and platelet count
- Creatinemia
- Sodium and kaliemia
- Glycemia
- Transaminase
- Bilirubin
- PT-INR
- Troponinemia
- Calculation of SOFA (sequential organ failure assessment) score from clinical and paraclinical data. This score evaluates organ dysfunctions (hemodynamic, respiratory, neurological, hepatic, hemostatic, renal) and is routinely used in intensive care; it is correlated with mortality.
- Calculation of CAHP score

Post-CA patients frequently undergo hemodynamic evaluations by echography or invasive cardiac output monitoring, due to the high frequency of associated heart failure. The use and choice of the type of monitoring will be left to the discretion of the clinician. If one of these means is in use at the time of inclusion, the following hemodynamic data will be collected:

- By echocardiography: left ventricular ejection fraction (Simpson's method), subaortic velocity-time index (subaortic VTI), calculation of cardiac output and cardiac index;
- By invasive monitoring (pulmonary arterial catheter or PiCCO® or other): cardiac output and cardiac index, mixed venous oxygen saturation (SvO_2) or central venous oxygen saturation ($ScVO_2$). These data will be recorded as a function of the type of invasive monitoring.

Follow-up of the participants

No investigation specific to this study will be performed except centralized phone interview by a psychologist or a nurse six months after inclusion. All further clinical and paraclinical data collected will be obtained during routine practice in the framework of post-CA management.

During the first 24 hours after inclusion:

- Collection, every hour, of systolic, diastolic and mean arterial blood pressure, and heart rate;
- Maximum dose of vasopressors and inotropes and calculation of the vasoactive inotropic score. Norepinephrine dose will be reported as norepinephrine base;
- Collection every four hours of body temperature, SpO2, FiO2, and glycemia;
- Cumulative dose of sedation and opioids;
- Neuromuscular blockers infusion;
- Cumulative dose of fluid volume expansion and cumulative urine output;
- Protocol discontinuation during the first 24 hours and reasons;
- Use of antihypertensive agents during the first 24 hours;

From 24h to 72h after inclusion:

- Maximum dose of vasopressors and inotropes and calculation of the vasoactive inotropic score.
- Collection, every four hours, of systolic, diastolic and mean arterial blood pressure;
- Collection every four hours of temperature, SpO2, FiO2/oxygen flow rate, glycemia;
- Cumulative dose of fluid volume and cumulative urine output;
- Neuromuscular blockers infusion;

At day 1:

- Performance of an ECG and troponinemia;
- If appropriate, hemodynamic monitoring data (obtained by echography or invasive monitoring);
- Simplified Acute Physiology Score II (SAPS II) will be calculated from clinical and laboratory tests. This score measures the seriousness of the patient's condition and is used in intensive care. It is based on the data for the first 24 hours and is correlated with mortality.

At days 2 and 3:

- Performance of an ECG and troponinemia;
- If appropriate, hemodynamic monitoring data (obtained by echography or invasive monitoring).

Neuropronostication during the ICU stay:

Evaluating an intervention that cannot be blinded to the treating clinicians, the METAPHORE trial will employ a conservative and strict protocol for neurological prognostication and related decisions regarding limitations in level-of-care to mitigate potential bias.

- Prognostication will be performed on *all* participants still in the ICU at day 4 after inclusion. The prognostication will be based on the ERC and European Society for Intensive Care Medicine recommendations. The prognostication will be based on the TTM-2 trial protocol.

- The result of the prognostication will be categorized as "YES" or "NO", based on the answer to the question *"Does this patient fulfill the METAPHORE trial criteria for a likely poor neurological outcome?"*. This assessment will be recorded in the case report form. Patients who do not fulfill these criteria for a likely poor neurological outcome or if there is still one or more confounders (such as sedation or neuromuscular blockade agents, hypotension, hypothermia, sepsis, metabolic or respiratory derangements) at day 4 after randomization, should be reexamined daily.
- Any decision to withdraw active life support will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. In making this decision the treating physician may use the information from the prognostication. Efforts will be made to sufficiently delay prognostication to ensure that any lingering effects of sedative agents will not affect the assessment.
- Prognostication will be based on two mandatory, and four optional modalities:

    - Clinical examination (mandatory): A clinical examination including assessment of brainstem reflexes and described using the FOUR- score will be performed daily on all patients. An exception to the FOUR-score is that myoclonus will be considered separately in this trial. Absent or extensor motor response to pain (FOUR- score motor response 0-1) at day 4 or later in a patient who is considered unaffected by sedative agents, is a prerequisite to consider the neurologic prognosis poor. The bilateral absence of pupillary and corneal reflexes at 72h after CA or later, is a finding indicative of a poor prognosis. The daily clinical examination by the ICU-staff should also include an assessment of status myoclonus (continuous and generalized myoclonus persisting for at least 30 min). A prospectively documented early status myoclonus (within 48 hours) is indicative of a poor prognosis. Information from daily examinations including evaluation of status myoclonus should be available to the physician performing the evaluation.
    - EEG (mandatory): An EEG performed at > 24 hours will be performed on all participants who survive, and remain unconscious to this point, in line with standard clinical practice. If it is not possible to perform an EEG study in the specified time frame due to practical reasons, the EEG should be performed as soon as possible. An EEG with a

highly malignant pattern, and without reactivity to sound and pain is indicative of a poor prognosis

- Brain CT or brain MRI (optional): If a brain-CT shows signs of global ischaemic injury, such as: generalized oedema with reduced grey/white matter differentiation, this is indicative of a poor prognosis. A CT should be considered in patients who remain unconscious to exclude other pathologies such as intracranial haemorrhage or infarction. A brain MRI at 3-5 days may be incorporated into prognostication if it has been performed. Signs of global, diffuse, or bilateral multifocal ischaemic lesions are indicative of a poor prognosis.
- Biological markers (optional): high level of neuron specific enolase (> 60 µg/L without hemolysis) is indicative of a poor prognosis
- SSEP (optional): Absent SSEP N20-responses bilaterally may be seen as indicative of a poor prognosis, if SSEP is performed more than 48h after randomization

The following criteria, evaluated 4 days after randomization or later, need to be fulfilled to establish a likely poor neurological outcome:

- Absent or extensor motor response to pain AND at least two of the following:

    1. Bilaterally absent pupillary and corneal reflexes
    2. Bilaterally absent SSEP N20-responses
    3. Diffuse anoxic brain injury on CT or MRI
    4. Documented status myoclonus within 48h of randomization
    5. High levels of serum NSE (> 60 µg/L) without hemolysis
    6. An EEG with a highly malignant pattern and without any observed reactivity to sound or pain. Patterns that are considered highly malignant are:
        - Suppressed background (amplitude <10mV, 100% of the recording) without discharges.
        - Suppressed background with superimposed continuous periodic discharges.
        - Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges.
        - Burst-suppression with superimposed discharges.

All the patients in the trial will be actively treated until 4 days after randomization. There will be two exemptions from this rule:

- Participants in whom further treatment is considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons;
- Participants in whom brain death is established, however this will be defined as death and not decision to withhold or withdraw active treatment.

At ICU discharge:

- Date of ICU discharge;
- Vital status and date and cause of death, if appropriate;
- Rankin modified scale;
- Date of intubation and extubation;
- Date of introduction and cessation of vasopressor and inotrope treatments;
- Higher rate of creatinine during the ICU stay and exposure to nephrotoxic agents during ICU stay;
- Lower hemoglobin level during ICU stay and red blood cell transfusion;
- Date of start and cessation of renal replacement therapy;
- Performance (or not) of complementary examinations for neuroprognostication: electroencephalogram, evoked potentials, neuronal biomarkers and types of biomarkers, brain imaging, and the results of these examinations, if performed;
- Performance (or not) of complementary examinations for CA cause diagnosis: coronary angiography, CT scan, lumbar punction, CT pulmonary angiogram, or other;
- Performance (or not) of specific cardiac treatment during ICU stay: coronary artery bypass grafting, implantable cardiac defibrillator;
- Performance (or not) of CT scan before inclusion
- Date of start of nutrition and route (enteral or parenteral or both)

- Final diagnosis (CA cause);
- Decision and date to withhold or withdraw active treatment and the reasons for this decision;
- Occurrence or not of complications from D1 to D7 and date of the first ones:
    - Cardiovascular complications: newly occurring or recurrent severe cardiac arrhythmia; newly occurring or recurrent ST-Elevation Myocardial Infarction (STEMI); need for extracorporeal life support (ECMO or Impella or other) for refractory cardiogenic shock; recurrent cardiac arrest;
    - Neurological complications: stroke (ischemic stroke, subarachnoid hemorrhage or cerebral hematoma);
    - Cutaneous complications: necrosis of the extremities;
    - Digestive complications: digestive ischemia;
    - Major bleeding.

At hospital discharge:

- Date of hospital discharge;
- Vital status and the date of death, if appropriate;

At 28 days:

- Vital status and the date of death, if appropriate.
- Date of hospital discharge.

This evaluation will be undertaken by telephone by local clinical research assistant.

At six months (± 15 days) (telephone or visio follow-up):

This evaluation will be undertaken by telephone or visio by a psychologist or a clinical research nurse specially trained for this follow-up. The follow-up will be centralized for all patients included in the study and alive at ICU and hospital discharge. Health personnel responsible for

outcome assessment at follow-up will be blinded to the allocation of the intervention (blinded-endpoint). The assessor will collect:

- Vital status and date of death, if appropriate;
- **Modified Rankin score (to measure primary endpoint);**
- Clinical Frailty Scale;
- Living situation;
- EuroQol-5D-5L;

Outcome-assessors will be provided with a written trial manual with detailed guidelines for performing the questionnaires and assessments. Modified Rankin Scale will be done during a telephone or visio semi structured interview. Training sessions will be provided by the trial coordinating team. At the end of each training session participants will perform mRS scoring on several practice cases. Outcome-assessors will also be encouraged to perform all follow-up procedures on several pilot persons.

The psychologist must make every effort possible to contact the subject. If the contact is not re-established after 3 phone calls, the patient's general practitioner or a proxy will be contacted. In third line, the French national death certificate database (CépiDc) will be consulted. If the contact is not re-established, then the subject is considered lost to follow-up and mRS 6 will be applied.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Mean arterial pressure after out-of-hospital cardiac arrest (METAPHORE): study protocol for a multicentre controlled trial with blinded primary outcome assessor

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Keywords:	Out-of-Hospital Cardiac Arrest, Brain Injuries, Blood Pressure

Mean arterial pressure after out-of-hospital cardiac arrest (METAPHORE): study protocol for a multicentre controlled trial with blinded primary outcome assessor

ABSTRACT

Introduction: Out-of-hospital cardiac arrest is a public health concern with a high mortality rate. Hypoxic ischemic brain injury is the primary cause of death in patients admitted to intensive care unit (ICU) after return of spontaneous circulation (ROSC). Several systemic factors, such as hypotension, can exacerbate brain injuries. International guidelines recommend targeting mean arterial pressure (MAP) of at least 65 mmHg. Several observational studies suggest that a higher MAP may be associated with better outcomes but no randomised trials have shown an effect of higher MAP. The ongoing METAPHORE (mean arterial pressure after out-of-hospital cardiac arrest) trial aims to compare a standard MAP threshold (MAP ≥ 65 mmHg) with a high MAP threshold (MAP ≥ 90 mmHg) to evaluate whether implementing a higher MAP threshold can improve neurological outcomes in patients admitted to ICU after cardiac arrest.

Methods and analysis: METAPHORE is a randomised, controlled, multicentre, open-label trial with blinded primary outcome assessor, comparing two parallel groups of patients 18 years of age or older, receiving invasive mechanical ventilation for coma defined by a Glasgow Coma Score ≤ 8/15 after out-of-hospital cardiac arrest and sustained ROSC. Eligible patients are randomly assigned in a 1:1 ratio to either a MAP target threshold of 65 mmHg or higher throughout the ICU stay (control group) or a

MAP target threshold of 90 mmHg or higher during the first 24 hours after randomisation, followed by 65 mmHg or higher for the remainder of the ICU stay (intervention group). Both groups receive the same general care concerning post-cardiac arrest syndrome management according to international guidelines. The primary endpoint is the proportion of patients with a favourable neurological outcome as defined by a modified Rankin scale (mRS) of 0 to 3 measured on day 180 after inclusion by a psychologist blinded to the allocation of the intervention. Secondary outcomes are: proportion of patients alive at ICU and hospital discharge, at day 28 and day 180; proportion of patients alive at ICU discharge with a mRS of 0 to 3; the EuroQOL-5D-5L at day 180; the Clinical Frailty Scale at day 180; the number of ICU-free days, ventilator-free days, catecholamine-free days, and renal replacement therapy-free days at day 28 ; the proportion of patients with acute kidney injury stage 3 and need for renal replacement therapy within ICU stay and proportion of patients with persistent need for renal replacement therapy at ICU discharge; and safety outcomes (cardiovascular, neurological, cutaneous, digestive and hemorrhagic complications within 7 days after inclusion). Subgroup analyses are planned according to initial cardiac arrest rhythm (shockable or non-shockable), chronic hypertension and Cardiac Arrest Hospital Prognosis (CAHP) score. Outcomes will be analysed on an intention-to-treat basis. Recruitment started in October 2024 in 27 French ICUs and a sample of 1380 patients is expected by October 2027.

Ethics and dissemination: The study received approval from the national ethics review board on 8 February 2024 (Comité de Protection des Personnes Sud-Est V – 2023-

A00257-38). Patients are included after informed consent has been obtained either from a proxy or through an emergency procedure. Results will be submitted for publication in peer-reviewed journals.

Trial registration: ClinicalTrials.gov, NCT05486884.

Keywords:

Out-of-hospital cardiac arrest; arterial pressure; brain injury

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a pragmatic, randomised, multicentre study comparing two MAP thresholds in patients who are comatose after out-of-hospital cardiac arrest resuscitation.
- The primary endpoint is the proportion of patients with a good neurological outcome, assessed by the modified Rankin Scale measured 180 days after inclusion, and evaluated by an independent psychologist blinded to the intervention allocation through a semi-structured interview.
- Safety outcomes are assessed through cardiovascular, neurological, cutaneous, digestive and major bleeding complications.
- A limitation is that blinding of the healthcare staff to MAP targets is not possible without a specific device.

INTRODUCTION

Background and rationale

Out-of-hospital cardiac arrest (OHCA) is a significant public health concern associated with high mortality rates and severe disability in survivors [1,2]. The primary cause of death in patients admitted to intensive care unit (ICU) after return of spontaneous circulation (ROSC) is brain injury [3,4]. Hypoxic-ischemic brain injury (HIBI) is the consequence of circulatory arrest and reperfusion. Several factors can exacerbate HIBI after ROSC such as arterial hypotension. In patients resuscitated from OHCA, cerebral autoregulation is often impaired, rendering the brain vulnerable to ischemia and secondary injuries [5,6]. International guidelines suggest maintaining a mean arterial pressure (MAP) of 65 or 70 mmHg [7]. Several observational studies support that a higher MAP target is associated with better survival and neurological outcomes [8]. However, evidence supporting this strategy remains limited. Three interventional studies have shown no effect of a higher MAP in OHCA patients [9-11]. However, two of these studies were pilot feasibility trials, lacking the power to show statistical differences in clinical outcomes [9,10]. The most recent study included 800 patients who were randomly assigned to one of two MAP target groups: a lower target of 63 mmHg and a higher target of 77 mmHg [11]. To ensure blinding, clinicians used a blood pressure monitoring device that was randomly calibrated to display values either 10% lower or 10% higher than the actual blood pressure. As a result, all treating physicians aimed for a standardised target MAP of 70 mmHg, while in reality, one group maintained a MAP of approximately 63 mmHg and the other a MAP of approximately

77 mmHg. However, this trial had several limitations, including a highly selected study population, a high MAP target that remained below the cerebral autoregulation threshold suggested by previous studies [5,12], and only minimal differences in MAP values between the two groups [13]. These limitations prevent definitive conclusions regarding the absence of an effect of a higher MAP level after cardiac arrest.In collaboration with the After ROSC network and the CRICS-TRIGGERSEP-F-CRIN network, we designed the MEan arTeriAl Pressure after out-of-HOspital cardiac arREst (METAPHORE) trial.

Herein, we report the trial protocol according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. This trial is registered at ClinicalTrials.gov and this manuscript was written in accordance with SPIRIT guidelines (www.spirit-statement.org/spirit-statement/). We provided all WHO trial Registration Data Set (see supplemental material 1).

Objectives

The study hypothesis is that a strategy targeting a MAP threshold ≥ 90 mmHg within 24 hours after ROSC will significantly reduce the proportion of patients with poor neurological outcomes on day 180 after inclusion compared with standard care (MAP ≥ 65 mmHg).

The main objective of the study is to demonstrate the efficacy of a high MAP threshold (MAP ≥ 90 mmHg) on neurological prognosis at six months in patients resuscitated from out-of-hospital cardiac arrest relative to the standard threshold (MAP ≥ 65 mmHg).

The secondary objectives of the study are:

- To demonstrate the superiority of a high MAP threshold (MAP ≥ 90 mmHg) compared to the standard threshold (MAP ≥ 65 mmHg) in terms of survival at ICU discharge, at hospital discharge, at day 28, and six months,
- To demonstrate the superiority of a high MAP threshold compared to the standard MAP threshold in terms of neurofunctional prognosis at ICU discharge, quality of life at six months, length of stay in the ICU, duration of organ support and organ failure,
- To demonstrate the safety of a high MAP threshold compared to the standard threshold in terms of global and specific complications within 7 days of inclusion.

Additionally, subgroup analysis will be performed to assess:

- Neurofunctional prognosis at six months according to initial cardiac arrest rhythm (shockable or non-shockable);
- Neurofunctional prognosis at six months according to presence or absence of chronic arterial hypertension;
- Neurofunctional prognosis at six months according to Cardiac Arrest Hospital Prognosis score (CAHP score) at admission.

METHODS AND ANALYSIS

Trial design

The METAPHORE (mean arterial pressure after out-of-hospital cardiac arrest) study is designed as a pragmatic, multicentre, open-label randomised controlled superiority trial with two parallel groups, a 1:1 allocation and with blinded outcome assessment.

Study setting

The study is being conducted in 27 ICUs across France. Sites characteristics are listed in supplemental material 2. All ICU staff participating in the study receive mandatory training on the study procedures before the study begins.

Eligibility criteria

The trial includes adults (age ≥ 18 years) admitted to a participating ICU after resuscitated out-of-hospital cardiac arrest with initially shockable or non-shockable rhythm, with a sustained ROSC (defined as 20 minutes with signs of circulation without the need for chest compressions) and who need mechanical ventilation for coma (defined by a Glasgow Coma Scale ≤ 8). Patients are excluded from the study if they meet any of the following criteria:

- In-hospital cardiac arrest (first cardiac arrest in case of several ones)
- Unwitnessed cardiac arrest with initial rhythm of asystole
- Delay between ROSC and attempting randomisation > 6 hours
- Cardiac arrest in context of multiple trauma

- Cardiac arrest in context of hemorrhagic shock or severe hemorrhage necessitating hemostasis (by surgery, radiological procedure or endoscopic procedure)
- Cardiac arrest secondary to an acute brain disease (ischemic or hemorrhagic stroke, subarachnoid hemorrhage, severe traumatic brain injury)
- Refractory shock defined as a MAP < 65 mmHg for more than one hour on norepinephrine or epinephrine at a dose > 1 μg/kg/min despite adequate fluid resuscitation
- Extracorporeal circulatory support prior to inclusion
- Known allergy to norepinephrine or any of its excipients
- Decision to limit care before inclusion
- Modified Rankin scale (mRS) of 4 or 5 before cardiac arrest
- Inclusion in another interventional study in which the primary endpoint is neurological prognosis
- Pregnancy or breast feeding
- Patients in detention by judicial or administrative decision, under forced psychiatric care or under legal protection (guardianship or curatorship)
- Non-French speaking
- Patient already included in this trial
- Lack of social security coverage.

Interventions

High MAP threshold

For patients who are assigned to the high MAP threshold group, norepinephrine is titrated to maintain MAP ≥ 90 mmHg. This threshold is maintained for the first 24 hours following randomisation by the infusion of norepinephrine at an appropriate dose. The minimum dose of norepinephrine required to maintain MAP above the threshold is sought. The vasopressor infusion rate is decreased in increments of 0.05 µg/kg/min at least every hour. Thus, if MAP falls below 90 mmHg, the dose of norepinephrine is increased by 0.05 µg/kg/min every ten minutes. The titration rate is adjusted according to the depth of arterial hypotension, particularly in cases of hemodynamic instability, and is left to the discretion of the physician. No maximum threshold of MAP is defined. Lowering MAP is not recommended within 24 hours after randomisation except if the intervention is suspected to cause severe adverse events. This decision is left to the discretion of the clinician and drugs used are documented in the case report form. Norepinephrine dose will be reported as base equivalence.

From 24 hours after randomisation until ICU discharge, a MAP ≥ 65 mmHg is targeted. The management of vasopressor therapy, sedation/analgesia and antihypertensive agents after 24 hours is left to the discretion of the clinician.

Standard MAP threshold

For patients who are assigned to the standard MAP threshold group, norepinephrine is titrated to maintain MAP ≥ 65 mmHg during all the ICU stay. The minimum dose of

norepinephrine required to maintain MAP above the threshold is sought. The vasopressor infusion rate is decreased in increments of 0.05 µg/kg/min at least every hour. Thus, if MAP falls below 65 mmHg, the dose of norepinephrine is increased by 0.05 µg/kg/min every ten minutes. The titration rate is adjusted according to the depth of arterial hypotension, particularly in cases of hemodynamic instability, and is left to the discretion of the physician. No maximum threshold of MAP is defined, and lowering MAP is not recommended within 24 hours after inclusion except in case of severe adverse events. This decision is left to the discretion of the clinician and drugs used are documented in the case report form. Norepinephrine dose will be reported as base equivalence.

Discontinuing or modifying allocated interventions

The investigator is allowed to temporarily or permanently discontinue a patient's participation in the study for any reason that would best serve the interests of the subject, particularly in the case of serious adverse events suspected to be associated with the strategy used.

Other interventions in both groups

Because of the risk of increased cardiac afterload due to the use of vasopressors and high levels of MAP, the scientific board recommends that clinicians monitor cardiac function and use inotropic agents if appropriate. Monitoring method (echocardiography or invasive hemodynamic monitoring) is left to the discretion of the physician.

General ICU care, including respiratory management, sedation, glycemic control and transfusion, is delivered similarly in both allocation groups according to international guidelines [7]. Fever is actively prevented by targeting a temperature ≤ 37.8°C for at least 72 hours in patients who remain comatose [14].

Central line and arterial catheter insertion are left to the discretion of the physician.

In both groups, decisions regarding limitation or withdrawal of treatment follow European guidelines and neuroprognostication algorithm [7]. Decisions to withhold or withdraw active treatment are reported in the case report form.

Outcomes

The primary outcome is the proportion of patients with a good neurological outcome 180 days afterinclusion. Good neurological outcome is defined by a mRS of 0 to 3. This scale is a global evaluation scale of disability, with seven levels (0 = no symptoms; 6 = patient dead). This score is commonly used to assess neurological prognosis after CA [15,16]. mRS is measured by a psychologist (blinded to the randomisation arm) during a semi-structured telephone interview.

The secondary outcomes are:

- Proportion of patients alive at ICU discharge, at hospital discharge, at day 28 (D28) and six months (D180) afterinclusion;
- Proportion of patients alive at ICU discharge with a modified Rankin scale of 0 to 3;

- The EuroQol-5D-5L six months after inclusion. EuroQol-5D-5L is a measure of health-related quality of life and comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression);
- The Clinical Frailty Scale (CFS) six months after inclusion. CFS summarizes the overall level of fitness or frailty of a patient with a score from 1 (very fit) to 9 (terminally ill);
- Number of ICU-free days calculated from the number of days alive outside the ICU by D28;
- Number of ventilator-free days, number of catecholamine-free days and number of renal replacement therapy-free days calculated from the number of days alive without invasive mechanical ventilation, catecholamine infusion or renal replacement therapy by D28;
- The proportion of patients with acute kidney injury stage 3 according to the Kidney Disease Improving Global Outcomes (KDIGO) classification and need for renal replacement therapy (RRT) (for patients without renal replacement therapy before cardiac arrest) within ICU stay and persistent need for RRT at ICU discharge. Acute kidney injury stage 3 is defined by at least one of the following criteria: serum creatinine concentration of more than 4 mg/dl (354 µmol/liter) or greater than 3 times the baseline creatinine level, anuria (urine output of 100 mL/day or less) for more than 12 hours,

oliguria (urine output below 0.3 ml/kg/h or below 500 mL/day) for more than 24 hours.

The safety outcomes are:

- **Cardiovascular complications** assessed by determining the number of patients presenting a severe cardiovascular complication within 7 days of inclusion. A severe cardiovascular complication is defined by at least one of the following criteria:
    - newly occurring or recurrent ventricular fibrillation or ventricular tachycardia requiring antiarrhythmic drugs and/or electrical cardioversion and/or resuscitation due to hemodynamic instability or cardiac arrest; or
    - severe atrial flutter or atrial fibrillation, requiring treatment (antiarrhythmic drugs or rate slowing medication) and/or electrical cardioversion due to hemodynamic instability (a patient with chronic atrial flutter or atrial fibrillation but not requiring urgent treatment for hemodynamic instability will be not concerned); or
    - bradycardia (<40 beats per minute) requiring pacing or resuscitation due to hemodynamic instability or cardiac arrest; or
    - newly occurring or recurrent ST-Elevation Myocardial Infarction (STEMI) diagnosed using an electrocardiogram and confirmed by coronary angiography; or

- need for extracorporeal life support (ExtraCorporeal Membrane Oxygenation or Impella) for refractory cardiogenic shock; or
- unexpected recurrent cardiac arrest (cardiac arrest due to discontinuation of treatments will not be concerned);

- **Neurological complications** assessed by determining the number of patients presenting with stroke (ischemic stroke, subarachnoid hemorrhage or cerebral hematoma), confirmed by imaging (CT-scan or MRI) within 7 days of inclusion(systematic cerebral imaging is not required by the protocol but only in case of clinical suspicion of stroke or for neuroprognostication);
- **Cutaneous complications** assessed by determining the number of patients presenting ischemia or necrosis of the extremities within 7 days of inclusion;
- **Digestive complications**, assessed by determining the number of patients presenting a clinical suspicion of digestive ischemia, confirmed by imaging (CT-scan), endoscopy or exploratory laparotomy, within 7 days of inclusion;
- **Major bleeding** assessed by determining the number of patients presenting one of the International Society on Thrombosis and Haemostasis (ISTH) criteria within 7 days of inclusion(fatal bleeding and/or symptomatic bleeding in a critical area or in an organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 20 g.L-1 or more or leading to transfusion of two or more units of red cells) ;

- **Global complications** defined by the proportion of patients with at least one complication (cardiovascular, neurological, cutaneous, digestive or hemorrhagic) within 7 days of inclusion;

Subgroup analysis

Patients are analysed by subgroups concerning neurological outcome at six months. Three subgroups are defined for this analysis:

- Subgroups of patients with and without confirmed chronic hypertension (defined as the need for chronic treatment);
- Subgroups of patients with an initial non-shockable rhythm and an initial shockable rhythm;
- Subgroup of patients with CAHP score < 150, CAHP score 150-200 and CAHP score > 200. The CAHP score represents a simple tool for early risk stratification of patients admitted to ICU after OHCA, using seven variables (age, rhythm, time from collapse to basic life support, time from basic life support to ROSC, location of cardiac arrest, epinephrine dose and arterial pH) [17].

Participant timeline

Figure 1 shows the Consort diagram of the METAPHORE trial and Table 1 assessments and visits for participants (supplemental material 3).

Sample size estimation

The required number of subjects is based on an anticipated difference in proportion of patients with mRS 0 to 3 at D180 between the two groups. Based on previous studies and After ROSC registry [18], we estimate that 30% of the patients included in the standard group will have a good neurological outcome (mRS 0 to 3) at six months. By expecting 38% of patients with good neurological outcome at six months in the experimental group, 550 patients are required in each group (power of 80% and alpha risk of 5%). The sample size calculation corresponds to a relative risk reduction of 11.4% concerning worse neurological outcome and an absolute risk reduction of 8%. The number requiring treatment is 12.5. Assuming 20% of patients included in the standard group will have a spontaneous MAP over 90 mmHg during the first 24 hours after inclusion (personal data not published), 690 patients will be included in each arm (total = 1380 patients). Patients lost to follow-up will be considered deceased (mRS 6).

Recruitment

All patients admitted to participating ICU after out-of-hospital cardiac arrest during the study period are screened for eligibility. A log of patients considered for study participation will be maintained, including the reasons for non-inclusion.

All the participating centers currently manage patients after cardiac arrest. All the participating centers have already participated in clinical trials and the trial is supported by two clinical research networks:

- AfterROSC network, associating physicians from several intensive care units in France and Belgium aiming to promote and develop research and teaching in post cardiac arrest management;
- CRICS-TRIGGERSEP F-CRIN network, a national network for research on sepsis bringing together leaders in the field from fundamental and translational research, biostatistics research and clinical investigations.

Randomisation and treatment allocation

Using a web-based system (Ennov Clinical® Software), patients are randomised in a 1:1 ratio within 6 hours after ROSC to a high MAP threshold (MAP target ≥ 90 mmHg within 24 hours) or a standard MAP threshold (MAP target ≥ 65 mmHg). A minimization algorithm based on presumed chronic hypertension, initial cardiac arrest rhythm (shockable or not shockable) and participating center is used for the randomisation process. After enrolment and randomisation, patients, treating physicians and study personnel are not blinded to study group assignment. Only the primary outcome assessor is blinded to study group allocation. The day of randomisation is defined as D0, and the time of randomisation is defined as H0. The designated strategy is initiated immediately after randomisation.

Blinding

The clinical team responsible for the participants (physicians, nurses and others) and involved with direct patient care will not be blinded to allocation group due to the

inherent difficulty in blinding the intervention. Health personnel responsible for outcome assessment at follow-up will be blinded to the allocation of the intervention. Potential bias will be mitigated by using conservative and strict protocols for neuroprognostication and related decision making (i.e., regarding limitations in level of care). The same neuroprognostication algorithm, based on European Resuscitation Council and European Society of Intensive Care Medicine guidelines [7], will be used for all patients included in the study.

Data collection

Data collection for this study is described in supplemental material 4 and can be found in the protocol version 1.1 dated 2024/01/24.

Data management

An internet-based data collection tool will be used for this study to store the data of all participants. This electronic case report form (eCRF) is a secure, interactive, web response system available at each study centre. The data manager of the Clinical Research Unit of Le Mans Hospital will monitor collected data and screening forms in each participating centre. A blind review of the data will be performed before the database is locked. The database will be locked according to standard operating procedures in force at the DRCI, and the data will be extracted for statistical analyses.

Statistical methods

The main analysis will be conducted on an intention-to-treat basis: all patients included in the study will be analysed according to their group assigned by randomisation. A statistical analysis report will be prepared following the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) Statement (http://www.consort-statement.org/). Any modification of the presented statistical analysis strategy will be indicated in the final publication.

Descriptive statistics

Descriptive statistics will be used to summarize the characteristics of the control and experimental groups. Continuous variables will be presented as mean and SD if they follow a normal distribution or as median and IQR as appropriate. Categorical variables will be described using exact numbers and percentages.

Analysis of the primary endpoint

The primary endpoint will be the proportion of patients in each arm with good neurofunctional prognosis evaluated 180 days after inclusion by the modified Rankin scale (mRS). A mRS of 0 to 3 will be considered as a good neurological outcome, whereas a mRS of 4 to 6 will be considered as a poor one. The proportion of patients with a good neurofunctional outcome at D180 will be compared between the two arms in a chi-squared test or Fisher's exact test as appropriate.

Analysis of secondary endpoints

Survival analysis at ICU discharge, at hospital discharge, at D28 and 6 months will be characterised by Kaplan Meier curves (or actuarial according to the type of temporal distribution of the events of interest) to determine the median of survival with its 95% confidence interval. If the realization conditions are favorable, they will be compared by a log-rank test.

All the other secondary endpoints will be analysed using standard descriptive statistics tools, diagrams, histograms for qualitative variables, box plots or bar charts for quantitative variables. If the comparative conditions are respected, the appropriate statistical tests will be implemented (Chi 2 or Fisher's exact test, Student's t or Mann-Whitney test).

Level of statistical significance

A two-sided p-value of 0.05 or less will be considered statistically significant.

Handling of missing data

Due to the primary endpoint being evaluated remotely from inclusion and outside of ICUs, it is possible that some patients may be lost to follow-up. These patients will be considered as mRS 6 (deceased). In addition, sensitivity analyses will be carried out using best worst and worst best case scenarios as well as a Last Observation Carried Forward approach (using mRS at ICU discharge).

Data monitoring

The Data Monitoring Committee (DMC) comprises three clinicians with experience in the conduct, monitoring and analysis of RCTs. None of the members are directly involved in the study. Each member has signed a conflict-of-interest form. The DMC has approved the study protocol and the operating charter.

Two interim analyses are planned, after the inclusion of 400 and 800 patients. We will apply the Peto and Haybittle rule:

- significance threshold for the first analysis: 0.01;

- significance threshold for the second analysis: 0.01;

The significance threshold for the final analysis will be 0.049.

Alternative endpoints will be used for interim analyses: death of any cause at day 28 and global complications within 7 days after inclusion (safety outcomes).

At interim analysis, the committee will monitor the rate of inclusion and record expected adverse effects (complications such as secondary endpoints of the study) and will make the final decision to continue the study or not. Results of interim analysis on day 28 mortality will be provided as well as the proportion of expected adverse events. Patients' characteristics recorded at randomisation will be also provided. Early stop for safety reasons will be left at the discretion of the DMC.

Monitoring of AEs

Post cardiac arrest patients are at high risk for developing complications no matter the strategy of MAP management. Several expected AEs will not be recorded as an entity

(only such as complications in the CRF, secondary endpoints of the study). A list of serious AEs requiring an immediate declaration is established.

Patient and public involvement

We plan to engage patient representatives to determine exploratory analysis objectives (patient-centred outcome), as well as for communication or dissemination of results.

ETHICS AND DISSEMINATION

Research ethics approval

The METAPHORE trial received approval from the national ethics review board on 8 February 2024 (Comité de Protection des Personnes Sud-Est V, registration number 2023-A00257-38). For any major change in the protocol, the sponsor will request the approval of the ethic committee, inform the French health authority (ANSM), the investigators and the DMC, and update trial registry at ClinicalTrials.gov.

Consent to participate

Only patients who are comatose after resuscitation from OHCA are included in the trial, and the intervention should be implemented the earliest after ROSC in patients who are comatose. Consequently, it is anticipated that eligible patients will be unable to provide consent due to impaired consciousness and information about the study will be provided to their next of kin. Informed written consent will be obtained from the relative by the investigator or by a doctor representing the investigator before definitive inclusion in the study. A copy of the information form and the consent form signed by the two parties will be delivered to the relative.

In cases where no relative is available to consent within 6 hours after ROSC, an emergency consent form completed by the physician allows inclusion according to French law.

Patients who regain their decision-making capacity will be asked to confirm their willingness to participate in the trial (the patient consent form is presented in

supplemental material 5). Patients' data of patients without relatives who die without previously recovering consciousness will be included in the statistical analysis.

If the patient at ICU discharge is not able to receive the information and give his consent, this will be collected in the medical file of the patient. The investigator will make every effort to obtain consent, as soon as the patient's health permits.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

The publication policy will follow international recommendations (N Engl J Med 1997; 336:309-315) and the CONSORT statement (http://www.consort-statement.org). Findings will be published in peer-reviewed journals and presented at national and international scientific meetings. The coordinating investigator (NC), the statistician (PS), the members of the scientific committee (JBL, AC, CG) and all investigators who have included at least ten patients in proportion of number patients recruited per month will be considered as authors. The study coordinator (NC) will be responsible for

communications and scientific reports, ensuring approval from the other investigators. We do not intend to use professional writers at this date. Data will be shared on reasonable request from the principal investigator.

Trial status

Inclusions started in October 2024. Data collection is ongoing, and inclusions are expected to reach completion in October 2027.

REFERENCES

1. Grubb NR, Elton RA, Fox KA. In-hospital mortality after out-of-hospital cardiac arrest. Lancet Lond Engl. 1995 Aug 12;346(8972):417–21.
2. Bunch TJ, White RD, Gersh BJ, Meverden RA, Hodge DO, Ballman KV, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. N Engl J Med. 2003 Jun 26;348(26):2626–33.
3. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004 Nov;30(11):2126–8.
4. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013 Nov;39(11):1972–80.
5. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke. 2001 Jan;32(1):128–32.
6. Ameloot K, Genbrugge C, Meex I, Jans F, Boer W, Vander Laenen M, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-

cardiac arrest patients: time to drop “one-size-fits-all” hemodynamic targets? Resuscitation. 2015 May;90:121–6.

7. Nolan JP, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med. 2021 Apr;47(4):369–421.

8. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Shea L, Donnino M, et al. Association Between Elevated Mean Arterial Blood Pressure and Neurologic Outcome After Resuscitation From Cardiac Arrest: Results From a Multicenter Prospective Cohort Study. Crit Care Med. 2019 Jan;47(1):93–100.

9. Jakkula P, Pettilä V, Skrifvars MB, Hästbacka J, Loisa P, Tiainen M, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med. 2018 Dec;44(12):2091–101.

10. Ameloot K, De Deyne C, Eertmans W, Ferdinande B, Dupont M, Palmers PJ, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. Eur Heart J. 2019 Jun 7;40(22):1804–14.

11. Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B, et al. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022 20;387(16):1456–66.

12. Ameloot K, Meex I, Genbrugge C, Jans F, Boer W, Verhaert D, et al. Hemodynamic targets during therapeutic hypothermia after cardiac arrest: A prospective observational study. Resuscitation. 2015 Jun;91:56–62.

13. Chudeau N, Guitton C, Cariou A. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2023 Jan 19;388(3):284.

14. Sandroni C, Nolan JP, Andersen LW, Böttiger BW, Cariou A, Cronberg T, et al. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Intensive Care Med. 2022 Mar;48(3):261–9.

15. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May;19(5):604–7.

16. Iqbal MB, Al-Hussaini A, Rosser G, Salehi S, Phylactou M, Rajakulasingham R, et al. Predictors of survival and favorable functional outcomes after an out-of-hospital cardiac arrest in patients systematically brought to a dedicated heart attack center (from the Harefield Cardiac Arrest Study). Am J Cardiol. 2015 Mar 15;115(6):730–7.

17. Maupain C, Bougouin W, Lamhaut L, Deye N, Diehl JL, Geri G, et al. The CAHP (Cardiac Arrest Hospital Prognosis) score: a tool for risk stratification after out-of-hospital cardiac arrest. Eur Heart J. 2016 Nov 7;37(42):3222–8.

18. Lascarrou JB, Bougouin W, Chelly J, Bourenne J, Daubin C, Lesieur O, et al. Prospective comparison of prognostic scores for prediction of outcome after out-of-hospital cardiac arrest: results of the AfterROSC1 multicentric study. Ann Intensive Care. 2023 Oct 11;13(1):100.

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Competing interests

The METAPHORE study is an investigator-initiated trial funded by the French Ministry of Health obtained in 2021 from a national hospital clinical research program

(Programme Hospitalier de Recherche Clinique National, PHRC-21-0056). A scientific committee including NC, JBL, AC and CG conceived, drafted and wrote the project. All authors reviewed the manuscript for important intellectual content and approved the final version submitted. The research networks AfterROSC and CRICS-TRIGGERSEP have endorsed the study project. The study is promoted by Le Mans Hospital. None of the authors has declared competing of interests.

CONTRIBUTORS

NC conceived the study and is the guarantor of the trial. JBL, AC and CG helped with implementation. PS and EPS provided statistical and methodological expertise in clinical trial design. All authors contributed to refinement of the study protocol and approved the final manuscript.

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FIGURE TITLE

Figure 1. Study flowchart

SUPPLEMENTARY MATERIALS

Supplemental material 1.docx: WHO trial registration data set (version 1.3.1)

Supplemental material 2.docx: Participating ICU list

Supplemental material 3.docx: Flowchart of timing in collection of different variables

Supplemental material 4.docx: Data collection

Supplemental material 5.docx: Patient's consent form

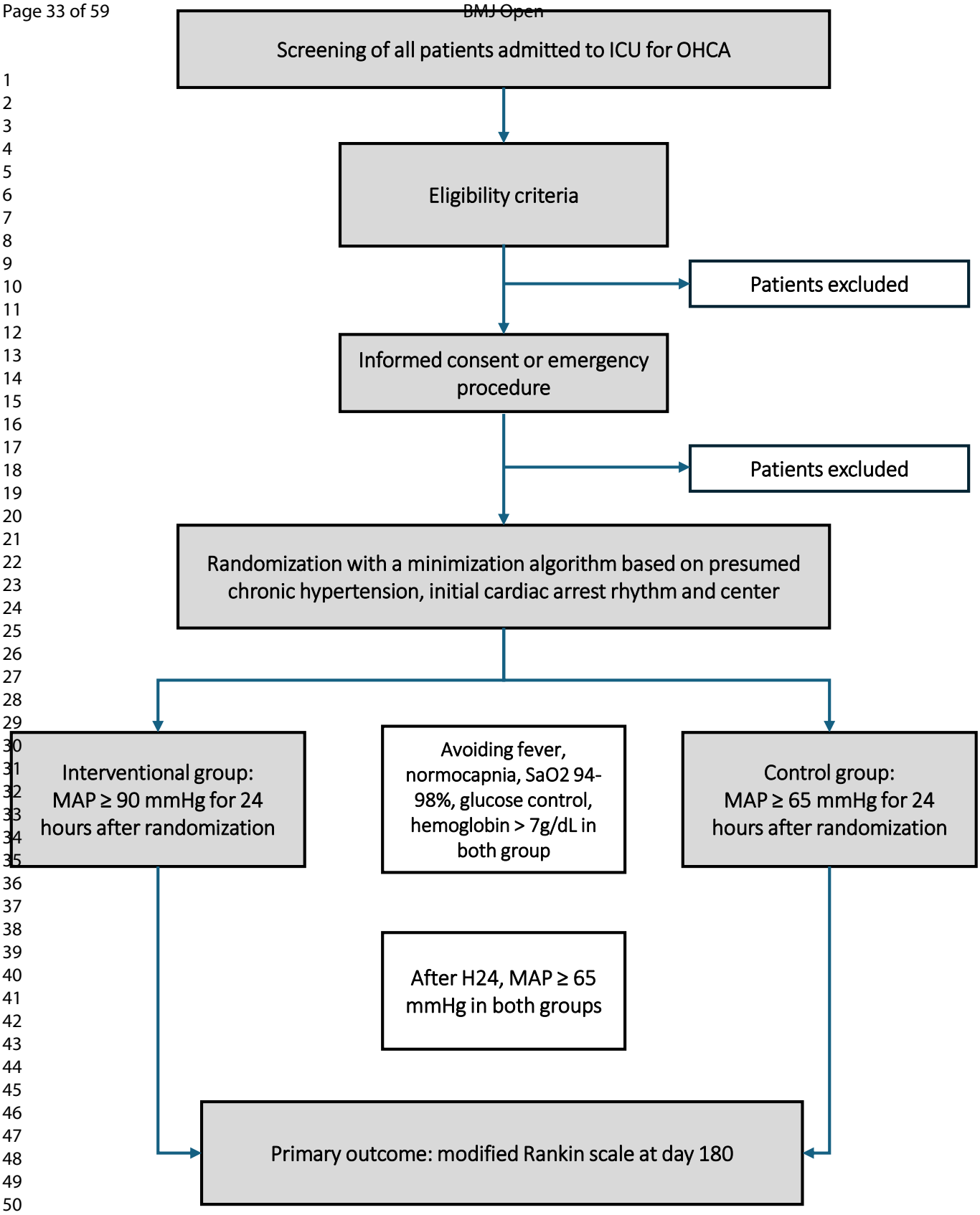

Figure 1: Flow chart. ICU, Intensive Care Unit; OHCA, Out-of-Hospital Cardiac Arrest; MAP, Mean arterial pressure

SUPPLEMENTARY MATERIAL 1: WHO Trial Registration Data Set (Version 1.3.1)

Data category	Information
Primary Registry and Trial Identifying Number	ID-RCB : 2023-A00257-38
Date of Registration in Primary Registry	January 30, 2023
Secondary Identifying Numbers	NCT05486884 ; PHRC-21-0056
Source(s) of Monetary or Material Support	French National « Programme Hospitalier de Recherche Clinique 2021 »
Primary Sponsor	Clinical Research Unit of the Centre Hospitalier du Mans
Secondary Sponsor(s)	NA
Contact for Public Queries	NC (see page 1)
Contact for Scientific Queries	NC (see page 1)
Public Title	Comparaison de deux niveaux de pression artérielle moyenne après arrêt cardiaque extra-hospitalier : étude multicentrique, randomisée, contrôlée, METAPHORE
Scientific Title	Mean arterial pressure after out-of-hospital cardiac arrest : the METAPHORE randomised trial
Countries of Recruitment	France
Health Condition(s) or Problem(s) Studied	Patients who are resuscitated after out-of-hospital cardiac arrest and remain comatose
Intervention(s)	High mean arterial pressure threshold (90 mmHg or more) versus Standard mean arterial pressure threshold (65 mmHg or more) within 24 hours after return of spontaneous circulation
Key Inclusion and Exclusion Criteria	Inclusion criteria : Admission to ICU following an out-of-hospital cardiac arrest with an initially shockable or non-shockable rhythm; Sustained ROSC defined as 20 minutes with signs of circulation without the need for chest compressions; Under invasive mechanical ventilation for coma, defined as a Glasgow score ≤ 8/15; Consent of a relative or emergency inclusion procedure (due to the temporary incapacity of patients to express their consent). Exclusion criteria :

	Age < 18 years ; In-hospital cardiac arrest ; Unwitnessed CA with initial rhythm of asystole ; Time between ROSC and attempted randomisation > 6 hours (360 min); Cardiac arrest in a context of multiple trauma; Cardiac arrest in a context of hemorrhagic shock or severe hemorrhage necessitating hemostasis (surgery or radiological or endoscopic hemostasis); Cardiac arrest secondary to an acute brain disease (ischemic or hemorrhagic stroke, subarachnoid hemorrhage, severe traumatic brain injury); Refractory shock ; Extracorporeal circulatory support prior to inclusion; Known allergy to norepinephrine or to any of its excipients; Decision to limit care before inclusion; Modified Rankin score of 4 or 5 before cardiac arrest; Inclusion in another interventional study in which the principal endpoint is neurological prognosis; Pregnancy or breast feeding ; Adult patient deprived of freedom or under legal protection (patients under guardianship or curatorship) (article L1121-6 of the French Health Code) ; Non-French speaking; Patient already included in this trial; Absence of social security cover.
Study Type	multicentre, open-label randomised controlled superiority trial with two parallel groups, a 1:1 allocation and with blinded outcome assessment
Date of First Enrollment	October 2024
Sample Size	Planned to enroll 1380 participants (currently enrolled 95 participants on March 14th, 2025)
Recruitment Status	Recruiting
Primary Outcome(s)	The primary outcome is the proportion of patients with a good neurological outcome 180 days after inclusion. A good neurological outcome is defined by a mRS of 0 to 3.
Key Secondary Outcomes	Proportion of patients alive at ICU discharge, at hospital discharge, at day 28 (D28) and six months (D180) after inclusion; Proportion of patients alive at ICU discharge with a

	modified Rankin scale of 0 to 3; The EuroQol-5D-5L six months after inclusion. EuroQol-5D-5L is a measure of health-related quality of life and comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression); The Clinical Frailty Scale (CFS) six months after inclusion. CFS summarizes the overall level of fitness or frailty of a patient with a score from 1 (very fit) to 9 (terminally ill); Number of ICU-free days calculated from the number of days alive outside the ICU by D28; Number of ventilator-free days, number of catecholamine-free days and number of renal replacement therapy-free days calculated from the number of days alive without invasive mechanical ventilation, catecholamine infusion or renal replacement therapy by D28; The proportion of patients with acute kidney injury stage 3 according to the Kidney Disease Improving Global Outcomes (KDIGO) classification and need for renal replacement therapy (RRT) (for patients without renal replacement therapy before cardiac arrest) within ICU stay and persistent need for RRT at ICU discharge; safety outcomes (cardiovascular complications, neurological complications, cutaneous complications, digestive complications, major bleeding); subgroup analysis (proportion of patients with good

	neurological outcome at D180 in subgroups of patients with and without chronic hypertension, in subgroups of patients with a non-shockable and a shockable cardiac arrest rhythm, and in subgroups of patients according to CAHP score).
Ethics Review	The METAPHORE trial received approval from the national ethics review board on 8 February 2024 (Comité de Protection des Personnes Sud-Est V, registration number 2023-A00257-38)
Completion date	NA
Summary Results	NA
IPD sharing statement	After publication of the main results, the anonymised data necessary for carrying out additional analyses may be made available upon request addressed to the coordinating investigator and the scientific committee

SUPPLEMENTARY MATERIAL 2 : PARTICIPATING ICU LIST

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SUPPLEMENTARY MATERIAL 3: FLOWCHART OF TIMING IN COLLECTION OF DIFFERENT VARIABLES

Table 1: Flowchart of timing in collection of different variables. CA, cardiac arrest; SOFA, Sequential organ failure assessment; SAPS II, Simplified acute physiology score II; FOUR score, Full outline of unresponsiveness score; ICU, intensive care unit.

Data	Inclusion Day 0	H0 to H24	H24 to H72	D1	D2	D3	D4	ICU discharge	Hospital discharge	D28	D180
Eligibility screen	X										
Informed consent signed or emergency procedure	X										
Demographic data	X										
Comorbidities	X										
Modified Rankin Scale	X (before CA)							X			X
Clinical Frailty Scale	X (before CA)										X
Characteristics of CA	X										
Hemodynamic and clinical data	X	X	X								
Neurological examination	X										
Laboratory tests (at the discretion of the physician)	X			X	X	X	X				
Electrocardiogram	X			X	X	X					
SOFA score	X										
Cardiac function evaluation or invasive hemodynamic monitoring (at the discretion of the physician)	X			X	X	X					
Complications (between inclusion and D7)								X			
SAPS II				X							
Catecholamines		X	X								
Sedation and analgesia		X	X	X	X	X	X				
Vital status				X	X	X	X	X	X	X	X
Glasgow score	X										
FOUR Score	X										

Characteristics of ICU stay								X			
Characteristics of organ support								X		X	
Neuroprognostication							X	X			
Telephone interview											X
Living situation											X
EuroQol-5D-5L	X (before CA)										X
Patient consent (as soon as possible)								X	X	X	X

SUPPLEMENTARY MATERIAL 4: DATA COLLECTION

Data at day 0 (day 0 starts at inclusion and ends at 11.59 pm the same day):

- Sex
- Weight and height
- Principal comorbid conditions (Charlson index)
- Confirmed chronic hypertension requiring treatment
- Chronic atrial fibrillation or atrial flutter
- Modified Rankin score before cardiac arrest obtained from a relative
- Clinical Frailty Scale before cardiac arrest obtained from a relative
- EuroQol-5D-5L questionnaire before cardiac arrest obtained from a relative
- Date and time of hospital admission and ICU admission
- Characteristics of the cardiac arrest (CA) and prehospital resuscitation: initial rhythm, ,CA localization (home, public place, nursing facility, work, or other), witnessed arrest, bystander cardiopulmonary resuscitation or defibrillation performed, duration of no flow (time from CA to the start of cardiopulmonary resuscitation (CPR)), duration of low flow (time between the start of CPR and return of spontaneous circulation ROSC), time from arrest to advanced life support, specific characteristics of CPR (number of external electric shocks, total dose of epinephrine)
- Glasgow Coma Scale following ROSC before sedation
- Hemodynamic data at the time of inclusion: systolic, diastolic and mean arterial pressure, heart rate, shock, doses of vasopressors and inotropes, fluid resuscitation volume between ROSC and inclusion
- Other clinical data: body temperature and temperature management, pupil examination, cerebral trunk reflexes and FOUR score (Full Outline of UnResponsiveness Score),

presence or absence of status myoclonus, presence of diarrhea, presence of gastrointestinal bleeding

- EKG at inclusion
- Presumed mechanism of CA (acute coronary syndrome, non-ischemic cardiac cause, pulmonary embolism, hypoxemia, shock, accidental hypothermia, metabolic cause, toxic cause, anaphylaxis or other origin)

Laboratory tests and other data analyzed will not be specific to the study and will be collected during routine care in the framework of the management of patients after CA. All biological tests will be performed by the laboratories at the investigating centers.

- Lactatemia
- Arterial blood gases (pH, PaO_2, $PaCO_2$, bicarbonates)
- Blood formula and platelet count
- Creatinemia
- Sodium and kaliemia
- Glycemia
- Transaminase
- Bilirubin
- PT-INR
- Troponinemia
- Calculation of SOFA (sequential organ failure assessment) score from clinical and paraclinical data. This score evaluates organ dysfunctions (hemodynamic, respiratory, neurological, hepatic, hemostatic, renal) and is routinely used in intensive care; it is correlated with mortality.
- Calculation of CAHP score

Post-CA patients frequently undergo hemodynamic evaluations by echography or invasive cardiac output monitoring, due to the high frequency of associated heart failure. The use and choice of the type of monitoring will be left to the discretion of the clinician. If one of these means is in use at the time of inclusion, the following hemodynamic data will be collected:

- By echocardiography: left ventricular ejection fraction (Simpson's method), subaortic velocity-time index (subaortic VTI), calculation of cardiac output and cardiac index;
- By invasive monitoring (pulmonary arterial catheter or PiCCO® or other): cardiac output and cardiac index, mixed venous oxygen saturation (SvO_2) or central venous oxygen saturation ($ScVO_2$). These data will be recorded as a function of the type of invasive monitoring.

Follow-up of the participants

No investigation specific to this study will be performed except centralized phone interview by a psychologist or a nurse six months after inclusion. All further clinical and paraclinical data collected will be obtained during routine practice in the framework of post-CA management.

During the first 24 hours after inclusion:

- Collection, every hour, of systolic, diastolic and mean arterial blood pressure, and heart rate;
- Maximum dose of vasopressors and inotropes and calculation of the vasoactive inotropic score. Norepinephrine dose will be reported as norepinephrine base;
- Collection every four hours of body temperature, SpO2, FiO2, and glycemia;
- Cumulative dose of sedation and opioids;
- Neuromuscular blockers infusion;
- Cumulative dose of fluid volume expansion and cumulative urine output;
- Protocol discontinuation during the first 24 hours and reasons;
- Use of antihypertensive agents during the first 24 hours;

From 24h to 72h after inclusion:

- Maximum dose of vasopressors and inotropes and calculation of the vasoactive inotropic score.
- Collection, every four hours, of systolic, diastolic and mean arterial blood pressure;
- Collection every four hours of temperature, SpO2, FiO2/oxygen flow rate, glycemia;
- Cumulative dose of fluid volume and cumulative urine output;
- Neuromuscular blockers infusion;

At day 1:

- Performance of an ECG and troponinemia;
- If appropriate, hemodynamic monitoring data (obtained by echography or invasive monitoring);
- Simplified Acute Physiology Score II (SAPS II) will be calculated from clinical and laboratory tests. This score measures the seriousness of the patient's condition and is used in intensive care. It is based on the data for the first 24 hours and is correlated with mortality.

At days 2 and 3:

- Performance of an ECG and troponinemia;
- If appropriate, hemodynamic monitoring data (obtained by echography or invasive monitoring).

Neuropronostication during the ICU stay:

Evaluating an intervention that cannot be blinded to the treating clinicians, the METAPHORE trial will employ a conservative and strict protocol for neurological prognostication and related decisions regarding limitations in level-of-care to mitigate potential bias.

- Prognostication will be performed on *all* participants still in the ICU at day 4 after inclusion. The prognostication will be based on the ERC and European Society for Intensive Care Medicine recommendations. The prognostication will be based on the TTM-2 trial protocol.

- The result of the prognostication will be categorized as "YES" or "NO", based on the answer to the question *"Does this patient fulfill the METAPHORE trial criteria for a likely poor neurological outcome?"*. This assessment will be recorded in the case report form. Patients who do not fulfill these criteria for a likely poor neurological outcome or if there is still one or more confounders (such as sedation or neuromuscular blockade agents, hypotension, hypothermia, sepsis, metabolic or respiratory derangements) at day 4 after randomization, should be reexamined daily.
- Any decision to withdraw active life support will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. In making this decision the treating physician may use the information from the prognostication. Efforts will be made to sufficiently delay prognostication to ensure that any lingering effects of sedative agents will not affect the assessment.
- Prognostication will be based on two mandatory, and four optional modalities:

    - Clinical examination (mandatory): A clinical examination including assessment of brainstem reflexes and described using the FOUR- score will be performed daily on all patients. An exception to the FOUR-score is that myoclonus will be considered separately in this trial. Absent or extensor motor response to pain (FOUR- score motor response 0-1) at day 4 or later in a patient who is considered unaffected by sedative agents, is a prerequisite to consider the neurologic prognosis poor. The bilateral absence of pupillary and corneal reflexes at 72h after CA or later, is a finding indicative of a poor prognosis. The daily clinical examination by the ICU-staff should also include an assessment of status myoclonus (continuous and generalized myoclonus persisting for at least 30 min). A prospectively documented early status myoclonus (within 48 hours) is indicative of a poor prognosis. Information from daily examinations including evaluation of status myoclonus should be available to the physician performing the evaluation.
    - EEG (mandatory): An EEG performed at > 24 hours will be performed on all participants who survive, and remain unconscious to this point, in line with standard clinical practice. If it is not possible to perform an EEG study in the specified time frame due to practical reasons, the EEG should be performed as soon as possible. An EEG with a

highly malignant pattern, and without reactivity to sound and pain is indicative of a poor prognosis

- Brain CT or brain MRI (optional): If a brain-CT shows signs of global ischaemic injury, such as: generalized oedema with reduced grey/white matter differentiation, this is indicative of a poor prognosis. A CT should be considered in patients who remain unconscious to exclude other pathologies such as intracranial haemorrhage or infarction. A brain MRI at 3-5 days may be incorporated into prognostication if it has been performed. Signs of global, diffuse, or bilateral multifocal ischaemic lesions are indicative of a poor prognosis.
- Biological markers (optional): high level of neuron specific enolase (> 60 µg/L without hemolysis) is indicative of a poor prognosis
- SSEP (optional): Absent SSEP N20-responses bilaterally may be seen as indicative of a poor prognosis, if SSEP is performed more than 48h after randomization

The following criteria, evaluated 4 days after randomization or later, need to be fulfilled to establish a likely poor neurological outcome:

- Absent or extensor motor response to pain AND at least two of the following:

    1. Bilaterally absent pupillary and corneal reflexes
    2. Bilaterally absent SSEP N20-responses
    3. Diffuse anoxic brain injury on CT or MRI
    4. Documented status myoclonus within 48h of randomization
    5. High levels of serum NSE (> 60 µg/L) without hemolysis
    6. An EEG with a highly malignant pattern and without any observed reactivity to sound or pain. Patterns that are considered highly malignant are:
        - Suppressed background (amplitude <10mV, 100% of the recording) without discharges.
        - Suppressed background with superimposed continuous periodic discharges.
        - Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges.
        - Burst-suppression with superimposed discharges.

All the patients in the trial will be actively treated until 4 days after randomization. There will be two exemptions from this rule:

- Participants in whom further treatment is considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons;
- Participants in whom brain death is established, however this will be defined as death and not decision to withhold or withdraw active treatment.

At ICU discharge:

- Date of ICU discharge;
- Vital status and date and cause of death, if appropriate;
- Rankin modified scale;
- Date of intubation and extubation;
- Date of introduction and cessation of vasopressor and inotrope treatments;
- Higher rate of creatinine during the ICU stay and exposure to nephrotoxic agents during ICU stay;
- Lower hemoglobin level during ICU stay and red blood cell transfusion;
- Date of start and cessation of renal replacement therapy;
- Performance (or not) of complementary examinations for neuroprognostication: electroencephalogram, evoked potentials, neuronal biomarkers and types of biomarkers, brain imaging, and the results of these examinations, if performed;
- Performance (or not) of complementary examinations for CA cause diagnosis: coronary angiography, CT scan, lumbar punction, CT pulmonary angiogram, or other;
- Performance (or not) of specific cardiac treatment during ICU stay: coronary artery bypass grafting, implantable cardiac defibrillator;
- Performance (or not) of CT scan before inclusion
- Date of start of nutrition and route (enteral or parenteral or both)

- Final diagnosis (CA cause);
- Decision and date to withhold or withdraw active treatment and the reasons for this decision;
- Occurrence or not of complications from D1 to D7 and date of the first ones:
    - Cardiovascular complications: newly occurring or recurrent severe cardiac arrhythmia; newly occurring or recurrent ST-Elevation Myocardial Infarction (STEMI); need for extracorporeal life support (ECMO or Impella or other) for refractory cardiogenic shock; recurrent cardiac arrest;
    - Neurological complications: stroke (ischemic stroke, subarachnoid hemorrhage or cerebral hematoma);
    - Cutaneous complications: necrosis of the extremities;
    - Digestive complications: digestive ischemia;
    - Major bleeding.

At hospital discharge:

- Date of hospital discharge;
- Vital status and the date of death, if appropriate;

At 28 days:

- Vital status and the date of death, if appropriate.
- Date of hospital discharge.

This evaluation will be undertaken by telephone by local clinical research assistant.

At six months (± 15 days) (telephone or visio follow-up):

This evaluation will be undertaken by telephone or visio by a psychologist or a clinical research nurse specially trained for this follow-up. The follow-up will be centralized for all patients included in the study and alive at ICU and hospital discharge. Health personnel responsible for

outcome assessment at follow-up will be blinded to the allocation of the intervention (blinded-endpoint). The assessor will collect:

- Vital status and date of death, if appropriate;
- **Modified Rankin score (to measure primary endpoint);**
- Clinical Frailty Scale;
- Living situation;
- EuroQol-5D-5L;

Outcome-assessors will be provided with a written trial manual with detailed guidelines for performing the questionnaires and assessments. Modified Rankin Scale will be done during a telephone or visio semi structured interview. Training sessions will be provided by the trial coordinating team. At the end of each training session participants will perform mRS scoring on several practice cases. Outcome-assessors will also be encouraged to perform all follow-up procedures on several pilot persons.

The psychologist must make every effort possible to contact the subject. If the contact is not re-established after 3 phone calls, the patient's general practitioner or a proxy will be contacted. In third line, the French national death certificate database (CépiDc) will be consulted. If the contact is not re-established, then the subject is considered lost to follow-up and mRS 6 will be applied.

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Full research title :

Mean arterial pressure after out-of-hospital cardiac arrest : a multicentre, randomised, controlled trial (METAPHORE)

Sponsor : Le Mans Hospital, 194 avenue Rubillard, 72000 LE MANS

INFORMATION NOTE – CONTINUED PARTICIPATION

Dear Sir/Madam,

Due to the severity of your condition and the medical emergency, we were unable to obtain your prior consent, and you were included on …../……/…… in an interventional research study entitled **"Mean arterial pressure after out-of-hospital cardiac arrest : a multicentre randomised controlled trial (METAPHORE)**."

In accordance with the law (Article L.1122-1-1 of the French Public Health Code), the attending doctor/professor (name, surname) …… at (hospital name) …… sought consent from your designated trusted person, a parent, or a close relative present at the time of your admission. If no relative was present, you were included in the study without prior consent, as authorized by law in medical emergencies. Now that you are able to understand and express your will, we seek your consent to continue participating in this interventional study.

It is important that you carefully read this document before making your decision; please do not hesitate to ask for further clarification. If you decide to continue participating, written consent will be required.

1) What is the purpose of this research ?

This study investigates the effects of a high mean arterial pressure (MAP) target in patients admitted to intensive care following an out-of-hospital cardiac arrest.

Patients in this condition, as you were, are at risk of severe and irreversible neurological damage (coma, paralysis, memory disorders...), which account for the majority of in-hospital deaths. In the hours following cardiac arrest, cerebral blood flow decreases, even when arterial pressure is normal. Increasing blood pressure through medication may enhance cerebral blood flow, limit neurological damage, and improve survival and neurological prognosis.

This study aims to assess the efficacy of a higher MAP target in this medical context to improve patient management. A total of 1,380 patients admitted to intensive care after out-of-hospital cardiac arrest requiring respiratory support will be included. This study is being conducted because current scientific data are insufficient to determine the effectiveness of this strategy as an adjunct to standard care in this situation.

2) What does the research involve ?

In this study, we will evaluate the benefit of maintaining a high MAP target (≥ 90 mmHg) for 24 hours compared to the standard MAP target (≥ 65 mmHg).

Each participant has been randomly assigned to one of two groups:

- High MAP target (≥ 90 mmHg for 24 hours, then ≥ 65 mmHg for the remainder of the ICU stay)
- Standard MAP target (≥ 65 mmHg throughout the ICU stay)

To ensure objective evaluation, neither the participants nor those conducting long-term follow-up are aware of the assigned treatment group.

3) What is the research timeline ?

Participation lasts 180 days (6 months). On day 180 (±15 days), your condition will be assessed via telephone or video consultation with a study psychologist (a 15-minute interview). A simple questionnaire will evaluate potential disability and your quality of life. The psychologist will have access to your personal contact information, stored in a secure database that will be deleted after study follow-up completion.

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4) What are the expected benefits of this trial ?

If a high MAP target proves effective, patients treated this way may experience better and faster recovery, fewer complications, shorter hospital stays, and a lower risk of neurological sequelae and disability. Additionally, your participation will contribute to improving patient care after cardiac arrest.

5) What treatments are permitted or restricted ?

Throughout the study, especially during ICU hospitalization, all standard treatments were administered identically in both groups according to guidelines.

The study's MAP targets were achieved using medications commonly used in ICU settings (continuous infusion of norepinephrine and dobutamine, administration of IV fluids).

All necessary treatments were allowed following current medical recommendations. Your participation in this study has not and will not affect your overall medical management, except for the MAP target applied during the first 24 hours.

6) What are the potential risks and constraints ?

Theoretical risks associated with a high MAP target include:

- Cardiovascular: cardiac arrhythmia, pulmonary edema, heart failure
- Neurological: brain edema, brain hemorrhage
- Digestive: intestinal ischemia
- Cutaneous: ischemia of fingers, toes, or limbs
- Hemorrhagic: bleeding complications

However, previous studies on high MAP targets have not demonstrated increased complications compared to standard management, including no significant negative impact from cardiac arrhythmias.

If you agree to take part, you must comply with the following points:

- Complete the telephone survey on day 180. If this is not possible, we will ask you to contact the study's investigating doctor as soon as possible.

- Follow your doctor's recommendations regarding your participation in the study.

- Inform the doctor of the research, of the use of any treatment and of any event occurring during the research.

- Not to take part in another research project without your doctor's agreement.

- Be affiliated to a social security scheme or be a beneficiary of such a scheme.

No blood tests or radiological examinations other than those usually prescribed will be required as part of this study.

7) Are there alternative medical options ?

If you choose not to participate, all standard treatments will still be provided according to current guidelines. Declining participation will not impact your medical care.

8) What happens after the study ?

Your participation incurs no additional costs beyond usual medical follow-up. Your doctor may decide to end your participation at any time and will explain the reasons to you.

9) What happens to the data collected in the study ?

Le Mans Hospital will process your personal data to analyze study results. Your medical and lifestyle data will be shared with the research sponsor (Centre Hospitalier du Mans) under public interest regulations. Data will be coded (ID number and initials) without including your name, surname, or address. These data may be securely transmitted to French health authorities and may be used for future research in collaboration with public or private partners, in compliance with confidentiality regulations and European legislation.

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You may withdraw consent for future data use at any time by notifying the study physician. Data collected before withdrawal will still be used unless you specify otherwise.

Your data will be retained for 15 years after study completion. The data controller for this study is the sponsor, Le Mans Hospital, which has appointed a Data Protection Officer (dpo@ch-lemans.fr or by post: M. le Délégué à la Protection des données du Centre Hospitalier Le Mans 194 avenue Rubillard 72037 Le Mans Cedex 9).

10) How is this research regulated ?

This study adheres to French Public Health Code regulations on human research. The sponsor has liability insurance (Policy No. 128173) with Relyens (18 rue Edouard Rochet, 69372 Lyon Cedex 08). The study was approved by Comité de Protection des Personnes Sud-Est V on 02/13/2024 and by the Agence Nationale de Sécurité du Médicament et des Produits de Santé on 01/12/2024.

11) What are your rights ?

The decision to take part in this research is entirely free and voluntary. Your decision will not affect the quality of care and treatment you are entitled to expect. Throughout the course of the research, you may ask the doctor treating you for information about your state of health and for explanations about how the research is being carried out. You may withdraw from the research at any time without justification, without any consequences for the continuation of your treatment or the quality of the care you receive, and without any consequences for your relationship with your doctor, who must be informed of this choice. In accordance with article L.1122-1-1 of the French Public Health Code, if you decide to discontinue your participation, your personal data collected prior to your withdrawal will be retained unless you object to the doctor who will be treating you as part of the research. The computer file used for this research is implemented in accordance with the provisions of the General Data Protection Regulation - RGPD (European regulation 2016/679) and the provisions of the law relating to information technology, files and freedoms (Law n◦78-17 of 6 January 1978 as amended). You also have the following rights:

- Right of access, rectification and opposition to the processing of personal data,

- Right to restrict the processing of personal data relating to the data subject,

- Right to erase personal data,

- Right to lodge a complaint with the supervisory authority (the CNIL: https://www.cnil.fr, address: 3 Place de Fontenoy - TSA 80715 - 75334 PARIS CEDEX 07).

These rights may be exercised with the investigator of the department in which you are hospitalised, who is following you as part of the research and who knows your identity. They may also be exercised with the data protection officer appointed by the sponsor. Your medical file will remain confidential and may only be consulted under the responsibility of the doctor in charge of your treatment, by the health authorities and by persons duly authorised by Le Mans Hospital for the research and subject to professional secrecy. At the end of the research and after analysis of the data relating to this research, you may be informed of the overall results by asking the doctor who is treating you as part of this research.

Once you have read all this information, discussed all aspects with the doctor and been given time to reflect, if you agree to take part in the research, you will be asked to sign and date the informed consent form at the end of this document.

You can request further information from the doctor who suggested you take part in this research at any time by calling : _____

Thank you for your attention.

Centre Hospitalier Le Mans

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CONSENT FORM

I, the undersigned (full name) :

……

……

freely and voluntarily agree to continue to take part in the clinical research entitled 'Mean arterial pressure after out-of-hospital cardiac arrest : **a multicentre randomised controlled trial (METAPHORE)**' organised by Le Mans Hospital and proposed to me by Doctor/Professor (surname, first name, telephone).....

....., the investigating physician in this study.

- I have read the information note version 1.1 dated 24/01/2024 explaining the purpose of this research, the way in which it has been carried out and what my participation involves,
- I have received and fully understood the written and oral information given to me by the investigating doctor.
- He has explained to me the nature, aims and duration of this research, as well as the expected benefits and possible disadvantages.
- I will keep a copy of the information note and the consent form,
- I received appropriate answers to all my questions,
- I understood that to be able to take part in this research I must be affiliated to a social security scheme or be the beneficiary of such a scheme. I confirm that this is the case.
- I have been informed that my participation in this research will last 180 days (6 months), and that this means that I will not be able to consider taking part in any other research without informing the doctor who is treating me for the research,
- I have been informed that participation in this research does not involve any additional examinations (blood or radiological),
- I have had sufficient time to make my decision,
- My consent does not relieve the research organisers of their responsibilities. I retain all my rights guaranteed by law.
- I understand that my participation is voluntary and that I have the right to refuse to take part and to withdraw from the study at any time without justification or

consequences for the quality of care I will receive. I will then inform the investigating doctor. I will also inform him/her whether or not I wish the data collected up to the time of my decision to be used.

- I have been informed that the data collected as part of the research may be re-used for further research, and that I may object to this at any time.
- I am aware that my participation may also be interrupted by the doctor if necessary,
- I will be able to ask the investigating doctor for explanations throughout the study.
- I accept that my GP will be informed of my participation in this clinical study.

□ Yes □ No

- I confirm that my rights regarding my personal data collected for this study have been explained to me.
- I understand that my data will only be used for scientific research purposes.
- I accept that my personal data and information may be consulted by persons designated by the investigators and by a representative of the sponsor or the health authorities, who are bound by professional secrecy.
- I authorise the study sponsor to use the data collected as part of this study for other scientific research (in the field of intensive care).

□ Yes □ No

For scientific publications, only information that does not mention my name or address may be used. My anonymity is strictly preserved.

I accept that the data recorded in the course of this scientific research may be processed electronically by the investigating doctor. However, the data concerning me will remain strictly confidential and I authorise it to be consulted only by persons authorised by the research organiser or by a representative of the Health Authorities. I may request any additional information from the investigating doctor at any time.

- I have the right to access and rectify my personal data at any time, in accordance with the French Data Protection Act. I also have the right to object to the transmission of data covered by professional secrecy that may be used and processed as part of this research. These rights may be exercised with the doctor conducting the research or through the doctor of my choice.

Signature of participant	Signature of investigator
Name :	Name :
First name :	First name :
Date :	Date :
Signature :	Signature :

This document must be produced in 2 copies, the original to be kept for 15 years by the investigator, the second to be given to the person giving consent.