

# BMJ Open 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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## ABSTRACT

**Introduction** Out-of-hospital cardiac arrest is a public health concern with a high mortality rate. Hypoxic ischaemic brain injury is the primary cause of death in patients admitted to the intensive care unit (ICU) after return of spontaneous circulation (ROSC). Several systemic factors, such as hypotension, can exacerbate brain injuries. International guidelines recommend targeting a mean arterial pressure (MAP) of at least 65 mm Hg. 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  $\geq 65$  mm Hg) with a high MAP threshold (MAP  $\geq 90$  mm Hg) 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 a 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  $\leq 8/15$  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 mm Hg or higher throughout the ICU stay (control group) or a MAP target threshold of 90 mm Hg or higher during the first 24 hours after randomisation, followed by 65 mm Hg 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

## 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.

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 the 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 haemorrhagic 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 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 number** ClinicalTrials.gov: [NCT05486884](https://clinicaltrials.gov/ct2/show/study/NCT05486884).

## 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.<sup>1 2</sup> The primary cause of death in patients admitted to the intensive care unit (ICU) after return of spontaneous circulation (ROSC) is brain injury.<sup>3 4</sup> Hypoxic-ischaemic 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 ischaemia and secondary injuries.<sup>5 6</sup> International guidelines suggest maintaining a mean arterial pressure (MAP) of 65 or 70 mmHg.<sup>7</sup> Several observational studies support that a higher MAP target is associated with better survival and neurological outcomes.<sup>8</sup> However, evidence supporting this strategy remains limited. Three interventional studies have shown no effect of a higher MAP in OHCA patients.<sup>9–11</sup> However, two of these studies were pilot feasibility trials, lacking the power to show statistical differences in clinical outcomes.<sup>9 10</sup> 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.<sup>11</sup> 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,<sup>5 12</sup> and only minimal differences in MAP values between the two groups.<sup>13</sup> 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/](http://www.spirit-statement.org/spirit-statement/)). We provided all WHO trial Registration Data Set (see online supplemental material 1).

### Objectives

The study hypothesis is that a strategy targeting a MAP threshold  $\geq 90$  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  $\geq 65$  mmHg).

The main objective of the study is to demonstrate the efficacy of a high MAP threshold (MAP  $\geq 90$  mmHg) on neurological prognosis at 6 months in patients resuscitated from out-of-hospital cardiac arrest relative to the standard threshold (MAP  $\geq 65$  mmHg).

The secondary objectives of the study are as follows:

- ▶ To demonstrate the superiority of a high MAP threshold (MAP  $\geq 90$  mmHg) compared with the standard threshold (MAP  $\geq 65$  mmHg) in terms of survival at ICU discharge, at hospital discharge, at day 28 and 6 months.
- ▶ To demonstrate the superiority of a high MAP threshold compared with the standard MAP threshold in terms of neurofunctional prognosis at ICU discharge, quality of life at 6 months, length of stay in the ICU, duration of organ support and organ failure.
- ▶ To demonstrate the safety of a high MAP threshold compared with the standard threshold in terms of global and specific complications within 7 days of inclusion.

Additionally, subgroup analysis will be performed to assess the following:

- ▶ Neurofunctional prognosis at 6 months according to initial cardiac arrest rhythm (shockable or non-shockable).
- ▶ Neurofunctional prognosis at 6 months according to the presence or absence of chronic arterial hypertension.
- ▶ Neurofunctional prognosis at 6 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 a blinded outcome assessment.

### Study setting

The study is being conducted in 27 ICUs across France. Site characteristics are listed in (online 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  $\geq 18$  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 min with signs of circulation without the need for chest compressions) and who need mechanical ventilation for coma (defined by a Glasgow Coma Scale  $\leq 8$ ). 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 an initial rhythm of asystole.
- ▶ Delay between ROSC and attempting randomisation  $> 6$  hours.
- ▶ Cardiac arrest in the context of multiple trauma.
- ▶ Cardiac arrest in the context of haemorrhagic shock or severe haemorrhage necessitating haemostasis (by surgery, radiological procedure or endoscopic procedure).
- ▶ Cardiac arrest secondary to an acute brain disease (ischaemic or haemorrhagic stroke, subarachnoid haemorrhage, severe traumatic brain injury).
- ▶ Refractory shock defined as a MAP  $< 65$  mmHg for more than 1 hour on norepinephrine or epinephrine at a dose  $> 1$   $\mu\text{g/kg/min}$  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 breastfeeding.
- ▶ 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  $\geq 90$  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  $\mu\text{g/kg/min}$  at least every hour. Thus, if MAP falls below 90 mmHg, the dose of norepinephrine is increased by 0.05  $\mu\text{g/kg/min}$  every

ten minutes. The titration rate is adjusted according to the depth of arterial hypotension, particularly in cases of haemodynamic 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  $\geq 65$  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  $\geq 65$  mmHg during the entire 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  $\mu\text{g/kg/min}$  at least every hour. Thus, if MAP falls below 65 mmHg, the dose of norepinephrine is increased by 0.05  $\mu\text{g/kg/min}$  every ten minutes. The titration rate is adjusted according to the depth of arterial hypotension, particularly in cases of haemodynamic 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. The monitoring method (echocardiography or invasive haemodynamic monitoring) is left to the discretion of the physician.

General ICU care, including respiratory management, sedation, glycaemic control and transfusion, is delivered similarly in both allocation groups according to international guidelines.<sup>7</sup> Fever is actively prevented by targeting a temperature  $\leq 37.8^\circ\text{C}$  for at least 72 hours in patients who remain comatose.<sup>14</sup>



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 the neuroprognostication algorithm.<sup>7</sup> 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 inclusion. Good neurological outcome is defined by an 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.<sup>15 16</sup> mRS is measured by a psychologist (blinded to the randomisation arm) during a semi-structured telephone interview.

The secondary outcomes are as follows:

- ▶ Proportion of patients alive at ICU discharge, at hospital discharge, at day 28 (D28) and 6 months (D180) after inclusion.
- ▶ Proportion of patients alive at ICU discharge with a modified Rankin scale of 0 to 3.
- ▶ The EuroQol-5D-5L 6 months after inclusion. EuroQol-5D-5L is a measure of health-related quality of life and comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).
- ▶ The Clinical Frailty Scale (CFS) 6 months after inclusion. CFS summarises 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 three 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 three is defined by at least one of the following criteria: serum creatinine concentration of more than 4mg/dL (354 µmol/litre) or greater than three 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 as follows:

- ▶ **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 haemodynamic instability or cardiac arrest.
- Severe atrial flutter or atrial fibrillation, requiring treatment (antiarrhythmic drugs or rate-slowing medication) and/or electrical cardioversion due to haemodynamic instability (a patient with chronic atrial flutter or atrial fibrillation but not requiring urgent treatment for haemodynamic instability will be not concerned).
- Bradycardia (<40 beats per minute) requiring pacing or resuscitation due to haemodynamic instability or cardiac arrest.
- Newly occurring or recurrent ST elevation myocardial infarction diagnosed using an ECG and confirmed by coronary angiography.
- Need for extracorporeal life support (extracorporeal membrane oxygenation or Impella) for refractory cardiogenic shock.
- Unexpected recurrent cardiac arrest (cardiac arrest due to discontinuation of treatments will not be a concern).
- ▶ **Neurological complications** assessed by determining the number of patients presenting with stroke (ischaemic stroke, subarachnoid haemorrhage or cerebral haematoma), 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 with ischaemia 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 ischaemia, 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 haemoglobin level of 20 g/L 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 haemorrhagic) within 7 days of inclusion.

## SUBGROUP ANALYSIS

Patients are analysed by subgroups concerning neurological outcome at 6 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).<sup>17</sup>

## Participant timeline

Figure 1 shows the CONSORT diagram of the META-PHORE trial and table 1 assessments and visits for participants (online supplemental material 3).

## Sample size estimation

The required number of subjects is based on an anticipated difference in the proportion of patients with mRS 0 to 3 at D180 between the two groups. Based on previous studies and the After ROSC registry,<sup>18</sup> we estimate that 30% of the patients included in the standard group will have a good neurological outcome (mRS 0 to 3) at 6 months. By expecting 38% of patients with a good neurological outcome at 6 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 outcomes 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 mm Hg 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 ICUs 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 centres currently manage patients after cardiac arrest. All the participating centres 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  $\geq 90$  mm Hg within 24 hours) or a standard MAP threshold (MAP target  $\geq 65$  mm Hg). A minimisation algorithm based on presumed chronic hypertension, initial cardiac arrest rhythm (shockable or not shockable) and participating centre 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

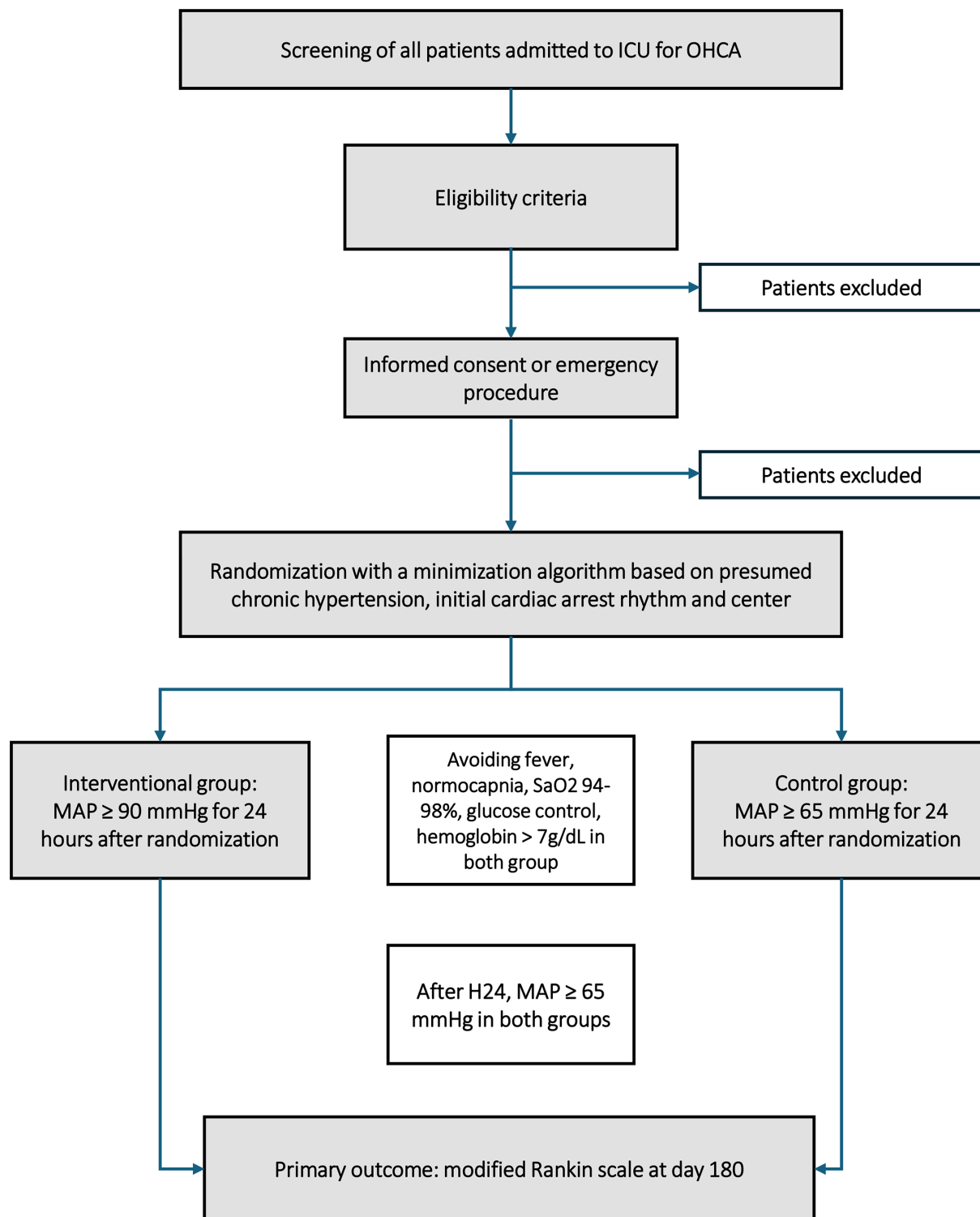
The clinical team responsible for the participants (physicians, nurses and others) and involved with direct patient care will not be blinded to the allocation group due to the inherent difficulty in blinding the intervention. Health personnel responsible for outcome assessment at follow-up will be blinded to the allocation of the intervention. Potential bias will be mitigated by using conservative and strict protocols for neuroprognostication and related decision-making (ie, regarding limitations in level of care). The same neuroprognostication algorithm, based on European Resuscitation Council and European Society of Intensive Care Medicine guidelines,<sup>7</sup> will be used for all patients included in the study.

## Data collection

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

## 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.



**Figure 1** Study flowchart.

### 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 summarise 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 a 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% CI. If the realisation conditions are favourable, 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 the 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 the interim analysis on day 28 mortality will be provided, as well as the proportion of expected adverse events. Patients' characteristics recorded at randomisation will also be provided. An 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 ethics committee, inform the French health authority (ANSM), the investigators and the DMC and update the 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 online 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 to the number of 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.

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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 Nationale, 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 interests.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Comité de Protection des Personnes Sud-Est V – 2023-A00257-38. 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.

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**Data availability statement** Data are available upon reasonable request. After publication of the main results, the anonymised data necessary for carrying

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