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Risk, Rate, or Rhythm control for new onset supraventricular arrhythmia during septic shock: protocol for the CAFS multicentre, parallel-group, open-label trial

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ABSTRACT

Introduction: New-onset supraventricular arrhythmia (NOSVA) is the most common arrhythmia in patients with septic shock, and is associated with haemodynamic alterations and increased mortality rates. With no data available from randomised trials, clinical practice for patient management varies widely. In this setting, rate control or rhythm control could be beneficial in limiting the duration of shock and preventing evolution to multi-organ dysfunction.

Methods and analysis: The Control Atrial Fibrillation in Septic shock (CAFS) study is a binational (French and Belgium), multicentre, parallel-group, open-label, randomised controlled superiority trial to compare the efficacy and safety of three management strategies in patients with NOSVA during septic shock. Patients will be randomised to receive either risk control (magnesium and control of risk factors for NOSVA), rate control (risk control and low dose of amiodarone), or rhythm control (risk control and cardioversion using high dose of amiodarone with external electrical shock if NOSVA persists) for 7 days. Patients with a history of SVA, NOSVA lasting more than 48 h, recent cardiac surgery, or a contraindication to amiodarone will not be included. We plan to recruit 240 patients. Patients will be randomised on a 1:1:1 basis, and stratified by centre. The primary endpoint is a hierarchical criterion at day 28 including all-cause mortality and the duration of septic shock defined as time from randomisation to successful weaning of vasopressors. Secondary outcomes include: individual components of the primary endpoint; arterial lactate clearance at day 3; efficacy at controlling cardiac rhythm at day 7; proportion of patients free from organ dysfunction at day 7; ventricular arrhythmia, conduction disorders, thrombotic events, major bleeding events, and acute hepatitis related to amiodarone at day 28; and ICU and hospital lengths of stay at day 28.

Ethics and dissemination: The study has been approved by the French and Belgian ethics committees. Patients will be included after obtaining signed informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04844801

Strengths and limitations of the study

- ►This randomised controlled trial may contribute to the establishment of recommendations with a high level of evidence on the best management strategy in patients with septic shock and new onset atrial fibrillation.
- ► Pragmatic design comparing three common strategies in an intention-to-treat approach.
- ► Limitation: not blinded.

INTRODUCTION

Background and rationale

New-onset supraventricular arrythmia (including atrial fibrillation, atrial flutter, and atrial tachycardia, NOSVA) is reported in 40% of patients with septic shock and is associated with haemodynamic alterations and increased mortality [1,2]. Efforts to determine the most effective haemodynamic management strategy in this setting are therefore important. In a recent preliminary study from our research team, successful cardioversion of NOSVA in patients with sepsis seemed to be associated with a better prognosis [3]. However, because no randomised clinical trial data are available, there is no consensus regarding the best management strategy for NOSVA during septic shock, which has led to major variations in practice [1,2,4–7]. Three treatment strategies are commonly used: (i) control of modifiable risk factors for NOSVA without using antiarrhythmic drugs (risk control) [8]; (ii) control of heart rate with the use of antiarrhythmic drugs, often with low dose amiodarone (rate control) [9–11]; (ii) cardioversion using antiarrhythmic drugs (often with high doses of amiodarone) and/or electrical cardioversion (rhythm control) [10,11].

Rhythm control may improve haemodynamics (by restoring diastolic function and decreasing cardiac metabolic demand), reduce thromboembolic risk, and minimise exposure to anticoagulants. Rate control limits the potential adverse effects of high dose amiodarone and/or of electrical cardioversion, while still improving haemodynamics. The risk control strategy minimises the adverse effects of amiodarone while still resulting in conversion of NOSVA in some patients.

Determining the efficacy and safety of these three strategies may provide valuable information to improve clinical decision-making and resource utilisation for this highly prevalent condition. Therefore, we will conduct a multicentre, parallel group, open-label, randomised controlled superiority trial to compare head-to-head risk control, rate control, and rhythm control in this setting.

Hypotheses

Our hypotheses are as follows: i) compared to risk control, rate control and rhythm control each improve haemodynamics, thus decreasing shock duration and mortality; ii) rhythm control outperforms rate control in this setting.

Objectives

Primary objective

The main objective is to compare the efficacy of the three strategies (risk control, rate control, and rhythm control) in reducing mortality and duration of shock in septic patients with NOSVA.

Secondary objectives

Secondary objectives are to compare the benefit and risks of the three strategies in terms of haemodynamics, organ dysfunction, morbidity, mortality, safety (including thrombotic events, bleeding events and serious adverse events related to amiodarone and electrical cardioversion), and net clinical benefit.

METHODS AND ANALYSIS

Trial design

This is a binational, multicentre, parallel-group, open-label, randomised controlled superiority trial in patients with NOSVA during septic shock. The trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) reporting guidelines.

Study setting

The study will be conducted in 28 intensive care units (ICUs) in 23 hospitals in France and 5 hospitals in Belgium (list of study sites in Appendix A).

Eligibility criteria

Inclusion criteria

Adult patients (age ≥18 years) admitted to the ICU will be eligible as soon as they meet all the following criteria:

1- Septic shock, defined by the association of the following criteria:
   - Documented or suspected infection, with initiation of antibiotic therapy
   - Initiation of vasopressors (noradrenaline or adrenaline) for at least 1 hour to maintain the mean arterial pressure (MAP) >65 mmHg;
2- NOSVA (including atrial fibrillation, atrial flutter, and atrial tachycardia) with heart rate ≥110 bpm lasting at least 5 minutes;
3- Written informed consent (patient, next of kin or emergency situation);
4- Member of a social security system.

Exclusion criteria

Patients presenting any of the following criteria will not be included:

1. Refractory shock, defined as a dose of noradrenaline base or adrenaline base >1.2 µg/kg/min;
2. Heart surgery or heart transplant in the previous month;
3. Aortic or mitral valve mechanical prosthesis, significant mitral stenosis (mitral surface < 1.5 cm^2);
4. Congenital heart disease other than bicuspid aortic valve, atrial defect, or patent foramen ovale;
5. History of SVA before septic shock, defined as paroxysmal SVA with long-term antiarrhythmic and/or therapeutic anticoagulation, or permanent SVA;
6. NOSVA lasting more than 48 hours (or more than 24 hours under vasopressor therapy): the patient can still be included if transoesophageal echocardiography (under mechanical ventilation) excludes intracardiac thrombus and the patient is receiving therapeutic anticoagulation;
7. Electrical cardioversion or use of amiodarone or another bradycardic drug (beta-blocker, bradycardic calcium channel blocker, digitalis, flecainide) within the 6 hours preceding inclusion;
8. Contraindication to amiodarone: history of serious adverse event, lung disease, or hyperthyroidism related to amiodarone, PR interval >240ms, severe sinus node dysfunction with no pacemaker, second- or third-degree atrioventricular block with no pacemaker, QTc >480ms, known or treated hyperthyroidism, hypersensitivity to iodine, amiodarone or to any of the excipients, severe hepatocellular insufficiency (prothrombin rate <20%), diffuse interstitial lung disease;
9. Serum potassium <3 mmol/L;
10. Pregnancy or breast-feeding;
11. Moribund or death expected from underlying disease during the current admission;
12. Patients deprived of liberty and persons receiving institutional psychiatric care;
13. Participation in another interventional trial on septic shock and/or rhythm disorder.

Intervention

The experimental plan is shown in **Figure 1.** After verification of the eligibility criteria, the patient will be enrolled and randomised (Day 1) as soon as possible, and within 48 hours from the onset of NOSVA (or 24 hours if NOSVA occurs when receiving vasopressor treatment).

Patients should then immediately receive the allocated strategy, for 7 days (or until death or ICU discharge, whichever comes first). The risk control strategy will consist of (i) intravenous bolus of 2 g magnesium sulphate over 20 min (if creatinine clearance >30 mL/min), and (ii) control of risk factors for NOSVA, such as hypovolaemia and metabolic disorders (details in **Table 1**). The rate control strategy will consist of (i) control of NOSVA risk factors as described above, and (ii) 'low dose' amiodarone (details in **Figure 1**). The rhythm control strategy will consist of (i) control of NOSVA risk factors as described above, (ii) 'high dose' amiodarone (details in **Figure 1**), and (iii) if NOSVA persists, electrical cardioversion in sedated patients receiving invasive mechanical ventilation (modalities according to the European Society of Cardiology (ESC) guidelines [12]; details in **Figure 1**). Details of the three strategies according to rhythm and haemodynamic evolution are given in **Figure 2**. In all groups, therapeutic anticoagulation is recommended in the absence of contraindications if NOSVA persists more than 48 hours; modalities of therapeutic anticoagulation will be left to the discretion of the attending physicians. After Day 7 (or discharge from the ICU, whichever comes first), NOSVA management will be left to the discretion of the attending physician. All patients will be followed until Day 28.

In all groups, current recommendations for the management of septic shock will be followed [13].

Criteria and procedures for premature withdrawal of a participant from the study

In compliance with the conventional management of patients with NOSVA during septic shock, the rate control and rhythm control strategies will be discontinued if one of the following occurs:

- Ventricular arrhythmia: torsade de pointe, sustained ventricular tachycardia, ventricular fibrillation;
- Conduction disorders: severe bradycardia (<50 beats per minute), second- or third-degree atrioventricular block, sinus dysfunction (significant sinus pause of at least 3 seconds), need for a pacemaker, QTc prolongation >480 ms;
- Acute hepatitis related to amiodarone, defined by a significant (10-fold) increase in transaminases (hepatic cytolysis), as compared to values before the first dose, and with no other identified cause for hepatitis;
- Hyperthyroidism, as defined by a thyroid-stimulating hormone concentration <0.1 mIU/L in the blood sampled before amiodarone initiation [14].

Follow-up visits

The trial follow-up visits will be on days 2 to 7, and day 28.

Endpoints

Primary endpoint

The primary endpoint is a hierarchical endpoint assessed at day 28 and includes all-cause mortality and the duration of shock. The Finkelstein-Schoenfeld method is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. The pairwise comparison proceeds in hierarchical fashion, using all-cause mortality, followed by the duration of septic shock when patients cannot be differentiated on the basis of mortality. This method gives a higher importance to all-cause mortality [15,16].

The duration (days) of septic shock is defined as the period from randomization to successful weaning of vasopressors (patient alive with no reintroduction during the first 48 hours after discontinuation).

Secondary endpoints

Secondary endpoints will include the following:

(1) Rhythm control at day 7

- Number of patients with sinus rhythm;
- Number of days alive with sinus rhythm;
- Number of days alive with NOSVA and heart rate <110 bpm;
- Proportion of patients receiving therapeutic anticoagulation after randomization;

(2) Morbidity, mortality, and organ function

- Duration of septic shock at day 28;
- Proportion of patients alive and free from vasopressors at day 7 (or discharge or death whichever comes first);
- Arterial lactate clearance at day 3 [17];
- Proportion of patients alive and free from organ dysfunction at day 7 (or discharge or death whichever comes first). Organ dysfunction is defined as a sequential organ failure assessment (SOFA) score ≥3 for the following organs: cardiovascular, renal, neurological, hepatic, respiratory, or coagulation [18];

- Length of ICU stay at day 28;
- Length of hospital stay at day 28;
- All-cause deaths at day 28.

(3) Safety

- Arterial thrombotic events, including ischaemic stroke and non-cerebrovascular arterial thrombotic event [19];
- Major bleeding events defined as bleeds that meet at least one of the following criteria: bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal); bleeding requiring surgical, endoscopic or endovascular haemostasis action; a life-threatening bleed; and a fatal bleed [20];
- Serious adverse events related to amiodarone or to magnesium, including ventricular arrhythmia, conduction disorders, and acute hepatitis related to amiodarone as described above;
- Serious adverse events associated with electrical cardioversion (for patients receiving electrical cardioversion) including ventricular arrhythmia, conduction disorders, and arterial thrombotic events.

(4) Combined efficacy and safety

- Net clinical outcome as assessed by the presence of all-cause death, arterial thrombotic event, major bleeding event, or at least one serious adverse event related to amiodarone or to magnesium or to electrical cardioversion at day 28.

Sample size and its statistical justification

The sample size was calculated by considering pairwise comparisons between the groups. For each comparison, 1000 samples were simulated using SAS software. Based on data from our two previous studies in patients with NOSVA during sepsis [3,6], the distribution characteristics of the samples were defined according to the following assumptions: (i) 28-day mortality rates of 35%, 30%, and 25% for the risk control, rate control, and rhythm control groups, respectively; (ii) durations of septic shock of 4.9 ± 2.4 days (standard deviation), 3.9 ± 2.4 days, and 2.9 ± 2.4 days for the risk control, rate control, and rhythm control groups, respectively. Within each sample/pairwise comparison, an individual score was calculated by comparing each patient in one group with all patients in the other groups [15,16]. These scores were then compared between groups using a Mann-Whitney/Wilcoxon test in each of the 1000

samples, and the p-value of each test was recorded. For each pairwise group comparison, the proportion of tests with a p-value <0.05 was at least 81% with 80 subjects in each group. Therefore, we expect that having 80 subjects per group will provide a minimum power of 81% to detect a difference in the primary outcome with alpha = 5%.

Recruitment

The expected duration of patient enrolment is 42 months starting from November 2021. The study timeline is as follows: i) 2018: Grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique) for academic sponsor (Assistance Publique-Hôpitaux de Paris, AP-HP); ii) July 2020: approval by independent ethics committees and competent authority; iii) November 2021: start of patient enrolment; iv) 2025: end of patient enrolment, monitoring, cleaning and database lock, blind review to screen for protocol violation; iv) 2025-2026: data analysis, writing of the manuscript, and submission for publication.

Allocation of intervention and data management

Randomisation in a 1:1:1 ratio will be prepared by an independent statistician from the Clinical Research Unit before the start of the trial. Randomisation will be stratified by centre and block balanced. The width of the blocks will not be communicated to the investigators. Patients will be randomised using the electronic case report forms (e-CRFs).

Non-identifying data will be entered into the e-CRFs by a trained investigator or research assistant at each centre. Patient follow-up and task schedules are detailed in the study Gantt chart **(Table 2).** The e-CRF was devised by the principal investigator and the scientific supervisor of the study in collaboration with the data manager of the Clinical Research Unit. e-CRFs and a data dictionary (containing coding variables and definitions) will be saved and archived in the Clinical Research Unit and AP-HP secured servers. The computer files used for this research are implemented in compliance with the French (amended "*Informatique et Libertés*" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations. The sponsor has already obtained authorisation from CNIL (French Data Protection Agency) to process data from this research (Ref.: MLD/MFI/AR2012389). Database quality control will be undertaken by a Data manager from the Clinical Research Unit.

Statistical methods

All analyses will be performed by a statistician form from the Clinical Research Unit according to the statistical analysis plan prepared before data base lock, using SAS software version 9.4 (SAS Institute, Cary, NC, USA), R software version 4.2.2 and Stata software (version 17; StataCorp).

In compliance with the SPIRIT statement, a flow diagram will describe the progress of the three groups of patients throughout the different phases of the trial (enrolment, allocation, received interventional agents, follow-up, and data analysis). The analysis will be performed on an intention-to-treat (ITT) basis. In case of premature interruption or withdrawal from the study, patients will not be substituted. Single imputation will be made for missing values of the primary endpoint, as a failure (i.e. death). Sensitivity analysis will be performed in the per-protocol population set (patients as randomized without major protocol violations).

Descriptive analysis

A flow chart will be provided. Descriptive statistical analyses will be conducted on the ITT population to describe general and baseline characteristics. Quantitative variables will be reported as mean (±standard deviation) or median (25^{th}-75^{th} percentiles) according to the distribution of the variable. Qualitative variables will be reported as numbers (%).

Analysis of the primary endpoint

The pre-specified primary endpoint will be a ranked composite score that incorporates death and duration of shock, calculated in such a manner that death constitutes a worse outcome than longer duration of shock. Each patient will be compared with every other patient in the study and assigned a score (equality: 0, win: +1, loss: −1) for each pairwise comparison based on who fared better. For example, if one patient survives and the other does not, the first will be attributed +1 and the latter −1 for that pairwise comparison. If both patients in the pairwise comparison survive, the scoring will depend on duration (days) of septic shock: fewer days earns a score of +1, and more days earns a score of −1. If both patients survive and had the same duration of septic shock, or if both patients die, both will score 0 for that pairwise comparison. For each patient, scores of all pairwise comparisons will be summed to obtain a cumulative score. These cumulative scores will be ranked and compared across the three groups using a non-parametric Mann-Whitney test [16].

Analysis of secondary endpoints

Comparisons between randomised groups at given timepoints will be conducted using Pearson Chi square or Fisher exact tests for categorical variables, and using ANOVA or non-parametric Kruskal Wallis tests for quantitative variables, as appropriate.

For 28-day all-cause mortality, the number of patients with sinus rhythm at day 7, the number of patients free from vasopressors at day 7, and survival without serious adverse event, calculation of time-to-event endpoints based on follow-up censored data will be employed, taking into account the competing risks of hospital discharge (for mortality evaluation) and death (for the number of patients with sinus rhythm at day 7 and the number of patients free of vasopressor at day 7). Kaplan-Meier survival curves and cumulative incidence curves will be plotted accoring to treatment group, and Cox models will be used to calculate hazard ratios along with their 95% confidence intervals.

Data monitoring

The trial steering committee (principal investigator, senior investigator, and methodologist) will supervise the progression and monitoring of the study. Clinical research assistants will regularly perform on site monitoring at all centres to check protocol adherence and accuracy of the recorded data. An investigator at each centre will be responsible for daily patient screening, patient enrolment, adherence to protocol, and completion of the e-CRF. Because the three treatment strategies are currently used in routine practice, no data safety monitoring board was required.

Patient and public involvement

Patients and/or the public were not involved in the development of this study.

ETHICS AND DISSEMINATION

Ethical approval

The study has been approved by independent ethics committees (Comité Sud-Ouest and Outre-Mer II, France, registration number 2019-A02624-53 and Comité éthique de l'hôpital Erasme, Belgium, registration number CCB B4062023000179).

Consent to participate

Patients will be included after signing written informed consent (Appendix B). If a patient is not able to understand the information given in the consent form, they can be included if a next of kin consents. Eligible patients unable to receive information and for whom a substitute decision maker is not present, can still be included through a process of deferred consent; after recovery, the patient's agreement to stay in the trial will be sought.

Confidentiality

Data will be handled according to the French law on data protection and the European General Data Protection Regulation (GDPR). All original records will be archived at the trial sites for 15 years.

Declaration of interest

This study was funded by a grant from the French Ministry of Health obtained in 2018 (Programme Hospitalier de Recherche Clinique). The sponsor is Assistance Publique-Hôpitaux de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI). Delegation (for Belgian centers) for ethics regulation and monitoring has been agreed by Les Cliniques Universitaires de Bruxelles- Hôpital Erasme.

Access to data

Investigators will make the documents and individual data required for monitoring, quality control, and audit of the study available to specified persons in accordance with French law.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports, and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the steering committee. Reporting will adhere to the SPIRIT statement, and rules of publication will follow international recommendations, for example *The Uniform Requirements for Manuscripts* (ICMJE, April 2010) (SPIRIT checklist, appendix C).

DISCUSSION

This pragmatic, multicentre, randomised controlled trial will compare the efficacy and safety of risk control, rate control, and rhythm control for NOSVA in patients with septic shock. Despite many observational studies showing that tachycardia and atrial fibrillation are key prognostic factors in septic shock [1,2,21], no randomised controlled trial has been conducted to investigate the best strategy to manage NOSVA in this setting.

Strengths of our trial come from its design comparing three distinct commonly used strategies in this setting in an ITT approach, the generalisability embedded in the multicentre design, in which university and non-university hospitals from two countries (France and Belgium) will recruit patients, and the carefully selected population. Indeed, in regards to this last point, we will exclude patients with a significant history of SVA (for whom the cardiovascular risk depends in part on their established previous medication regimen for SVA), and patients with a high thrombotic risk (SVA of more than 48 hours, recent cardiac surgery, and valvular heart disease classifying SVA as 'valvular SVA' [22]). Importantly, this is an investigator-initiated trial, funded by a grant from the French Ministry of Health with no competing commercial or financial interests.

Our study has several limitations. Because it is an open-label trial, some bias, such as clinical decision-making preferences, is inevitable. Assessment of the duration of septic shock, the second component of the hierarchical primary endpoint, may be subjective, thus liable to performance bias. Reporting bias is unlikely for the primary outcome given that (i) all-cause death is an objective measure, and (ii) ICU hospitalisation and haemodynamic support are unambiguously supported by medical records. Nonetheless, an independent clinical events committee will blindly adjudicate all relevant safety outcomes.

In summary, the CAFS trial is an open label, randomised controlled trial testing the efficacy of three routinely used strategies (risk control, rate control, and rhythm control) to improve survival and reduce duration of shock in patients with NOSVA during septic shock. The trial targets a well-selected population, with an appropriate, patient-relevant primary outcome and experimental design, to provide a robust response (best strategy with respect to adverse events). This trial's results may therefore provide high quality evidence to inform international recommendations for the optimal haemodynamic strategy in patients with NOSVA during septic shock.

APPENDICES

Appendix A: List of study sites

Appendix B: Model of the consent form

Appendix C: SPIRIT Checklist

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Table 1: Non-antiarrhythmic interventions for the risk control strategy [23]

Modifiable risk factor	**Objective**	**Modalities**
Hypovolaemia	MAP ≥ 65 mmHg with no fluid-responsiveness (at least one test) if the patient is still hypotensive	Fluid resuscitation with crystalloid or colloids according to sepsis guidelines [13]
Hypokalaemia	Potassium ≥3.5 mmol/L	Concurrent replacement of potassium [a]
Hyponatraemia	Sodium ≥135 mmol/L	Avoid hypotonic solutions for initial resuscitation and consider correcting hyponatraemia, if any [a]
Hypoxaemia	Arterial oxygen saturation > 90%	Adjustment of the inspiratory oxygen fraction and/or positive expiratory pressure in patients with ventilatory support
Acidosis	pH >7.35	Adjustment of tidal volume, circuit dead space and/or fluids, depending on the mechanism of acidosis
Excess chronotropy due to catecholamines	Limit the arrhythmic effects of catecholamines	According to the sepsis guidelines [13][a]: ○ Lowest vasopressor dose to achieve MAP of 65 mmHg ○ Noradrenaline as first line; ○ Dobutamine as a second-line drug, in cases of myocardial dysfunction requiring an inotrope to improve tissue perfusion; ○ Adrenaline as a second-line therapy in refractory shock.
Persistent fever	Body temperature ≤ 38.1°C	External cooling and anti-pyretics could be discussed [a]
Mal-positioned central venous catheter	Correctly positioned catheter	Withdraw catheter to caval-atrial junction

Abbreviations: MAP, mean arterial pressure

[a] Left to the discretion of the attending physician

Table 2 Study Gantt chart (task schedule)

Events	D1	D2-D7	D28 +/- *2 d*
Inclusion and non-inclusion criteria	R		
Enrolment			
Informed consent	R		
Intervention			
Risk control strategy	C	C	
Rate control strategy	C	C	
Rhythm control strategy	C	C	
Assessments			
Characteristics of the patient	C		
Characteristics of the septic shock	C	C	C
Organ dysfunction and management	C	C	
Thyroid blood sample	C		
Other biological data	C		
Cardiac rhythm	C	C	
Duration of septic shock			C
Adverse event(s)			C
ICU length of stay and hospital length of stay			C
Vital status			C
Abbreviations: C, usual Care; D, day; ICU, intensive care unit; R, specific to Research			

Figure 1: Study schema

Abbreviations: NOSVA, new onset supraventricular arrythmia; IV, intravenous

Figure 2: Schema of strategies for each group according to the evolution of the randomised patients

Abbreviations: EES, external electrical shock; NOSVA, new onset supraventricular arrythmia

Administrative information

Primary Registry and Trial Identification Number

ClinicalTrials.gov Identifier, NCT04844801

Date of Registration in Primary Registry

April 14, 2021

Secondary Identifying Numbers

APHP190070

Registry Identifier: IDRCB; 2019-A02624-53

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Public Title

Comparison of three strategies in patients with atrial fibrillation during septic shock

Scientific Title

Risk, Rate, or Rhythm control for new onset supraventricular arrhythmia during septic shock: protocol for the CAFS multicentre, parallel-group, open-label trial

Protocol version

Version 6.0 dated 19/06/2023

Funding

This study was funded by a grant from the French Ministry of Health obtained in 2018 (Programme Hospitalier de Recherche Clinique).

Primary sponsor

The primary sponsor is *Assistance Publique – Hôpitaux de Paris, AP-HP (Direction de la Recherche Clinique et de l'Innovation, DRCI*).

Contact details: Marie Chevereau, DRCI-Head Office project advisor, *Direction de la Recherche Clinique et de l'Innovation* - DRCI (Clinical Research and Innovation Department), *Hôpital Saint-Louis 1, avenue Claude Vellefaux, Paris, France.* Email: marie.chevereau@aphp.fr .Telephone number: + 33 (0)1.40.27.18.67

Disclaimer

None

Contributors

VL and AMD in collaboration with the other authors designed the study and wrote the manuscript together. AR provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan, and estimated the sample size. VL, CD, SP, DD, DC, FB, BS, VP, P-MB, GM, FB, PA, NB, JJ, OS, MD, FA, XM, SC, EV, NS, AW, SV, NH, DR, GC, FC, MP, LH, MF, FT, DD, GM, LB, AR, and AMD contributed to drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. VL, CD, SP, DD, DC, FB, BS, VP, P-MB, GM, FB, PA, NB, JJ, OS, MD, FA, XM, SC, EV, NS, AW, SV, NH, DR, GC, FC, MP, LH, MF, FT, DD, GM, LB, AR, and AMD gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of it.

Steering committee

Composition: principal investigator (AMD), scientific supervisor (VL), biostatistician (AR), and the sponsor's appointed representatives of the trial: Clinical Research Associate in charge of the project (GM) and project manager URC DRCI (clinical research unit, Saint-Antoine Hospital AP-HP), and project manager of the DRCI (sponsor)spo.

Role: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.

Competing interests

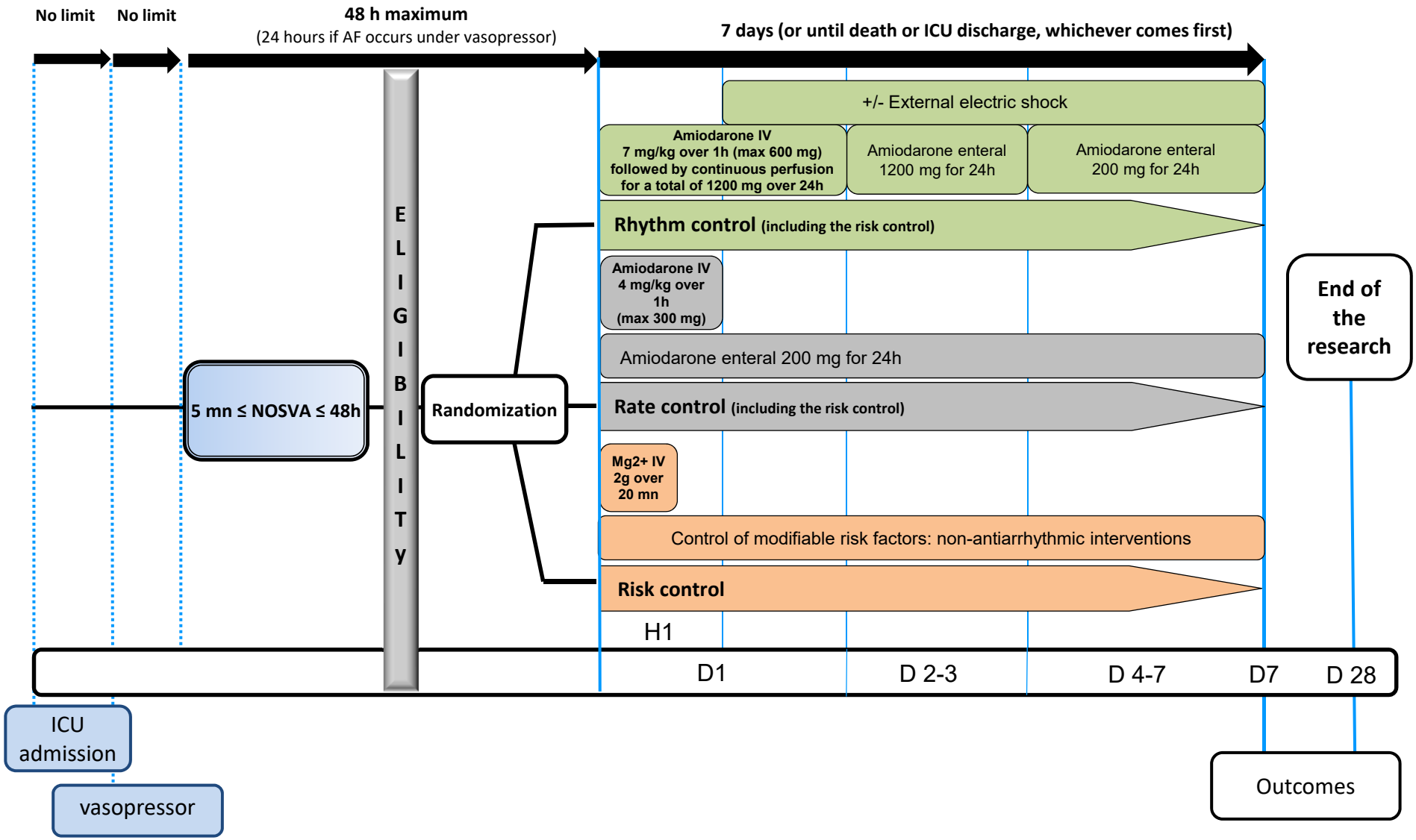
AMD reports lectures for Leo Pharma.

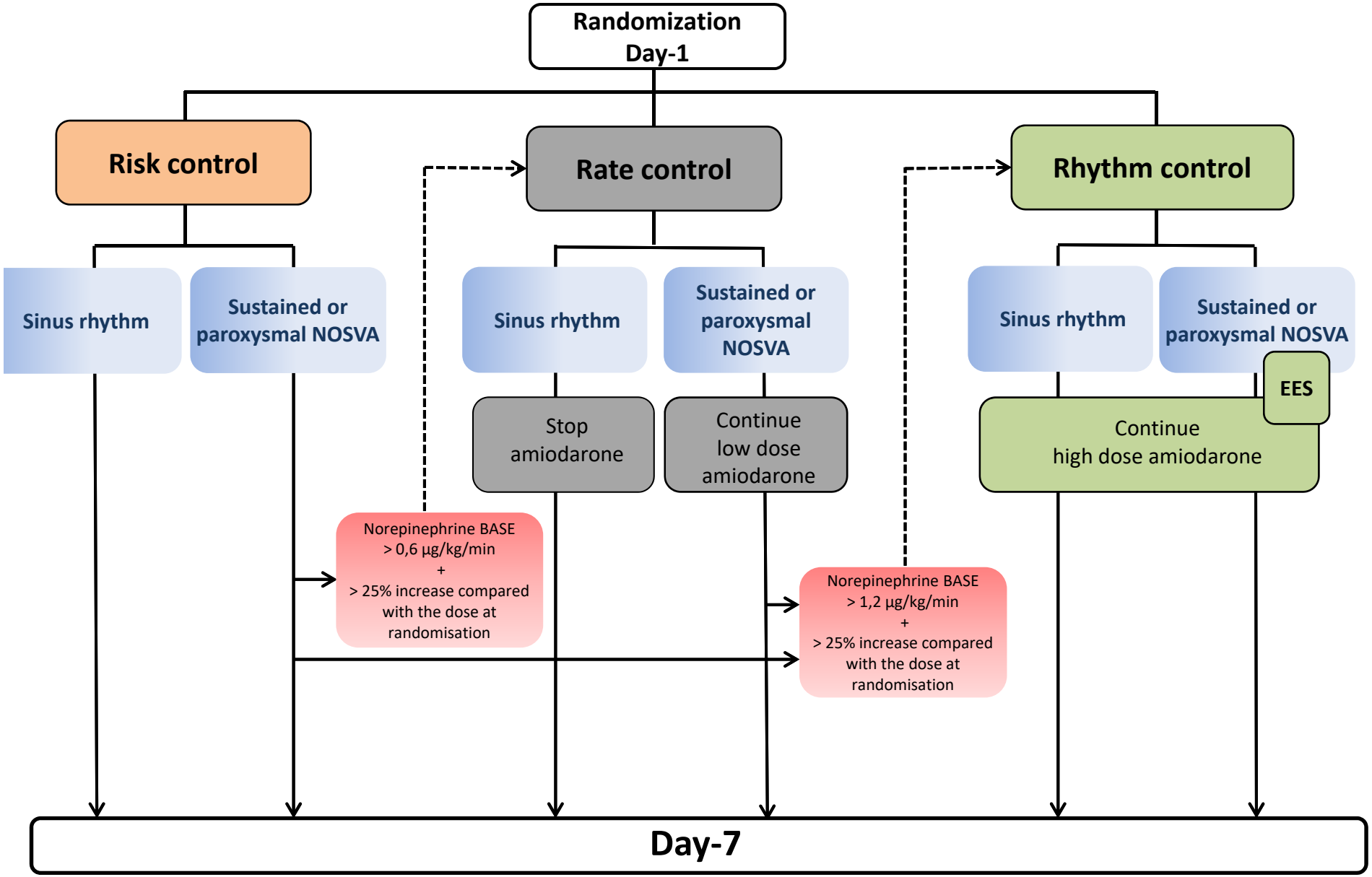
VL receives advisory board fees from AOP, and grants from Leo Pharma unrelated to the present study.

XM received fees for lectures from AOP health, Baxter healthcare and Getinge, and fees for consulting activities for Baxter healthcare and Getinge.

Provenance and peer review

Not commissioned; externally peer reviewed.





APPENDICE A: list of study sites

INSTITUTION	SERVICE	ADRESSE	CODE POSTAL	VILLE	PAYS
Hôpital Tenon - APHP	Médecine intensive réanimation	4 rue de la Chine	75020	Paris	France
Hôpital Saint Antoine - APHP	Médecine intensive réanimation	184 rue du Faubourg Saint Antoine	75012	Paris	France
Hôpital Mondor - APHP	Médecine intensive réanimation	51 Avenue du Maréchal de Lattre de Tassigny	94010	Créteil	France
Hôpital Lariboisière - APHP	Médecine intensive réanimation	2 Rue Ambroise Paré	75010	Paris	France
Hôpital Bicêtre - APHP	Médecine intensive réanimation	78 Rue du Général Leclerc	94270	Le Kremlin-Bicêtre	France
Hôpital La Pitié - APHP	Médecine intensive réanimation	47-83 Boulevard de l'Hôpital	75013	Paris	France
Centre hospitalier Melun Marc Jacquet	Réanimation médicale	270 Avenue Marc Jacquet	77000	Melun	France
Hôpital Raymond-Poincaré - APHP	Médecine intensive réanimation	104 Boulevard Raymond Poincaré	92380	Garches	France
Centre Hospitalier d'Argenteuil	Réanimation polyvalente	69 Rue du Lieutenant Colonel Prudhon	95107	Argenteuil	France
CHU de Poitiers	Médecine intensive réanimation	2 Rue de la Milétrie	86021	Poitiers	France
CHU Angers	Médecine intensive réanimation	4 Rue Larrey	49100	Angers	France
CHR d'Orléans	Médecine intensive réanimation	14 Avenue de l'Hôpital	45100	Orléans	France
CH Sud Francilien	Médecine intensive réanimation	40 avenue Serge Dassault	91106	Corbeil-Essonnes	France
CHU de Nice	Médecine intensive réanimation	151 route Saint-Antoine de Ginestière	62000	Nice	France
CHU de Lille	Médecine intensive réanimation	Avenue du Professeur Emile Laine	59037	Lille	France
CHU Gabriel Montpied	Médecine intensive réanimation	58, rue Montalembert	63003	Clermont-Ferrand	France
Hôpital Saint Camille	Médecine intensive réanimation	2 rue des Pères Camiliens	94360	Bry-sur-Marne	France
CH de Cannes	Médecine intensive réanimation	15 avenue des Broussailles	06400	Cannes	France
Hôpital Louis Mourier	Réanimation médico-chirurgicale	178 rue des Renouillers	92700	Colombes	France
Hôpital Avicenne-APHP	Réanimation médico-chirurgicale	125 Rue de Stalingrad	93000	Bobigny	France
Centre Hospitalier Saint Joseph Saint Luc	Réanimation Polyvalente	20 quai Claude Bernard	69365	Lyon	France

CHU Toulouse Rangueil	Réanimation Polyvalente	1 av du Pr Jean Poulhès	31059	Toulouse	France
CH Marnes La vallée	Médecine intensive réanimation	2-4 Cours de la Gondoire	77600	Marne-La-Vallée	France
Hôpital Erasme	Service de soins Intensifs	Route de Lennik, 808, 1070 Bruxelles	1070	Bruxelles	Belgique
Clinique St Pierre	Service de soins intensifs	Avenue Reine Fabiola,9	B-1340	Ottignies	Belgique
CHU Charleroi	Service de soins intensifs	44 rue de Leernes	6111	Charleroi	Belgique
Centre Hospitalier de Wallonie picarde (CHwapi)	Médecine intensive réanimation	9, avenue. Delmée	7500	Tournai	Belgique
Centre Hospitalier Universitaire Ambroise Paré	Service de soins intensifs	2, Boulevard Kennedy	7000	Mons	Belgique

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Comparison of three management strategies for de novo supraventricular arrhythmias in septic shock: a randomised controlled trial.
CAFS (Control Atrial Fibrillation during Septic shock) study

This research is promoted by *Assistance Publique - Hôpitaux de Paris*
Represented by the Director of
***Direction de la Recherche Clinique et de l'Innovation* (DRCI)**
1 avenue Claude Vellefaux
75010 Paris

INVITATION TO PARTICIPATE

Dear Madam, dear Sir

Dr./Pr. (delete as appropriate) ..... (First name, Surname), working at …….. Hospital, invites you to participate in a research study conducted to examine your disease.
We highly encourage you to read this document carefully before making any decision. Do not hesitate to ask for further information.
If you agree to participate in this research, you will be asked to sign a written consent.

1) What is the objective of this research?

You are admitted in intensive care to be treated for a septic shock. Septic shock is a critical infection that leads to a decrease in blood pressure (acute circulatory failure) and organ damage. This situation has been complicated by cardiac arrhythmia (irregular, faster and less efficient heartbeats), which may worsen your condition.
To limit this risk, there are three alternatives: attempting to reduce the heart rate, or to stop the arrhythmia with a return to normal rhythm (sinus rhythm) by managing its risk factors (risk control); slowing the heart rate (rate control) as a complement to risk factor management; or stopping the arrhythmia and returning to a normal heart rate (rhythm control), also as a complement to risk factor management. At present, there are no data to show which of these three strategies is the best to prevent deterioration in the health of patients with arrhythmia during septic shock, as is the case for you.
The aim of our research is to compare the three strategies (risk control, rate control, rhythm control) in patients with arrhythmia during septic shock. The strategy applied to each patient will be determined by random selection.
To perform this research study, we intend to include 240 patients with arrhythmia during septic shock who are admitted to French and Belgium hospitals.

2) What does the research consist in?

In the present study, we will compare the efficacy of risk control, rate control and rhythm control strategies. You will be treated for 7 days according to the strategy selected by random draw.
The aim of the risk control strategy is either to reduce the heart rate, or to stop the arrhythmia with a return to normal rhythm (sinus rhythm), by controlling the arrhythmia's risk factors (such as low serum magnesium, low serum potassium, fever...), without specific arrhythmia treatment which may cause side effects.
The aim of the rate control strategy is to reduce the heart rate by using a low dose of amiodarone in addition to the risk control strategy. When specific arrythmia treatment is prescribed for patients with septic shock, such as yourself, amiodarone is the most commonly used in France and Belgium. Amiodarone is an anti-arrhythmic drug, which have an action on the heart's electric impulsion. Its action varies according to the dose used: reduction in heart rate at low doses, or arrest of arrhythmia with return to normal heart rhythm at high doses. For rapid action, amiodarone is first administrated intravenously, then orally if available.

The aim of the rhythm control strategy (in addition to the risk control strategy) is to stop the arrhythmia and restore a normal heart rhythm using high-dose amiodarone. If high-dose amiodarone fails, one or more external electrical shocks may be administered if you are under sedation (general anesthesia), with intubation and mechanical ventilation to treat septic shock.

If you are not under sedation, an electric shock will not be given, even if high-dose amiodarone fails. External electrical shock consists of passing a brief electric current through the heart to restore a normal heart rhythm. The current is delivered to the chest through two paddles connected to a device called an external defibrillator. The procedure is carried out under general anesthesia.
In all cases, you will also receive the usual treatment for septic shock as recommended during your stay in hospital.

3) What is the work schedule of the research?

The study is expected to last 43 months and your participation will last 28 days. The trial will not involve any additional tests other than those performed as part of routine care. Your participation in the study will begin after you sign the consent form at your first visit.
Once you have read and signed the consent form, you will be randomised to the risk control, rate control or rhythm control strategy, which will start immediately. This randomisation corresponds to the first day of the trial (D1). You will receive the randomised strategy for 7 days, from D1 to D7. Your monitoring data (routine clinical examinations and blood tests) will be collected daily during your hospital stay.
If you leave the hospital before day 28, a clinical trial technician will contact you on day 28 to check your health.

4) What are the benefits of your participation?

The expected benefit is a reduction in the duration of acute circulatory failure during the 7 days of treatment to reduce the risk of organ failure. In addition, your participation will help us to improve our knowledge of the treatment of arrhythmias in septic shock.

5) Which treatments are authorized and which are not?

Drugs that can cause a cardiac arrhythmia called "torsades de pointes" are not approved for use with amiodarone and are prohibited for research purposes. The most common of these are: erythromycin, levofloxacin, moxyfloxacin and spiramycin.

6) What are the anticipated risks and constraints added by the research?

If you agree to take part in this study, you should take the following into account

- Take your treatment as prescribed by your doctor.
- Inform the research physician of any medication you are taking and of any events that occur during the research (hospitalisation, etc.).
- To be covered by or benefit from any social security scheme.
- Not to participate in another research project without your doctor's permission, in order to protect yourself from any health problems that may arise, for example, from possible incompatibilities between the drugs being studied or from other exposures.
- If you are a woman of childbearing potential, you should have a pregnancy test before starting this study.

7) What are the potential medical alternatives?

If you choose not to participate in this research, you will receive appropriate medical care according to your condition, in accordance with standard clinical practice.

8) What kind of medical care to have after participation?

Follow-up is not specific to this trial. You will continue to receive care that is appropriate to your condition, whether that is usual care in the event that the research is stopped early, or care at the end of your participation.
Your doctor can decide to stop your participation at any time and should explain the reasons to you.

9) If you participate, how will your collected data be used in the research?

In the context of the research in which you are invited to participate, your personal data will be processed by AP-HP, the research promoter in charge of data management, in order to analyse the results.

This data processing is necessary in order to carry out research of public health interest, in line with AP-HP's mission as a public university hospital.

To this end, your medical and lifestyle data will be communicated to the promoter or to persons or partners working on its behalf, in France or abroad, and will be kept for 15 years. This data will be identified by a registration number. These data may also be communicated to French or foreign health authorities under conditions that guarantee their confidentiality.

Your data may be used for further research or complementary analysis in collaboration with private or public partners in France or abroad, under conditions that guarantee their confidentiality and the same level of protection as required by European legislation.
You may at any time object to any further analysis of your data by informing the doctor who is following you in this research.

Your data will only be kept for as long as is strictly necessary and justified by the purpose of the research. It will be kept on the data manager's information systems for two years after the last publication of the research results. Your data will then be archived in accordance with the regulations in force.

The database used for this research is created in accordance with French law (modified "Informatique et Libertés" law) and European law (Règlement Général sur la Protection des Données - RGPD). You have the right to access, modify, limit and object to the processing of data covered by professional secrecy and used in the context of this research. These rights can be exercised with the doctor in charge of the research, who is the only person who knows your identity (identified on the first page of this document).

If you decide to discontinue your participation, the data collected prior to this decision will be used in accordance with the regulations and exclusively for the purposes of this research. Deletion of this data would compromise the validity of the research results. However, from that point on, your data will no longer be used in this research or in any other work.

If you have a problem concerning your rights, you can contact the AP-HP Data Protection Officer at the following address: protection.donnees.dsi@aphp.fr, who will be able to explain the channels available to you with the CNIL. You may also exercise your right to complain directly to the CNIL (for more information on this subject, please visit www.cnil.fr).

10) How is this research supervised?

AP-HP has taken all the measures necessary to carry out this research in compliance with the public health regulations applicable to research involving human volunteers.

AP-HP has taken out an insurance policy (number 0100518814033 200013) with its insurance broker BIOMEDICINSURE, whose address is Parc d'Innovation, Bretagne Sud C.P.142 56038 Vannes Cedex, to cover its civil liability and that of all its collaborators.

AP-HP has been approved by the Ethics Committee (CPP Sud-Ouest et Outre-Mer III) on [29/07/2020] and by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) on 21/02/2020.

11) What are your rights ?

Your participation in this research is free and voluntary. Your decision will not affect the quality of care and treatment you receive.

Before you agree to take part in this research, you will undergo an appropriate medical examination, the results of which will be reported to you.

Throughout the study, and at any time, you can ask your investigator for further information about your health and explanations of the research process.

You can withdraw from the research at any time without explanation, without any impact on your treatment or the quality of care you receive, and without any impact on your relationship with your doctor. After this withdrawal, you may be followed by the same medical team. In this case, the data collected up to the time of withdrawal will be used to analyse the research results.

Your medical file will remain confidential and can only be consulted under the responsibility of the doctor in charge of your treatment, as well as by the health authorities and persons authorised by AP-HP for research and bound by professional confidentiality.

At the end of the study and its data analysis, you will have access to the overall results by contacting the doctor treating you in the study.

You can also access all your medical data directly or through a doctor of your choice, in accordance with article L 1111-7 of the Public Health Code.

If, after reading all this information, discussing it with your doctor and having time to think about it, 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.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

CONSENT FORM

I, the undersigned, Mrs, Mr [delete as appropriate] (first name, surname) ..... agree to voluntarily participate in the study entitled
"Comparison of three management strategies for de novo supraventricular arrhythmias in septic shock: a randomised controlled trial." sponsored by Assistance Publique - Hôpitaux de Paris and I was informed by Dr./Pr. (name, surname, telephone)....., investigator of this study.

- I have read the Invitation to Participate version 3.0 dated 19.6.2023 (4 pages), which explains the purpose of this study, how it will be conducted, and what my participation will entail;
- I will keep a copy of the invitation to participate and the informed consent form:
- I have received adequate answers to all my questions;
- I have had enough time to make my decision;
- I understand that my participation is free of charge and that I can stop my participation at any time without any liability and without affecting the quality of care I receive;
- I have been informed that the data collected in the research may be used for other studies and that I may object to this at any time;
- I understand that my participation may also be interrupted at any time by the doctor, who should explain the reasons;
- I have undergone a medical examination appropriate to the research prior to taking part in this research, the results of which have been communicated to me;
- I am aware that, in order to participate in this research, I must be affiliated to or a beneficiary of a social security scheme. I confirm that this is the case;
- I have been informed that my participation in this research will last for 28 days, during which time I cannot consider taking part in any other research without informing the investigating physician in charge of my case in this study,
- My consent does not in any way relieve the doctor following me in the research or AP-HP of any responsibility, and I retain all the rights guaranteed to me by law.

Signature of the participating person		**Signature of the doctor**	
First name, Surname:		Fist name, Surname:	
Date:	Signature:	Date:	Signature:

This document must be produced in three copies: one copy must be kept by the investigator for 15 years, the second given to the consenting person, and the third sent to AP-HP in a sealed envelope at the end of the study.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Repored on page NO
Administrative information			**27-28-29**
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	24,25
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,3,4,25
	5b	Name and contact information for the trial sponsor	28
	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	n/a
	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)	12, 17, 24
Introduction			7

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	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	8
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)	8
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	8
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)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
	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)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10

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	11,12
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)	11
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	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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	13
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	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
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	13,15,16
	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	15,16
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	15,16
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	14,15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14,15
	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)	14
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	15

	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	n/a
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	10,12,15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
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	16
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	n/a

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	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	18
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	n/a

*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.

BMJ Open

Risk, Rate, or Rhythm control for new onset supraventricular arrhythmia during septic shock: protocol for the CAFS multicentre, parallel-group, open-label trial

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Infectious diseases
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Cardiovascular Disease, INFECTIOUS DISEASES, Clinical Protocols

Risk, Rate, or Rhythm control for new onset supraventricular arrhythmia during septic shock: protocol for the CAFS multicentre, parallel-group, open-label trial

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ABSTRACT

Introduction: New-onset supraventricular arrhythmia (NOSVA) is the most common arrhythmia in patients with septic shock, and is associated with haemodynamic alterations and increased mortality rates. With no data available from randomised trials, clinical practice for patient management varies widely. In this setting, rate control or rhythm control could be beneficial in limiting the duration of shock and preventing evolution to multi-organ dysfunction.

Methods and analysis: The Control Atrial Fibrillation in Septic shock (CAFS) study is a binational (French and Belgium), multicentre, parallel-group, open-label, randomised controlled superiority trial to compare the efficacy and safety of three management strategies in patients with NOSVA during septic shock. The expected duration of patient enrolment is 42 months starting from November 2021. Patients will be randomised to receive either risk control (magnesium and control of risk factors for NOSVA), rate control (risk control and low dose of amiodarone), or rhythm control (risk control and cardioversion using high dose of amiodarone with external electrical shock if NOSVA persists) for 7 days. Patients with a history of SVA, NOSVA lasting more than 48 h, recent cardiac surgery, or a contraindication to amiodarone will not be included. We plan to recruit 240 patients. Patients will be randomised on a 1:1:1 basis, and stratified by centre. The primary endpoint is a hierarchical criterion at day 28 including all-cause mortality and the duration of septic shock defined as time from randomisation to successful weaning of vasopressors. Secondary outcomes include: individual components of the primary endpoint; arterial lactate clearance at day 3; efficacy at controlling cardiac rhythm at day 7; proportion of patients free from organ dysfunction at day 7; ventricular arrhythmia, conduction disorders, thrombotic events, major bleeding events, and acute hepatitis related to amiodarone at day 28; and ICU and hospital lengths of stay at day 28.

Ethics and dissemination: The study has been approved by the French (Comité Sud-Ouest et Outre-Mer II, France, registration number 2019-A02624-53) and Belgian (Comité éthique de l'hôpital Erasme, Belgium, registration number CCB B4062023000179) ethics committees. Patients will be included after obtaining signed informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04844801

Strengths and limitations of the study

► This study is a binational, multicentre, parallel-group, open-label, randomised controlled superiority trial comparing head-to-head risk control, rate control, and rhythm control in patients with NOSVA during septic shock

► Pragmatic design comparing three common strategies in an intention-to-treat approach.

► Limitation: not blinded.

INTRODUCTION

Background and rationale

New-onset supraventricular arrythmia (including atrial fibrillation, atrial flutter, and atrial tachycardia, NOSVA) is reported in 40% of patients with septic shock and is associated with haemodynamic alterations and increased mortality [1,2]. Efforts to determine the most effective haemodynamic management strategy in this setting are therefore important. In a recent preliminary study from our research team, successful cardioversion of NOSVA in patients with sepsis seemed to be associated with a better prognosis [3]. However, because no randomised clinical trial data are available, there is no consensus regarding the best management strategy for NOSVA during septic shock, which has led to major variations in practice [1,2,4–7]. Three treatment strategies are commonly used: (i) control of modifiable risk factors for NOSVA without using antiarrhythmic drugs (risk control) [8]; (ii) control of heart rate with the use of antiarrhythmic drugs, often with low dose amiodarone (rate control) [9–11]; (ii) cardioversion using antiarrhythmic drugs (often with high doses of amiodarone) and/or electrical cardioversion (rhythm control) [10,11].

Rhythm control may improve haemodynamics (by restoring diastolic function and decreasing cardiac metabolic demand), reduce thromboembolic risk, and minimise exposure to anticoagulants. Rate control limits the potential adverse effects of high dose amiodarone and/or of electrical cardioversion, while still improving haemodynamics. The risk control strategy minimises the adverse effects of amiodarone while still resulting in conversion of NOSVA in some patients.

Determining the efficacy and safety of these three strategies may provide valuable information to improve clinical decision-making and resource utilisation for this highly prevalent condition. Therefore, we will conduct a multicentre, parallel group, open-label, randomised controlled superiority trial to compare head-to-head risk control, rate control, and rhythm control in this setting.

Hypotheses

Our hypotheses are as follows: i) compared to risk control, rate control and rhythm control each improve haemodynamics, thus decreasing shock duration and mortality; ii) rhythm control outperforms rate control in this setting.

Objectives

Primary objective

The main objective is to compare the efficacy of the three strategies (risk control, rate control, and rhythm control) in reducing mortality and duration of shock in septic patients with NOSVA.

Secondary objectives

Secondary objectives are to compare the benefit and risks of the three strategies in terms of haemodynamics, organ dysfunction, morbidity, mortality, safety (including thrombotic events, bleeding events and serious adverse events related to amiodarone and electrical cardioversion), and net clinical benefit.

METHODS AND ANALYSIS

Trial design

This is a binational, multicentre, parallel-group, open-label, randomised controlled superiority trial in patients with NOSVA during septic shock. The trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) reporting guidelines.

Study setting

The study will be conducted in 28 intensive care units (ICUs) in 23 hospitals in France and 5 hospitals in Belgium (list of study sites in Appendix A).

Eligibility criteria

Inclusion criteria

Adult patients (age ≥18 years) admitted to the ICU will be eligible as soon as they meet all the following criteria:

1- Septic shock, defined by the association of the following criteria:
   - Documented or suspected infection, with initiation of antibiotic therapy
   - Initiation of vasopressors (noradrenaline or adrenaline) for at least 1 hour to maintain the mean arterial pressure (MAP) >65 mmHg;

2- NOSVA (including atrial fibrillation, atrial flutter, and atrial tachycardia) with heart rate ≥110 bpm lasting at least 5 minutes;

3- Written informed consent (patient, next of kin or emergency situation);

4- Member of a social security system.

Exclusion criteria

Patients presenting any of the following criteria will not be included:

1. Refractory shock, defined as a dose of noradrenaline base or adrenaline base >1.2 µg/kg/min;
2. Heart surgery or heart transplant in the previous month;
3. Aortic or mitral valve mechanical prosthesis, significant mitral stenosis (mitral surface < 1.5 cm^2);
4. Congenital heart disease other than bicuspid aortic valve, atrial defect, or patent foramen ovale;
5. History of SVA before septic shock, defined as paroxysmal SVA with long-term antiarrhythmic and/or therapeutic anticoagulation, or permanent SVA;
6. NOSVA lasting more than 48 hours (or more than 24 hours under vasopressor therapy): the patient can still be included if transoesophageal echocardiography (under mechanical ventilation) excludes intracardiac thrombus and the patient is receiving therapeutic anticoagulation;
7. Electrical cardioversion or use of amiodarone or another bradycardic drug (beta-blocker, bradycardic calcium channel blocker, digitalis, flecainide) within the 6 hours preceding inclusion;
8. Contraindication to amiodarone: history of serious adverse event, lung disease, or hyperthyroidism related to amiodarone, PR interval >240ms, severe sinus node dysfunction with no pacemaker, second- or third-degree atrioventricular block with no pacemaker, QTc >480ms, known or treated hyperthyroidism, hypersensitivity to iodine, amiodarone or to any of the excipients, severe hepatocellular insufficiency (prothrombin rate <20%), diffuse interstitial lung disease;
9. Serum potassium <3 mmol/L;
10. Pregnancy or breast-feeding;
11. Moribund or death expected from underlying disease during the current admission;
12. Patients deprived of liberty and persons receiving institutional psychiatric care;
13. Participation in another interventional trial on septic shock and/or rhythm disorder.

Intervention

The experimental plan is shown in **Figure 1.** After verification of the eligibility criteria, the patient will be enrolled and randomised (Day 1) as soon as possible, and within 48 hours from

the onset of NOSVA (or 24 hours if NOSVA occurs when receiving vasopressor treatment). Patients should then immediately receive the allocated strategy, for 7 days (or until death or ICU discharge, whichever comes first). The risk control strategy will consist of (i) intravenous bolus of 2 g magnesium sulphate over 20 min (if creatinine clearance >30 mL/min), and (ii) control of risk factors for NOSVA, such as hypovolaemia and metabolic disorders (details in **Table 1**). The rate control strategy will consist of (i) control of NOSVA risk factors as described above, and (ii) 'low dose' amiodarone (details in **Figure 1**). The rhythm control strategy will consist of (i) control of NOSVA risk factors as described above, (ii) 'high dose' amiodarone (details in **Figure 1**), and (iii) if NOSVA persists, electrical cardioversion in sedated patients receiving invasive mechanical ventilation (modalities according to the European Society of Cardiology (ESC) guidelines [12]; details in **Figure 1**). Details of the three strategies according to rhythm and haemodynamic evolution are given in **Figure 2**. In all groups, therapeutic anticoagulation is recommended in the absence of contraindications if NOSVA persists more than 48 hours; modalities of therapeutic anticoagulation will be left to the discretion of the attending physicians. After Day 7 (or discharge from the ICU, whichever comes first), NOSVA management will be left to the discretion of the attending physician. All patients will be followed until Day 28.

In all groups, current recommendations for the management of septic shock will be followed [13].

Criteria and procedures for premature withdrawal of a participant from the study

In compliance with the conventional management of patients with NOSVA during septic shock, the rate control and rhythm control strategies will be discontinued if one of the following occurs:

- Ventricular arrhythmia: torsade de pointe, sustained ventricular tachycardia, ventricular fibrillation;
- Conduction disorders: severe bradycardia (<50 beats per minute), second- or third-degree atrioventricular block, sinus dysfunction (significant sinus pause of at least 3 seconds), need for a pacemaker, QTc prolongation >480 ms;
- Acute hepatitis related to amiodarone, defined by a significant (10-fold) increase in transaminases (hepatic cytolysis), as compared to values before the first dose, and with no other identified cause for hepatitis;
- Hyperthyroidism, as defined by a thyroid-stimulating hormone concentration <0.1 mIU/L in the blood sampled before amiodarone initiation [14].

Follow-up visits

The trial follow-up visits will be on days 2 to 7, and day 28.

Endpoints

Primary endpoint

The primary endpoint is a hierarchical endpoint assessed at day 28 and includes all-cause mortality and the duration of shock. The Finkelstein-Schoenfeld method is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. The pairwise comparison proceeds in hierarchical fashion, using all-cause mortality, followed by the duration of septic shock when patients cannot be differentiated on the basis of mortality. This method gives a higher importance to all-cause mortality [15,16].

The duration (days) of septic shock is defined as the period from randomization to successful weaning of vasopressors (patient alive with no reintroduction during the first 48 hours after discontinuation).

Secondary endpoints

Secondary endpoints will include the following:

(1) Rhythm control at day 7

- Number of patients with sinus rhythm;
- Number of days alive with sinus rhythm;
- Number of days alive with NOSVA and heart rate <110 bpm;
- Proportion of patients receiving therapeutic anticoagulation after randomization;

(2) Morbidity, mortality, and organ function

- Duration of septic shock at day 28;
- Proportion of patients alive and free from vasopressors at day 7 (or discharge or death whichever comes first);
- Arterial lactate clearance at day 3 [17];
- Proportion of patients alive and free from organ dysfunction at day 7 (or discharge or death whichever comes first). Organ dysfunction is defined as a sequential organ

failure assessment (SOFA) score ≥3 for the following organs: cardiovascular, renal, neurological, hepatic, respiratory, or coagulation [18];

- Length of ICU stay at day 28;
- Length of hospital stay at day 28;
- All-cause deaths at day 28.

(3) Safety

- Arterial thrombotic events, including ischaemic stroke and non-cerebrovascular arterial thrombotic event [19];
- Major bleeding events defined as bleeds that meet at least one of the following criteria: bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal); bleeding requiring surgical, endoscopic or endovascular haemostasis action; a life-threatening bleed; and a fatal bleed [20];
- Serious adverse events related to amiodarone or to magnesium, including ventricular arrhythmia, conduction disorders, and acute hepatitis related to amiodarone as described above;
- Serious adverse events associated with electrical cardioversion (for patients receiving electrical cardioversion) including ventricular arrhythmia, conduction disorders, and arterial thrombotic events.

(4) Combined efficacy and safety

- Net clinical outcome as assessed by the presence of all-cause death, arterial thrombotic event, major bleeding event, or at least one serious adverse event related to amiodarone or to magnesium or to electrical cardioversion at day 28.

Sample size and its statistical justification

The sample size was calculated by considering pairwise comparisons between the groups. For each comparison, 1000 samples were simulated using SAS software. Based on data from our two previous studies in patients with NOSVA during sepsis [3,6], the distribution characteristics of the samples were defined according to the following assumptions: (i) 28-day mortality rates of 35%, 30%, and 25% for the risk control, rate control, and rhythm control groups, respectively; (ii) durations of septic shock of 4.9 ± 2.4 days (standard deviation), 3.9 ± 2.4 days, and 2.9 ± 2.4 days for the risk control, rate control, and rhythm control groups, respectively. Within each sample/pairwise comparison, an individual score was calculated by

comparing each patient in one group with all patients in the other groups [15,16]. These scores were then compared between groups using a Mann-Whitney/Wilcoxon test in each of the 1000 samples, and the p-value of each test was recorded. For each pairwise group comparison, the proportion of tests with a p-value <0.05 was at least 81% with 80 subjects in each group. Therefore, we expect that having 80 subjects per group will provide a minimum power of 81% to detect a difference in the primary outcome with alpha = 5%.

Recruitment

The expected duration of patient enrolment is 42 months starting from November 2021. The study timeline is as follows: i) 2018: Grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique) for academic sponsor (Assistance Publique-Hôpitaux de Paris, AP-HP); ii) July 2020: approval by independent ethics committees and competent authority; iii) November 2021: start of patient enrolment; iv) 2025: end of patient enrolment, monitoring, cleaning and database lock, blind review to screen for protocol violation; iv) 2025-2026: data analysis, writing of the manuscript, and submission for publication.

Allocation of intervention and data management

Randomisation in a 1:1:1 ratio will be prepared by an independent statistician from the Clinical Research Unit before the start of the trial. Randomisation will be stratified by centre and block balanced. The width of the blocks will not be communicated to the investigators. Patients will be randomised using the electronic case report forms (e-CRFs).

Non-identifying data will be entered into the e-CRFs by a trained investigator or research assistant at each centre. Patient follow-up and task schedules are detailed in the study Gantt chart **(Table 2).** The e-CRF was devised by the principal investigator and the scientific supervisor of the study in collaboration with the data manager of the Clinical Research Unit. e-CRFs and a data dictionary (containing coding variables and definitions) will be saved and archived in the Clinical Research Unit and AP-HP secured servers. The computer files used for this research are implemented in compliance with the French (amended "*Informatique et Libertés*" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations. The sponsor has already obtained authorisation from CNIL (French Data Protection Agency) to process data from this research (Ref.: MLD/MFI/AR2012389). Database quality control will be undertaken by a Data manager from the Clinical Research Unit.

Statistical methods

All analyses will be performed by a statistician form from the Clinical Research Unit according to the statistical analysis plan prepared before data base lock, using SAS software version 9.4 (SAS Institute, Cary, NC, USA), R software version 4.2.2 and Stata software (version 17; StataCorp).

In compliance with the SPIRIT statement, a flow diagram will describe the progress of the three groups of patients throughout the different phases of the trial (enrolment, allocation, received interventional agents, follow-up, and data analysis). The analysis will be performed on an intention-to-treat (ITT) basis. In case of premature interruption or withdrawal from the study, patients will not be substituted. Single imputation will be made for missing values of the primary endpoint, as a failure (i.e. death). Sensitivity analysis will be performed in the per-protocol population set (patients as randomized without major protocol violations).

Descriptive analysis

A flow chart will be provided. Descriptive statistical analyses will be conducted on the ITT population to describe general and baseline characteristics. Quantitative variables will be reported as mean (±standard deviation) or median (25^{th}-75^{th} percentiles) according to the distribution of the variable. Qualitative variables will be reported as numbers (%).

Analysis of the primary endpoint

The pre-specified primary endpoint will be a ranked composite score that incorporates death and duration of shock, calculated in such a manner that death constitutes a worse outcome than longer duration of shock. Each patient will be compared with every other patient in the study and assigned a score (equality: 0, win: +1, loss: −1) for each pairwise comparison based on who fared better. For example, if one patient survives and the other does not, the first will be attributed +1 and the latter −1 for that pairwise comparison. If both patients in the pairwise comparison survive, the scoring will depend on duration (days) of septic shock: fewer days earns a score of +1, and more days earns a score of −1. If both patients survive and had the same duration of septic shock, or if both patients die, both will score 0 for that pairwise comparison. For each patient, scores of all pairwise comparisons will be summed to obtain a cumulative score. These cumulative scores will be ranked and compared across the three groups using a non-parametric Mann-Whitney test [16].

Analysis of secondary endpoints

Comparisons between randomised groups at given timepoints will be conducted using Pearson Chi square or Fisher exact tests for categorical variables, and using ANOVA or non-parametric Kruskal Wallis tests for quantitative variables, as appropriate.

For 28-day all-cause mortality, the number of patients with sinus rhythm at day 7, the number of patients free from vasopressors at day 7, and survival without serious adverse event, calculation of time-to-event endpoints based on follow-up censored data will be employed, taking into account the competing risks of hospital discharge (for mortality evaluation) and death (for the number of patients with sinus rhythm at day 7 and the number of patients free of vasopressor at day 7). Kaplan-Meier survival curves and cumulative incidence curves will be plotted accoring to treatment group, and Cox models will be used to calculate hazard ratios along with their 95% confidence intervals.

Data monitoring

The trial steering committee (principal investigator, senior investigator, and methodologist) will supervise the progression and monitoring of the study. Clinical research assistants will regularly perform on site monitoring at all centres to check protocol adherence and accuracy of the recorded data. An investigator at each centre will be responsible for daily patient screening, patient enrolment, adherence to protocol, and completion of the e-CRF. Because the three treatment strategies are currently used in routine practice, no data safety monitoring board was required.

Patient and public involvement

Patients and/or the public were not involved in the development of this study.

ETHICS AND DISSEMINATION

Ethical approval

The study has been approved by independent ethics committees (Comité Sud-Ouest and Outre-Mer II, France, registration number 2019-A02624-53 and Comité éthique de l'hôpital Erasme, Belgium, registration number CCB B4062023000179).

Consent to participate

Patients will be included after signing written informed consent (Appendix B). If a patient is not able to understand the information given in the consent form, they can be included if a next of kin consents. Eligible patients unable to receive information and for whom a substitute decision maker is not present, can still be included through a process of deferred consent; after recovery, the patient's agreement to stay in the trial will be sought.

Confidentiality

Data will be handled according to the French law on data protection and the European General Data Protection Regulation (GDPR). All original records will be archived at the trial sites for 15 years.

Declaration of interest

This study was funded by a grant from the French Ministry of Health obtained in 2018 (Programme Hospitalier de Recherche Clinique). The sponsor is Assistance Publique-Hôpitaux de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI). Delegation (for Belgian centers) for ethics regulation and monitoring has been agreed by Les Cliniques Universitaires de Bruxelles- Hôpital Erasme.

Access to data

Investigators will make the documents and individual data required for monitoring, quality control, and audit of the study available to specified persons in accordance with French law.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports, and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the steering committee. Reporting will adhere to the SPIRIT statement, and rules of publication will follow international recommendations, for example *The Uniform Requirements for Manuscripts* (ICMJE, April 2010) (SPIRIT checklist, appendix C).

DISCUSSION

This pragmatic, multicentre, randomised controlled trial will compare the efficacy and safety of risk control, rate control, and rhythm control for NOSVA in patients with septic shock. Despite many observational studies showing that tachycardia and atrial fibrillation are key prognostic factors in septic shock [1,2,21], no randomised controlled trial has been conducted to investigate the best strategy to manage NOSVA in this setting.

Strengths of our trial come from its design comparing three distinct commonly used strategies in this setting in an ITT approach, the generalisability embedded in the multicentre design, in which university and non-university hospitals from two countries (France and Belgium) will recruit patients, and the carefully selected population. Indeed, in regards to this last point, we will exclude patients with a significant history of SVA (for whom the cardiovascular risk depends in part on their established previous medication regimen for SVA), and patients with a high thrombotic risk (SVA of more than 48 hours, recent cardiac surgery, and valvular heart disease classifying SVA as 'valvular SVA' [22]). Importantly, this is an investigator-initiated trial, funded by a grant from the French Ministry of Health with no competing commercial or financial interests.

Our study has several limitations. Because it is an open-label trial, some bias, such as clinical decision-making preferences, is inevitable. Assessment of the duration of septic shock, the second component of the hierarchical primary endpoint, may be subjective, thus liable to performance bias. Reporting bias is unlikely for the primary outcome given that (i) all-cause death is an objective measure, and (ii) ICU hospitalisation and haemodynamic support are unambiguously supported by medical records. Nonetheless, an independent clinical events committee will blindly adjudicate all relevant safety outcomes.

In summary, the CAFS trial is an open label, randomised controlled trial testing the efficacy of three routinely used strategies (risk control, rate control, and rhythm control) to improve survival and reduce duration of shock in patients with NOSVA during septic shock. The trial targets a well-selected population, with an appropriate, patient-relevant primary outcome and experimental design, to provide a robust response (best strategy with respect to adverse events). This trial's results may therefore provide high quality evidence to inform international recommendations for the optimal haemodynamic strategy in patients with NOSVA during septic shock.

APPENDICES

Appendix A: List of study sites

Appendix B: Model of the consent form

Appendix C: SPIRIT Checklist

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Table 1: Non-antiarrhythmic interventions for the risk control strategy [23]

Modifiable risk factor	Objective	Modalities
Hypovolaemia	MAP ≥ 65 mmHg with no fluid-responsiveness (at least one test) if the patient is still hypotensive	Fluid resuscitation with crystalloid or colloids according to sepsis guidelines [13]
Hypokalaemia	Potassium ≥3.5 mmol/L	Concurrent replacement of potassium [a]
Hyponatraemia	Sodium ≥135 mmol/L	Avoid hypotonic solutions for initial resuscitation and consider correcting hyponatraemia, if any [a]
Hypoxaemia	Arterial oxygen saturation > 90%	Adjustment of the inspiratory oxygen fraction and/or positive expiratory pressure in patients with ventilatory support
Acidosis	pH >7.35	Adjustment of tidal volume, circuit dead space and/or fluids, depending on the mechanism of acidosis
Excess chronotropy due to catecholamines	Limit the arrhythmic effects of catecholamines	According to the sepsis guidelines [13][a]: o Lowest vasopressor dose to achieve MAP of 65 mmHg o Noradrenaline as first line; o Dobutamine as a second-line drug, in cases of myocardial dysfunction requiring an inotrope to improve tissue perfusion; o Adrenaline as a second-line therapy in refractory shock.
Persistent fever	Body temperature ≤ 38.1°C	External cooling and anti-pyretics could be discussed [a]
Mal-positioned central venous catheter	Correctly positioned catheter	Withdraw catheter to caval-atrial junction

Abbreviations: MAP, mean arterial pressure

[a] Left to the discretion of the attending physician

Table 2 Study Gantt chart (task schedule)

Events	D1	D2-D7	D28 +/- *2 d*
Inclusion and non-inclusion criteria	R		
Enrolment			
Informed consent	R		
Intervention			
Risk control strategy	C	C	
Rate control strategy	C	C	
Rhythm control strategy	C	C	
Assessments			
Characteristics of the patient	C		
Characteristics of the septic shock	C	C	C
Organ dysfunction and management	C	C	
Thyroid blood sample	C		
Other biological data	C		
Cardiac rhythm	C	C	
Duration of septic shock			C
Adverse event(s)			C
ICU length of stay and hospital length of stay			C
Vital status			C
Abbreviations: C, usual Care; D, day; ICU, intensive care unit; R, specific to Research			

Figure 1: Study schema

Abbreviations: NOSVA, new onset supraventricular arrythmia; IV, intravenous

Figure 2: Schema of strategies for each group according to the evolution of the randomised patients

Abbreviations: EES, external electrical shock; NOSVA, new onset supraventricular arrythmia

Administrative information

Primary Registry and Trial Identification Number

ClinicalTrials.gov Identifier, NCT04844801

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Secondary Identifying Numbers

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Disclaimer

None

Contributors

VL is responsible for the overall content as the guarantor. VL and AMD in collaboration with the other authors designed the study and wrote the manuscript together. AR provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan, and estimated the sample size. VL, CD, SP, DD, DC, FB, BS, VP, P-MB, GM, FB, PA, NB, JJ, OS, MD, FA, XM, SC, EV, NS, AW, SV, NH, CLB, GC, FC, MP, LH, MF, FT, DD, GM, LB, AR, and AMD contributed to drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. VL, CD, SP, DD, DC, FB, BS, VP, P-MB, GM, FB, PA, NB, JJ, OS, MD, FA, XM, SC, EV, NS, AW, SV, NH, CLB, GC, FC, MP, LH, MF, FT, DD, GM, LB, AR, and AMD gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of it.

Steering committee

Composition: principal investigator (AMD), scientific supervisor (VL), biostatistician (AR), and the sponsor's appointed representatives of the trial: Clinical Research Associate in charge of the project (GM) and project manager URC DRCI (clinical research unit, Saint-Antoine Hospital AP-HP), and project manager of the DRCI (sponsor)spo.

Role: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.

Competing interests

AMD reports lectures for Leo Pharma.

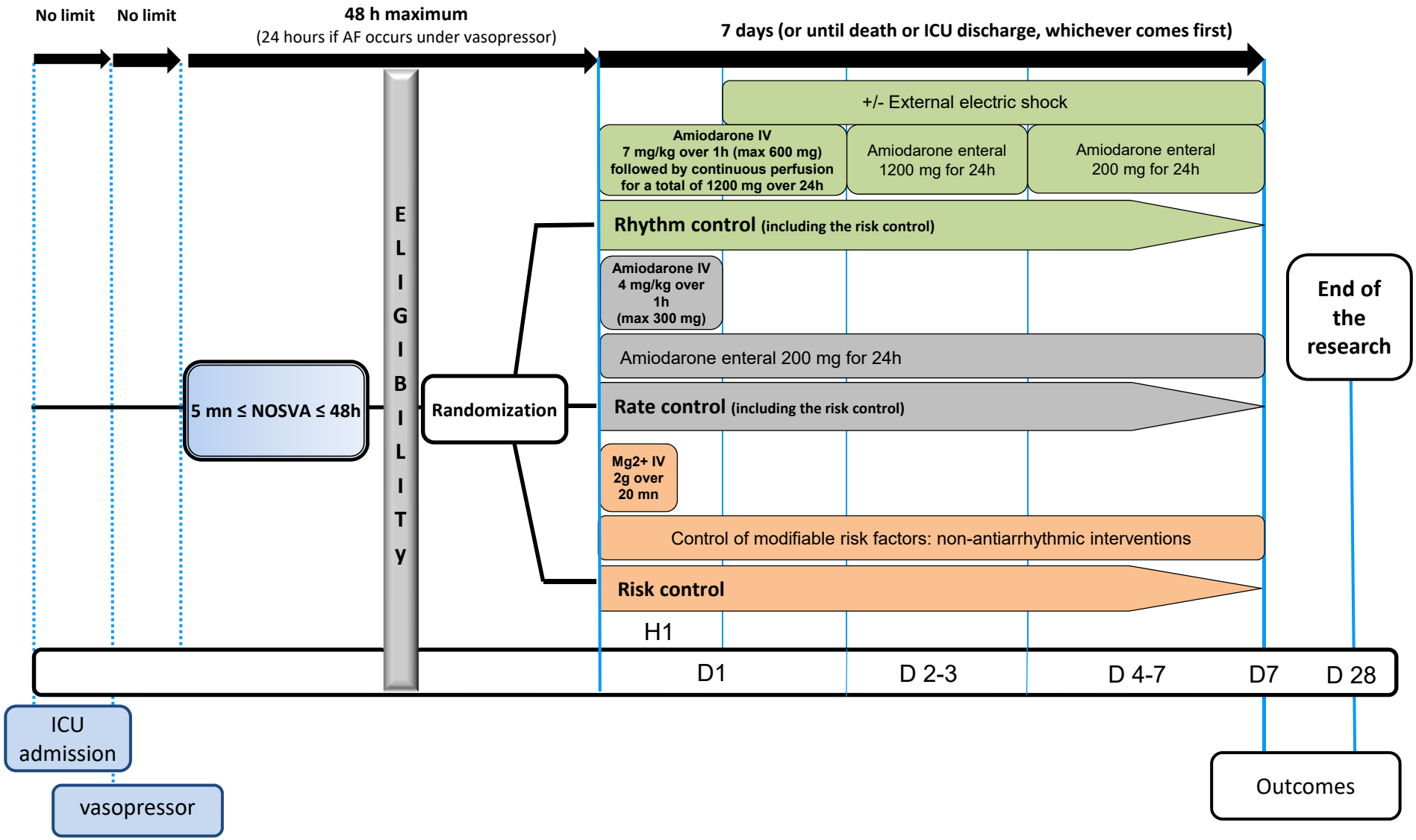
VL receives advisory board fees from AOP, and grants from Leo Pharma unrelated to the present study.

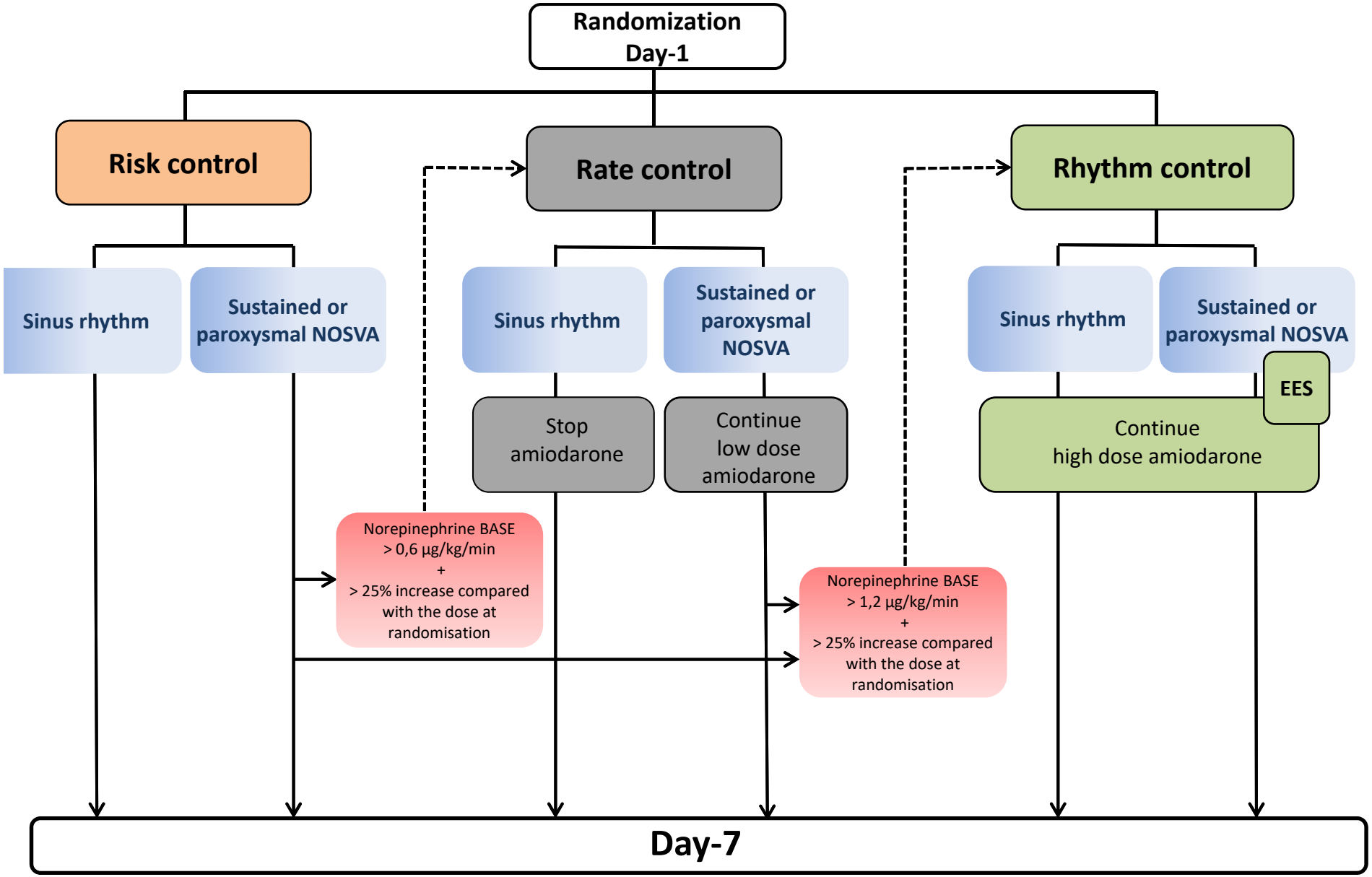
XM received fees for lectures from AOP health, Baxter healthcare and Getinge, and fees for consulting activities for Baxter healthcare and Getinge.

All other authors have no completing interest to declare.

Provenance and peer review

Not commissioned; externally peer reviewed.





APPENDICE A: list of study sites

INSTITUTION	SERVICE	ADRESSE	CODE POSTAL	VILLE	PAYS
Hôpital Tenon - APHP	Médecine intensive réanimation	4 rue de la Chine	75020	Paris	France
Hôpital Saint Antoine - APHP	Médecine intensive réanimation	184 rue du Faubourg Saint Antoine	75012	Paris	France
Hôpital Mondor - APHP	Médecine intensive réanimation	51 Avenue du Maréchal de Lattre de Tassigny	94010	Créteil	France
Hôpital Lariboisière - APHP	Médecine intensive réanimation	2 Rue Ambroise Paré	75010	Paris	France
Hôpital Bicêtre - APHP	Médecine intensive réanimation	78 Rue du Général Leclerc	94270	Le Kremlin-Bicêtre	France
Hôpital La Pitié - APHP	Médecine intensive réanimation	47-83 Boulevard de l'Hôpital	75013	Paris	France
Centre hospitalier Melun Marc Jacquet	Réanimation médicale	270 Avenue Marc Jacquet	77000	Melun	France
Hôpital Raymond-Poincaré - APHP	Médecine intensive réanimation	104 Boulevard Raymond Poincaré	92380	Garches	France
Centre Hospitalier d'Argenteuil	Réanimation polyvalente	69 Rue du Lieutenant Colonel Prudhon	95107	Argenteuil	France
CHU de Poitiers	Médecine intensive réanimation	2 Rue de la Milétrie	86021	Poitiers	France
CHU Angers	Médecine intensive réanimation	4 Rue Larrey	49100	Angers	France
CHR d'Orléans	Médecine intensive réanimation	14 Avenue de l'Hôpital	45100	Orléans	France
CH Sud Francilien	Médecine intensive réanimation	40 avenue Serge Dassault	91106	Corbeil-Essonnes	France
CHU de Nice	Médecine intensive réanimation	151 route Saint-Antoine de Ginestière	62000	Nice	France
CHU de Lille	Médecine intensive réanimation	Avenue du Professeur Emile Laine	59037	Lille	France
CHU Gabriel Montpied	Médecine intensive réanimation	58, rue Montalembert	63003	Clermont-Ferrand	France
Hôpital Saint Camille	Médecine intensive réanimation	2 rue des Pères Camiliens	94360	Bry-sur-Marne	France
CH de Cannes	Médecine intensive réanimation	15 avenue des Broussailles	06400	Cannes	France
Hôpital Louis Mourier	Réanimation médico-chirurgicale	178 rue des Renouillers	92700	Colombes	France
Hôpital Avicenne-APHP	Réanimation médico-chirurgicale	125 Rue de Stalingrad	93000	Bobigny	France
Centre Hospitalier Saint Joseph Saint Luc	Réanimation Polyvalente	20 quai Claude Bernard	69365	Lyon	France

CHU Toulouse Rangueil	Réanimation Polyvalente	1 av du Pr Jean Poulhès	31059	Toulouse	France
CH Marnes La vallée	Médecine intensive réanimation	2-4 Cours de la Gondoire	77600	Marne-La-Vallée	France
Hôpital Erasme	Service de soins Intensifs	Route de Lennik, 808, 1070 Bruxelles	1070	Bruxelles	Belgique
Clinique St Pierre	Service de soins intensifs	Avenue Reine Fabiola,9	B-1340	Ottignies	Belgique
CHU Charleroi	Service de soins intensifs	44 rue de Leernes	6111	Charleroi	Belgique
Centre Hospitalier de Wallonie picarde (CHwapi)	Médecine intensive réanimation	9, avenue. Delmée	7500	Tournai	Belgique
Centre Hospitalier Universitaire Ambroise Paré	Service de soins intensifs	2, Boulevard Kennedy	7000	Mons	Belgique

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Comparison of three management strategies for de novo supraventricular arrhythmias in septic shock: a randomised controlled trial.
CAFS (Control Atrial Fibrillation during Septic shock) study

This research is promoted by *Assistance Publique - Hôpitaux de Paris*
Represented by the Director of
***Direction de la Recherche Clinique et de l'Innovation* (DRCI)**
1 avenue Claude Vellefaux
75010 Paris

INVITATION TO PARTICIPATE

Dear Madam, dear Sir

Dr./Pr. (delete as appropriate) ..... (First name, Surname), working at …….. Hospital, invites you to participate in a research study conducted to examine your disease.
We highly encourage you to read this document carefully before making any decision. Do not hesitate to ask for further information.
If you agree to participate in this research, you will be asked to sign a written consent.

1) What is the objective of this research?

You are admitted in intensive care to be treated for a septic shock. Septic shock is a critical infection that leads to a decrease in blood pressure (acute circulatory failure) and organ damage. This situation has been complicated by cardiac arrhythmia (irregular, faster and less efficient heartbeats), which may worsen your condition.
To limit this risk, there are three alternatives: attempting to reduce the heart rate, or to stop the arrhythmia with a return to normal rhythm (sinus rhythm) by managing its risk factors (risk control); slowing the heart rate (rate control) as a complement to risk factor management; or stopping the arrhythmia and returning to a normal heart rate (rhythm control), also as a complement to risk factor management. At present, there are no data to show which of these three strategies is the best to prevent deterioration in the health of patients with arrhythmia during septic shock, as is the case for you.
The aim of our research is to compare the three strategies (risk control, rate control, rhythm control) in patients with arrhythmia during septic shock. The strategy applied to each patient will be determined by random selection.
To perform this research study, we intend to include 240 patients with arrhythmia during septic shock who are admitted to French and Belgium hospitals.

2) What does the research consist in?

In the present study, we will compare the efficacy of risk control, rate control and rhythm control strategies. You will be treated for 7 days according to the strategy selected by random draw.
The aim of the risk control strategy is either to reduce the heart rate, or to stop the arrhythmia with a return to normal rhythm (sinus rhythm), by controlling the arrhythmia's risk factors (such as low serum magnesium, low serum potassium, fever...), without specific arrhythmia treatment which may cause side effects.
The aim of the rate control strategy is to reduce the heart rate by using a low dose of amiodarone in addition to the risk control strategy. When specific arrythmia treatment is prescribed for patients with septic shock, such as yourself, amiodarone is the most commonly used in France and Belgium. Amiodarone is an anti-arrhythmic drug, which have an action on the heart's electric impulsion. Its action varies according to the dose used: reduction in heart rate at low doses, or arrest of arrhythmia with return to normal heart rhythm at high doses. For rapid action, amiodarone is first administrated intravenously, then orally if available.

The aim of the rhythm control strategy (in addition to the risk control strategy) is to stop the arrhythmia and restore a normal heart rhythm using high-dose amiodarone. If high-dose amiodarone fails, one or more external electrical shocks may be administered if you are under sedation (general anesthesia), with intubation and mechanical ventilation to treat septic shock.

If you are not under sedation, an electric shock will not be given, even if high-dose amiodarone fails. External electrical shock consists of passing a brief electric current through the heart to restore a normal heart rhythm. The current is delivered to the chest through two paddles connected to a device called an external defibrillator. The procedure is carried out under general anesthesia.
In all cases, you will also receive the usual treatment for septic shock as recommended during your stay in hospital.

3) What is the work schedule of the research?

The study is expected to last 43 months and your participation will last 28 days. The trial will not involve any additional tests other than those performed as part of routine care. Your participation in the study will begin after you sign the consent form at your first visit.
Once you have read and signed the consent form, you will be randomised to the risk control, rate control or rhythm control strategy, which will start immediately. This randomisation corresponds to the first day of the trial (D1). You will receive the randomised strategy for 7 days, from D1 to D7. Your monitoring data (routine clinical examinations and blood tests) will be collected daily during your hospital stay.
If you leave the hospital before day 28, a clinical trial technician will contact you on day 28 to check your health.

4) What are the benefits of your participation?

The expected benefit is a reduction in the duration of acute circulatory failure during the 7 days of treatment to reduce the risk of organ failure. In addition, your participation will help us to improve our knowledge of the treatment of arrhythmias in septic shock.

5) Which treatments are authorized and which are not?

Drugs that can cause a cardiac arrhythmia called "torsades de pointes" are not approved for use with amiodarone and are prohibited for research purposes. The most common of these are: erythromycin, levofloxacin, moxyfloxacin and spiramycin.

6) What are the anticipated risks and constraints added by the research?

If you agree to take part in this study, you should take the following into account

- Take your treatment as prescribed by your doctor.
- Inform the research physician of any medication you are taking and of any events that occur during the research (hospitalisation, etc.).
- To be covered by or benefit from any social security scheme.
- Not to participate in another research project without your doctor's permission, in order to protect yourself from any health problems that may arise, for example, from possible incompatibilities between the drugs being studied or from other exposures.
- If you are a woman of childbearing potential, you should have a pregnancy test before starting this study.

7) What are the potential medical alternatives?

If you choose not to participate in this research, you will receive appropriate medical care according to your condition, in accordance with standard clinical practice.

8) What kind of medical care to have after participation?

Follow-up is not specific to this trial. You will continue to receive care that is appropriate to your condition, whether that is usual care in the event that the research is stopped early, or care at the end of your participation.
Your doctor can decide to stop your participation at any time and should explain the reasons to you.

9) If you participate, how will your collected data be used in the research?

In the context of the research in which you are invited to participate, your personal data will be processed by AP-HP, the research promoter in charge of data management, in order to analyse the results.

This data processing is necessary in order to carry out research of public health interest, in line with AP-HP's mission as a public university hospital.

To this end, your medical and lifestyle data will be communicated to the promoter or to persons or partners working on its behalf, in France or abroad, and will be kept for 15 years. This data will be identified by a registration number. These data may also be communicated to French or foreign health authorities under conditions that guarantee their confidentiality.

Your data may be used for further research or complementary analysis in collaboration with private or public partners in France or abroad, under conditions that guarantee their confidentiality and the same level of protection as required by European legislation.
You may at any time object to any further analysis of your data by informing the doctor who is following you in this research.

Your data will only be kept for as long as is strictly necessary and justified by the purpose of the research. It will be kept on the data manager's information systems for two years after the last publication of the research results. Your data will then be archived in accordance with the regulations in force.

The database used for this research is created in accordance with French law (modified "Informatique et Libertés" law) and European law (Règlement Général sur la Protection des Données - RGPD). You have the right to access, modify, limit and object to the processing of data covered by professional secrecy and used in the context of this research. These rights can be exercised with the doctor in charge of the research, who is the only person who knows your identity (identified on the first page of this document).

If you decide to discontinue your participation, the data collected prior to this decision will be used in accordance with the regulations and exclusively for the purposes of this research. Deletion of this data would compromise the validity of the research results. However, from that point on, your data will no longer be used in this research or in any other work.

If you have a problem concerning your rights, you can contact the AP-HP Data Protection Officer at the following address: protection.donnees.dsi@aphp.fr, who will be able to explain the channels available to you with the CNIL. You may also exercise your right to complain directly to the CNIL (for more information on this subject, please visit www.cnil.fr).

10) How is this research supervised?

AP-HP has taken all the measures necessary to carry out this research in compliance with the public health regulations applicable to research involving human volunteers.

AP-HP has taken out an insurance policy (number 0100518814033 200013) with its insurance broker BIOMEDICINSURE, whose address is Parc d'Innovation, Bretagne Sud C.P.142 56038 Vannes Cedex, to cover its civil liability and that of all its collaborators.

AP-HP has been approved by the Ethics Committee (CPP Sud-Ouest et Outre-Mer III) on [29/07/2020] and by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) on 21/02/2020.

11) What are your rights ?

Your participation in this research is free and voluntary. Your decision will not affect the quality of care and treatment you receive.

Before you agree to take part in this research, you will undergo an appropriate medical examination, the results of which will be reported to you.

Throughout the study, and at any time, you can ask your investigator for further information about your health and explanations of the research process.

You can withdraw from the research at any time without explanation, without any impact on your treatment or the quality of care you receive, and without any impact on your relationship with your doctor. After this withdrawal, you may be followed by the same medical team. In this case, the data collected up to the time of withdrawal will be used to analyse the research results.

Your medical file will remain confidential and can only be consulted under the responsibility of the doctor in charge of your treatment, as well as by the health authorities and persons authorised by AP-HP for research and bound by professional confidentiality.

At the end of the study and its data analysis, you will have access to the overall results by contacting the doctor treating you in the study.

You can also access all your medical data directly or through a doctor of your choice, in accordance with article L 1111-7 of the Public Health Code.

If, after reading all this information, discussing it with your doctor and having time to think about it, 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.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

CONSENT FORM

I, the undersigned, Mrs, Mr [delete as appropriate] (first name, surname) ..... agree to voluntarily participate in the study entitled
"Comparison of three management strategies for de novo supraventricular arrhythmias in septic shock: a randomised controlled trial." sponsored by Assistance Publique - Hôpitaux de Paris and I was informed by Dr./Pr. (name, surname, telephone)....., investigator of this study.

- I have read the Invitation to Participate version 3.0 dated 19.6.2023 (4 pages), which explains the purpose of this study, how it will be conducted, and what my participation will entail;
- I will keep a copy of the invitation to participate and the informed consent form:
- I have received adequate answers to all my questions;
- I have had enough time to make my decision;
- I understand that my participation is free of charge and that I can stop my participation at any time without any liability and without affecting the quality of care I receive;
- I have been informed that the data collected in the research may be used for other studies and that I may object to this at any time;
- I understand that my participation may also be interrupted at any time by the doctor, who should explain the reasons;
- I have undergone a medical examination appropriate to the research prior to taking part in this research, the results of which have been communicated to me;
- I am aware that, in order to participate in this research, I must be affiliated to or a beneficiary of a social security scheme. I confirm that this is the case;
- I have been informed that my participation in this research will last for 28 days, during which time I cannot consider taking part in any other research without informing the investigating physician in charge of my case in this study,
- My consent does not in any way relieve the doctor following me in the research or AP-HP of any responsibility, and I retain all the rights guaranteed to me by law.

Signature of the participating person		**Signature of the doctor**	
First name, Surname:		Fist name, Surname:	
Date:	Signature:	Date:	Signature:

This document must be produced in three copies: one copy must be kept by the investigator for 15 years, the second given to the consenting person, and the third sent to AP-HP in a sealed envelope at the end of the study.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Repored on page NO
Administrative information			**27-28-29**
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	24,25
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,3,4,25
	5b	Name and contact information for the trial sponsor	28
	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	n/a
	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)	12, 17, 24
Introduction			7

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	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	8
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)	8
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	8
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)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
	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)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10

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	11,12
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)	11
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	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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	13
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	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
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	13,15,16
	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	15,16
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	15,16
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	14,15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14,15
	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)	14
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	15

	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	n/a
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	10,12,15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
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	16
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	n/a

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	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	18
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	n/a

*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.