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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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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

1 2		
3	1	Strengths and limitations of the study
4 5	2	► This randomised controlled trial may contribute to the establishment of recommendations
6 7	3	with a high level of evidence on the best management strategy in patients with septic shock and
8 9	4	new onset atrial fibrillation.
10 11	5	► Pragmatic design comparing three common strategies in an intention-to-treat approach.
12	6	► Limitation: not blinded.
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INTRODUCTION

2 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].

16 Rhythm control may improve haemodynamics (by restoring diastolic function and decreasing 27 cardiac metabolic demand), reduce thromboembolic risk, and minimise exposure to 28 anticoagulants. Rate control limits the potential adverse effects of high dose amiodarone and/or 29 of electrical cardioversion, while still improving haemodynamics. The risk control strategy 20 minimises the adverse effects of amiodarone while still resulting in conversion of NOSVA in 21 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.

28 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.

1 2		
3 4	1	Objectives
5 6	2	Primary objective
7	3	The main objective is to compare the efficacy of the three strategies (risk control, rate control,
o 9	4	and rhythm control) in reducing mortality and duration of shock in septic patients with NOSVA.
10 11	5	Secondary objectives
12 13	6	Secondary objectives are to compare the benefit and risks of the three strategies in terms of
14 15	7	haemodynamics, organ dysfunction, morbidity, mortality, safety (including thrombotic events,
16	8	bleeding events and serious adverse events related to amiodarone and electrical cardioversion),
17 18	9	and net clinical benefit.
19 20		
21 22	10	METHODS AND ANALYSIS
23 24	11	Trial design
25 26	12	This is a binational multicentre narallel-group open-label randomised controlled superiority
27 20	12	trial in patients with NOSVA during sentic shock. The trial protocol follows the Standard
20 29	14	Protocol Items: Recommendations for Interventional Trial (SPIRIT) reporting guidelines
30 31 32	15	Study setting
33 34	16	The study will be conducted in 28 intensive care units (ICUs) in 23 hospitals in France and 5
35	17	hospitals in Belgium (list of study sites in Appendix A).
30 37 38	18	Eligibility criteria
39 40	19	Inclusion criteria
41 42	20	Adult patients (age \geq 18 years) admitted to the ICU will be eligible as soon as they meet all the
43	21	following criteria:
44 45	22	1- Septic shock, defined by the association of the following criteria:
46 47	23	 Documented or suspected infection, with initiation of antibiotic therapy
48 49	24	• Initiation of vasopressors (noradrenaline or adrenaline) for at least 1 hour to maintain
50	25	the mean arterial pressure (MAP) >65 mmHg;
52	26	2- NOSVA (including atrial fibrillation, atrial flutter, and atrial tachycardia) with heart rate
53 54	27	\geq 110 bpm lasting at least 5 minutes;
55 56	28	3- Written informed consent (patient, next of kin or emergency situation);
57	29	4- Member of a social security system.
59 60	30	

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2 3	1	Evolusion aritaria
4	1	Exclusion criteria
5 6	2	Patients presenting any of the following criteria will not be included:
7 8	3	1. Refractory shock, defined as a dose of noradrenaline base or adrenaline base >1.2
9	4	μg/kg/min;
10 11	5	2. Heart surgery or heart transplant in the previous month;
12	6	3. Aortic or mitral valve mechanical prosthesis, significant mitral stenosis (mitral surface
13 14	7	$< 1.5 \text{ cm}^2$);
15 16	8	4. Congenital heart disease other than bicuspid aortic valve, atrial defect, or patent foramen
17	9	ovale;
18 19	10	5. History of SVA before septic shock, defined as paroxysmal SVA with long-term
20 21	11	antiarrhythmic and/or therapeutic anticoagulation, or permanent SVA;
22	12	6. NOSVA lasting more than 48 hours (or more than 24 hours under vasopressor therapy):
23 24	13	the patient can still be included if transoesophageal echocardiography (under
25 26	14	mechanical ventilation) excludes intracardiac thrombus and the patient is receiving
27	15	therapeutic anticoagulation;
28 29	16	7. Electrical cardioversion or use of amiodarone or another bradycardic drug (beta-
30 31	17	blocker, bradycardic calcium channel blocker, digitalis, flecainide) within the 6 hours
32	18	preceding inclusion;
33 34	19	8. Contraindication to amiodarone: history of serious adverse event, lung disease, or
35 36	20	hyperthyroidism related to amiodarone. PR interval >240ms, severe sinus node
37	21	dysfunction with no pacemaker, second- or third-degree atrioventricular block with no
39	22	pacemaker OTc $>$ 480ms known or treated hyperthyroidism hypersensitivity to iodine
40 41	23	amiodarone or to any of the excinients severe hepatocellular insufficiency (prothrombin
42 43	23 24	rate $< 20\%$ diffuse interstitial lung disease:
44	25	9 Serum potassium <3 mmol/L ·
45 46	25	10. Programov or broast fooding:
47	20	10. Freghancy of breast-recting,
48 49	27	11. Moribund of death expected from underlying disease during the current admission;
50 51	28	12. Patients deprived of liberty and persons receiving institutional psychiatric care;
52	29	13. Participation in another interventional trial on septic shock and/or rhythm disorder.
53 54	30	Intervention
55 56	31	The experimental plan is shown in Figure 1. After verification of the eligibility criteria, the
57 58	32	patient will be enrolled and randomised (Day 1) as soon as possible, and within 48 hours from
59	33	the onset of NOSVA (or 24 hours if NOSVA occurs when receiving vasopressor treatment).

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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.

17 In all groups, current recommendations for the management of septic shock will be followed18 [13].

20 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;
- 32 o Hyperthyroidism, as defined by a thyroid-stimulating hormone concentration <0.1
 33 mIU/L in the blood sampled before amiodarone initiation [14].

3 ⊿	1	Follow-up visits
5	2	The trial follow-up visits will be on days 2 to 7, and day 28.
6 7	3	
7 8 9	4	Endpoints
10 11	5	Primary endpoint
12	6	The primary endpoint is a hierarchical endpoint assessed at day 28 and includes all-cause
13 14	7	mortality and the duration of shock. The Finkelstein-Schoenfeld method is based on the
15 16	8	principle that each patient in the clinical trial is compared with every other patient within each
17 18	9	stratum in a pairwise manner. The pairwise comparison proceeds in hierarchical fashion, using
19	10	all-cause mortality, followed by the duration of septic shock when patients cannot be
20 21	11	differentiated on the basis of mortality. This method gives a higher importance to all-cause
22 23	12	mortality [15,16].
24 25	13	The duration (days) of septic shock is defined as the period from randomization to successful
26	14	weaning of vasopressors (patient alive with no reintroduction during the first 48 hours after
27 28	15	discontinuation).
29 30	16	
31	17	Secondary endpoints
32 33	18	Secondary endpoints will include the following:
34 35	19 20	(1) Rhythm control at day 7
36 37	20 21	- Number of patients with sinus rhythm;
38 30	22	- Number of days alive with sinus rhythm;
40 41	23	- Number of days alive with NOSVA and heart rate <110 bpm;
42	24	- Proportion of patients receiving therapeutic anticoagulation after randomization;
43 44	25	
45	26	(2) Morbidity, mortality, and organ function
46	27	
47 48	28	- Duration of septic shock at day 28;
49	29	- Proportion of patients alive and free from vasopressors at day 7 (or discharge or death
50 51	30	whichever comes first);
52 53	31	- Arterial lactate clearance at day 3 [17];
54 55	32	- Proportion of patients alive and free from organ dysfunction at day 7 (or discharge or
56	33	death whichever comes first). Organ dysfunction is defined as a sequential organ failure
57 58	34	assessment (SOFA) score ≥ 3 for the following organs: cardiovascular, renal,
59 60	35	neurological, hepatic, respiratory, or coagulation [18];

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3 4	1	- Length of ICU stay at day 28;				
5	2	- Length of hospital stay at day 28;				
7	3	- All-cause deaths at day 28.				
8 9	4					
10 11	5	(3) Safety				
12	6 7	- Arterial thrombotic events, including ischaemic stroke and non-cerebrovascular arterial				
13 14	, 8	thrombotic event [19].				
15 16	0	Major blooding events defined as bloods that most at least one of the following criterio:				
17	9	- Major bleeding events defined as bleeds that meet at least one of the following criteria.				
18 19	10	bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular,				
20	11	retroperitoneal); bleeding requiring surgical, endoscopic or endovascular haemostasis				
21 22	12	action; a life-threatening bleed; and a fatal bleed [20];				
23 24	13	- Serious adverse events related to amiodarone or to magnesium, including ventricular				
25	14	arrhythmia, conduction disorders, and acute hepatitis related to amiodarone as described				
26 27	15	above;				
28	16	- Serious adverse events associated with electrical cardioversion (for patients receiving				
29 30	17	electrical cardioversion) including ventricular arrhythmia, conduction disorders, and				
31 32	18	arterial thrombotic events.				
33 34	19	(4) Combined efficacy and safety				
35	20	- Net clinical outcome as assessed by the presence of all-cause death, arterial thrombotic				
37	21	event, major bleeding event, or at least one serious adverse event related to amiodarone				
38 39	22	or to magnesium or to electrical cardioversion at day 28.				
40 41	23					
42 43	24	Sample size and its statistical justification				
44 45	25	The sample size was calculated by considering pairwise comparisons between the groups. For				
46 47	26	each comparison, 1000 samples were simulated using SAS software. Based on data from our				
47 48	27	two previous studies in patients with NOSVA during sepsis [3,6], the distribution				
49 50	28	characteristics of the samples were defined according to the following assumptions: (i) 28-day				
51	29	mortality rates of 35%, 30%, and 25% for the risk control, rate control, and rhythm control				
53	30	groups, respectively; (ii) durations of septic shock of 4.9 ± 2.4 days (standard deviation), $3.9 \pm$				
54 55	31	2.4 days, and 2.9 \pm 2.4 days for the risk control, rate control, and rhythm control groups,				
56 57	32	respectively. Within each sample/pairwise comparison, an individual score was calculated by				
58	33	comparing each patient in one group with all patients in the other groups [15,16]. These scores				
60	34	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%.

6 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.

15 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.

1 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).

6 In compliance with the SPIRIT statement, a flow diagram will describe the progress of the three 7 groups of patients throughout the different phases of the trial (enrolment, allocation, received 8 interventional agents, follow-up, and data analysis). The analysis will be performed on an 9 intention-to-treat (ITT) basis. In case of premature interruption or withdrawal from the study, 10 patients will not be substituted. Single imputation will be made for missing values of the 11 primary endpoint, as a failure (i.e. death). Sensitivity analysis will be performed in the per-12 protocol population set (patients as randomized without major protocol violations).

14 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 (\pm standard deviation) or median (25th-75th percentiles) according to the distribution of the variable. Qualitative variables will be reported as numbers (%).

5 19 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].

 1 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

4 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.

14 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.

23 Patient and public involvement

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

25 ETHICS AND DISSEMINATION

26 Ethical approval

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

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Consent to participate 1

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 4 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 8

9 Data will be handled according to the French law on data protection and the European General 10 Data Protection Regulation (GDPR). All original records will be archived at the trial sites for 11 15 years.

Declaration of interest 13

14 This study was funded by a grant from the French Ministry of Health obtained in 2018 15 (Programme Hospitalier de Recherche Clinique). The sponsor is Assistance Publique-Hôpitaux 16 de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI). Delegation (for 17 Belgian centers) for ethics regulation and monitoring has been agreed by Les Cliniques 18 Universitaires de Bruxelles-Hôpital Erasme.

Access to data 20

21 Investigators will make the documents and individual data required for monitoring, quality 22 control, and audit of the study available to specified persons in accordance with French law.

Dissemination policy 24

25 Findings will be published in peer-reviewed journals and presented at national and international 26 meetings. Communications, reports, and publication of the results of the study will be placed 27 under the responsibility of the principal investigator-coordinator of the study and the steering 28 committee. Reporting will adhere to the SPIRIT statement, and rules of publication will follow 29 international recommendations, for example The Uniform Requirements for Manuscripts 30 (ICMJE, April 2010) (SPIRIT checklist, appendix C).

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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.

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2 3 4	1	A	PPENDICES
5 6	2	Ap	ppendix A: List of study sites
7 8	3	Ap	ppendix B: Model of the consent form
9 10 11	5 6	Ap	ppendix C: SPIRIT Checklist
12			
13 14	7	R	EFERENCES
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Modifiable risk factor	Objective	Modalities
Hypovolaemia	$MAP \ge 65 \text{ mmHg with no}$ 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 \leq 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, mea	an arterial pressure	

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

^aLeft to the discretion of the attending physician

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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	С	
Rate control strategy	C	С	
Rhythm control strategy	C	С	
Assessments			
Characteristics of the patient	C		
Characteristics of the septic shock	C	C	С
Organ dysfunction and management	С	С	
Thyroid blood sample	C		
Other biological data	С		
Cardiac rhythm	C	С	
Duration of septic shock			С
Adverse event(s)			С
ICU length of stay and hospital length of stay	2		С
Vital status			С

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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

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Administrative information
Primary Registry and Trial Identification Number
ClinicalTrials.gov Identifier, NCT04844801
Date of Registration in Primary Registry
April 14, 2021
Secondary Identifying Numbers
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$\frac{1}{2} = \frac{1}{2} = \frac{1}$
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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 I, avenue Claude Vellefaux. Paris. France. Email:
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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, ST, DD, GC, 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.

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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

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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

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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

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.

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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 restorements shocks.

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.

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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

The database used for this research is created in accordance with French law (modified "Informatigue et Libertés" law) and 10 European law (Règlement Général sur la Protection des Données - RGPD). You have the right to access, modify, limit and 11 object to the processing of data covered by professional secrecy and used in the context of this research. These rights can be 12 exercised with the doctor in charge of the research, who is the only person who knows your identity (identified on the first 13 page of this document). 14

15 If you decide to discontinue your participation, the data collected prior to this decision will be used in accordance with the 16 regulations and exclusively for the purposes of this research. Deletion of this data would compromise the validity of the 17 research results. However, from that point on, your data will no longer be used in this research or in any other work. 18 19

20 If you have a problem concerning your rights, you can contact the AP-HP Data Protection Officer at the following address: 21 protection.donnees.dsi@aphp.fr, who will be able to explain the channels available to you with the CNIL. You may also 22 exercise your right to complain directly to the CNIL (for more information on this subject, please visit www.cnil.fr). 23

10) How is this research supervised?

archived in accordance with the regulations in force.

26 AP-HP has taken all the measures necessary to carry out this research in compliance with the public health regulations 27 applicable to research involving human volunteers. 28

29 AP-HP has taken out an insurance policy (number 0100518814033 200013) with its insurance broker BIOMEDICINSURE, 30 whose address is Parc d'Innovation, Bretagne Sud C.P.142 56038 Vannes Cedex, to cover its civil liability and that of all its 31 collaborators. 32

33 AP-HP has been approved by the Ethics Committee (CPP Sud-Ouest et Outre-Mer III) on [29/07/2020] and by the Agence 34 Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) on 21/02/2020. 35

11) What are your rights ?

39 Your participation in this research is free and voluntary. Your decision will not affect the quality of care and treatment you 40 receive. 41

42 Before you agree to take part in this research, you will undergo an appropriate medical examination, the results of which will be 43 reported to you. 44

45 Throughout the study, and at any time, you can ask your investigator for further information about your health and explanations 46 of the research process. 47

48 You can withdraw from the research at any time without explanation, without any impact on your treatment or the guality of care 49 you receive, and without any impact on your relationship with your doctor. After this withdrawal, you may be followed by the 50 same medical team. In this case, the data collected up to the time of withdrawal will be used to analyse the research results.

52 Your medical file will remain confidential and can only be consulted under the responsibility of the doctor in charge of your 53 treatment, as well as by the health authorities and persons authorised by AP-HP for research and bound by professional 54 confidentiality. 55

56 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 57 the study. 58

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 obsign and date the informed consent rom at the end of this document xhtml



CONSENT FORM

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9 10	I, the undersigned, Mrs, participate in the study e	, Mr [delete as appropriate] (firs ntitled	st name, surname)	agree to voluntarily				
11	"Comparison of three management strategies for de novo supraventricular arrhythmias in septic shock: a randomised							
12 13	controlled trial." spons telephone)	ored by Assistance Publique -	Hôpitaux de Paris and I was inform	ned by Dr./Pr. (name, surname, y.				
14	· /							
15 16	- 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:							
17	It will be conducted, and what my participation will entail,							
18	- I will keep a copy of the invitation to participate and the informed consent form:							
19	- I have received adequate answers to all my questions;							
20	- I have had enough time to make my decision;							
21	- I understand that my pa	articipation is free of charge and	that I can stop my participation at ar	ny time without any liability and				
22	without affecting the qua	lity of care I receive;						
23 24	- I have been informed t any time:	hat the data collected in the res	earch may be used for other studies	and that I may object to this at				
25	- Lunderstand that my na	articipation may also be interrupt	ed at any time by the doctor, who sho	uld explain the reasons.				
26	by the understand that my participation may also be interrupted at any time by the doctor, who should explain the results of which							
27	⁷ - Thave undergone a medical examination appropriate to the research prior to taking part in this research, the results of which							
27	nave been communicated to me;							
20	- 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							
20	confirm that this is the case;							
50 21	- I have been informed t	hat my participation in this resea	arch will last for 28 days, during whic	h time I cannot consider taking				
22	part in any other researc	h without informing the investiga	ting physician in charge of my case in	this study,				
32	- My consent does not in	any way relieve the doctor follo	owing me in the research or AP-HP of	f any responsibility, and I retain				
33	all the rights guaranteed to me by law							
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55	person, and the third sent to AP-HP in a sealed envelope at the end of the study.							
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Repored on page NO
Administrative inf	ormation		27-28-29
Title		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

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Objective Trial des
Methods
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Study Se
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ackground and ationale	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
bjectives	7	Specific objectives or hypotheses	8
rial 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
lethods: Participa	nts, inte	rventions, and outcomes	
tudy 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
ligibility 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
nterventions	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

2 3 4 5 6 7 8 9 10 11	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
12 13 14 15 16 17 18	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
19 20 21 22 23 24 25	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
26 27 28	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
29 30	Methods: Assignm	ent of in	terventions (for controlled trials)	
31 32	Allocation:			
33	-			
34 35 36 37 38 39 40 41 42 43	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
44 45 46 47 48 49 50	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
51 52 53 54	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
55 56 57 58 59 60	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a

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	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 colle	ection, n	nanagement, 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: Monitorin	ng		
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

Harms22Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct10Auditing23Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsorn/aEthics and disseminationResearch ethics approval24Plans for seeking research ethics committee/institutional review board (REC/IRB) approval15Protocol amendments25Plans for communicating important protocol modifications (eq. changes to eligibility criterian/a	Э
Auditing23Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsorn/aEthics and disseminationPlans for seeking research ethics committee/institutional review board (REC/IRB) approval15Protocol25Plans for communicating important protocol modifications (eq. changes to eligibility criterian/a	1,12,15
Ethics and dissemination Research ethics 24 Plans for seeking research ethics 15 approval 24 Plans for seeking research ethics 15 protocol 25 Plans for communicating important protocol n/a amendments 25 Plans for communicating important protocol n/a	а
Research ethics approval24Plans for seeking research ethics committee/institutional review board (REC/IRB) approval15Protocol amendments25Plans for communicating important protocol modifications (eq. changes to eligibility criterian/a	
Protocol 25 Plans for communicating important protocol n/a	i
outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Э
Consent or assent 26a Who will obtain informed consent or assent from 16 potential trial participants or authorised surrogates, and how (see Item 32)	i
26b Additional consent provisions for collection and n/a use of participant data and biological specimens in ancillary studies, if applicable	а
Confidentiality 27 How personal information about potential and 16 enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	i
Declaration of28Financial and other competing interests for16interestsprincipal investigators for the overall trial and each study site	ì
Access to data 29 Statement of who will have access to the final trial 16 dataset, and disclosure of contractual agreements that limit such access for investigators	i
Ancillary and post-30Provisions, if any, for ancillary and post-trial care,n/atrial careand for compensation to those who suffer harmfrom trial participation	а

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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
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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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Primary Subject Heading :	Intensive care
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SCHOLARONE[™] Manuscripts

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.

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1 INTRODUCTION

2 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.

28 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.

1 Objectives

Primary objective

3 The main objective is to compare the efficacy of the three strategies (risk control, rate control,

4 and rhythm control) in reducing mortality and duration of shock in septic patients with5 NOSVA.

6 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.

11 METHODS AND ANALYSIS

12 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.

16 Study setting

17 The study will be conducted in 28 intensive care units (ICUs) in 23 hospitals in France and 5

18 hospitals in Belgium (list of study sites in Appendix A).

19 Eligibility criteria

- 20 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;
 - 27 2- NOSVA (including atrial fibrillation, atrial flutter, and atrial tachycardia) with heart
 28 rate ≥110 bpm lasting at least 5 minutes;
- 29 3- Written informed consent (patient, next of kin or emergency situation);
- 5859 30 4- Member of a social security system.

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3 4	1	Exclusion criteria
5 6	3	Patients presenting any of the following criteria will not be included:
7 8	4	1. Refractory shock, defined as a dose of noradrenaline base or adrenaline base >1.2
9 10	5	μg/kg/min;
11 12	6	2. Heart surgery or heart transplant in the previous month;
13	7	3. Aortic or mitral valve mechanical prosthesis, significant mitral stenosis (mitral surface
14 15	8	< 1.5 cm ²);
16 17	9	4. Congenital heart disease other than bicuspid aortic valve, atrial defect, or patent
18	10	foramen ovale;
20	11	5. History of SVA before septic shock, defined as paroxysmal SVA with long-term
21 22	12	antiarrhythmic and/or therapeutic anticoagulation, or permanent SVA;
23 24	13	6. NOSVA lasting more than 48 hours (or more than 24 hours under vasopressor
25 26	14	therapy): the patient can still be included if transoesophageal echocardiography (under
20	15	mechanical ventilation) excludes intracardiac thrombus and the patient is receiving
28 29	16	therapeutic anticoagulation;
30 31	17	7. Electrical cardioversion or use of amiodarone or another bradycardic drug (beta-
32 33	18	blocker, bradycardic calcium channel blocker, digitalis, flecainide) within the 6 hours
34	19	preceding inclusion;
35 36	20	8. Contraindication to amiodarone: history of serious adverse event, lung disease, or
37 38	21	hyperthyroidism related to amiodarone, PR interval >240ms, severe sinus node
39 40	22	dysfunction with no pacemaker, second- or third-degree atrioventricular block with no
41	23	pacemaker, QTc >480ms, known or treated hyperthyroidism, hypersensitivity to
42 43	24	iodine, amiodarone or to any of the excipients, severe hepatocellular insufficiency
44 45	25	(prothrombin rate <20%), diffuse interstitial lung disease;
46 47	26	9. Serum potassium <3 mmol/L;
48	27	10. Pregnancy or breast-feeding;
49 50	28	11. Moribund or death expected from underlying disease during the current admission;
51 52	29	12. Patients deprived of liberty and persons receiving institutional psychiatric care;
53 54	30	13. Participation in another interventional trial on septic shock and/or rhythm disorder.
54 55 56	31	Intervention
57 58	32	The experimental plan is shown in Figure 1. After verification of the eligibility criteria, the
59 60	33	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].

21 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;
- 33 o Hyperthyroidism, as defined by a thyroid-stimulating hormone concentration <0.1
 34 mIU/L in the blood sampled before amiodarone initiation [14].

1 2					
3	1				
4 5	2	Follow-up visits			
6 7	3	The trial follow-up visits will be on days 2 to 7, and day 28.			
8	4				
9 10 11	5	Endpoints			
12 13	6	Primary endpoint			
14 15	7	The primary endpoint is a hierarchical endpoint assessed at day 28 and includes all-cause			
15 16	8	mortality and the duration of shock. The Finkelstein-Schoenfeld method is based on the			
17 18	9	principle that each patient in the clinical trial is compared with every other patient within each			
19	10	stratum in a pairwise manner. The pairwise comparison proceeds in hierarchical fashion,			
20 21	11	using all-cause mortality, followed by the duration of septic shock when patients cannot be			
22 23	12	differentiated on the basis of mortality. This method gives a higher importance to all-cause			
24	13	mortality [15,16].			
25 26	14	The duration (days) of septic shock is defined as the period from randomization to successful			
27 28	15	weaning of vasopressors (patient alive with no reintroduction during the first 48 hours after			
29 30 31 32 33 34 35 36 37	16	discontinuation).			
	17				
	18	Secondary endpoints			
	19	Secondary endpoints will include the following:			
	20 21	(1) Rhythm control at day 7			
38 30	22	- Number of patients with sinus rhythm;			
40	23	- Number of days alive with sinus rhythm;			
41 42	24	- Number of days alive with NOSVA and heart rate <110 bpm;			
43 44	25	- Proportion of patients receiving therapeutic anticoagulation after randomization;			
45	26				
40 47 48	27 28	(2) Morbidity, mortality, and organ function			
49	29	- Duration of septic shock at day 28;			
50 51	30	- Proportion of patients alive and free from vasopressors at day 7 (or discharge or death			
52 53	31	whichever comes first);			
54	32	- Arterial lactate clearance at day 3 [17];			
55 56	33	- Proportion of patients alive and free from organ dysfunction at day 7 (or discharge or			
57 58 59 60	34	death whichever comes first). Organ dysfunction is defined as a sequential organ			

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3	1	failure assessment (SOFA) score ≥ 3 for the following organs: cardiovascular, renal,	
4 5	2	neurological, hepatic, respiratory, or coagulation [18];	
6 7	3	- Length of ICU stay at day 28;	
8 9	4	- Length of hospital stay at day 28;	
10	5	- All-cause deaths at day 28.	
11 12	6		
13 14	7	(3) Safety	
15	8		
16 17	9	- Arterial thrombotic events, including ischaemic stroke and non-cerebrovascular	
18	10	arterial thrombotic event [19];	
19 20	11	- Major bleeding events defined as bleeds that meet at least one of the following	
21 22	12	criteria: bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular,	
23	13	retroperitoneal); bleeding requiring surgical, endoscopic or endovascular haemostasis	
24 25	14	action; a life-threatening bleed; and a fatal bleed [20];	
26 27	15	- Serious adverse events related to amiodarone or to magnesium, including ventricular	
28	16	arrhythmia, conduction disorders, and acute hepatitis related to amiodarone as	
29 30	17	described above;	
31 32	18	- Serious adverse events associated with electrical cardioversion (for patients receiving	
33 34	19	electrical cardioversion) including ventricular arrhythmia, conduction disorders, and	
35	20	arterial thrombotic events.	
30 37	21	(4) Combined efficacy and safety	
38 39	22	- Net clinical outcome as assessed by the presence of all-cause death, arterial thrombotic	
40 41	23	event, major bleeding event, or at least one serious adverse event related to	
42	24	amiodarone or to magnesium or to electrical cardioversion at day 28.	
43 44	25		
45 46	26	Sample size and its statistical justification	
47 48	27	The sample size was calculated by considering pairwise comparisons between the groups. For	
49 50	28	each comparison, 1000 samples were simulated using SAS software. Based on data from our	
51 52	29	two previous studies in patients with NOSVA during sepsis [3,6], the distribution	
53	30	characteristics of the samples were defined according to the following assumptions: (i) 28-day	
54 55	31	mortality rates of 35%, 30%, and 25% for the risk control, rate control, and rhythm control	
⁵⁶ ₅₇ 32 groups, respectively; (ii) durations of septic shock of 4.9 ± 2.4 days (standard deviat			
58 22 \pm 24 days and 20 \pm 24 days for the risk control rate control and the three cont			

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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%.

8 Recruitment

9 The expected duration of patient enrolment is 42 months starting from November 2021. The 10 study timeline is as follows: i) 2018: Grant from the French Ministry of Health (Programme 11 Hospitalier de Recherche Clinique) for academic sponsor (Assistance Publique-Hôpitaux de 12 Paris, AP-HP); ii) July 2020: approval by independent ethics committees and competent 13 authority; iii) November 2021: start of patient enrolment; iv) 2025: end of patient enrolment, 14 monitoring, cleaning and database lock, blind review to screen for protocol violation; iv) 15 2025-2026: data analysis, writing of the manuscript, and submission for publication.

)

17 Allocation of intervention and data management

18 Randomisation in a 1:1:1 ratio will be prepared by an independent statistician from the
19 Clinical Research Unit before the start of the trial. Randomisation will be stratified by centre
20 and block balanced. The width of the blocks will not be communicated to the investigators.
21 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.

2 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).

15 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 (25th-75th percentiles) according to the distribution of the variable. Qualitative variables will be reported as numbers (%).

36
3720Analysis 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.

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APPENDICES

- Appendix A: List of study sites
- Appendix B: Model of the consent form
- Appendix C: SPIRIT Checklist

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Modifiable risk	Objective	Modalities
factor		
Hypovolaemia	$MAP \ge 65 \text{ mmHg with no}$ 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
Нурохаетіа	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

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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	С	
Rate control strategy	C	С	
Rhythm control strategy	C	С	
Assessments			
Characteristics of the patient	C		
Characteristics of the septic shock	C	С	С
Organ dysfunction and management	C	С	
Thyroid blood sample	C		
Other biological data	C		
Cardiac rhythm	C	С	
Duration of septic shock			С
Adverse event(s)			С
ICU length of stay and hospital length of stay			С
Vital status			С

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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

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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 **Contact for Public Queries** Gladys Monthieux, URC-Est - Hôpital Saint Antoine, Bat. Couvelaire, 184 rue du Fbg Saint Antoine - 75571 Paris cedex 12, France. Email: gladys.monthieux@aphp.fr .Telephone number: + 33 (0)1.49.28.22.02 **Contact for Scientific Queries** Vincent Labbé, Hôpital Erasme, Route de Lennik, 808. 1070 Brussels - BELGIUM . E-mail: vincent.labbe@hubruxelles.be Telephone number: +322 555 5126. Fax number: +322 555 4698. **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

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.





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APPENDICE A: list of study sites

	1	1	1		
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	Réanimation1 av du PrPolyvalenteJean Poulhès		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 réanimationCentre Hospitalier Universitaire Ambroise ParéService de soins intensifs		9, avenue. Delmée	7500	Tournai	Belgique
			2, Boulevard Kennedy	7000	Mons	Belgique

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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) 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.

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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 10 your first visit.

11 Once you have read and signed the consent form, you will be randomised to the risk control, rate control or rhythm control 12 strategy, which will start immediately. This randomisation corresponds to the first day of the trial (D1). You will receive the 13 randomised strategy for 7 days, from D1 to D7. Your monitoring data (routine clinical examinations and blood tests) will be 14 collected daily during your hospital stay. 15

If you leave the hospital before day 28, a clinical trial technician will contact you on day 28 to check your health. 16

What are the benefits of your participation? 4)

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.

58 This data processing is necessary in order to carry out research of public health interest, in line with AP-HP's mission as a 59 public university hospital. 60

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.

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Your data may be used for further research or complementary analysis in collaboration with private or public partners in 1 France or abroad, under conditions that guarantee their confidentiality and the same level of protection as required by 2 European legislation. 3 You may at any time object to any further analysis of your data by informing the doctor who is following you in this research. 4 5 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 6 the data manager's information systems for two years after the last publication of the research results. Your data will then be 7 archived in accordance with the regulations in force. 8 9 The database used for this research is created in accordance with French law (modified "Informatigue et Libertés" law) and 10 European law (Règlement Général sur la Protection des Données - RGPD). You have the right to access, modify, limit and 11 object to the processing of data covered by professional secrecy and used in the context of this research. These rights can be 12 exercised with the doctor in charge of the research, who is the only person who knows your identity (identified on the first 13 page of this document). 14 15 If you decide to discontinue your participation, the data collected prior to this decision will be used in accordance with the 16 regulations and exclusively for the purposes of this research. Deletion of this data would compromise the validity of the 17 research results. However, from that point on, your data will no longer be used in this research or in any other work. 18 19 20 If you have a problem concerning your rights, you can contact the AP-HP Data Protection Officer at the following address: 21 protection.donnees.dsi@aphp.fr, who will be able to explain the channels available to you with the CNIL. You may also 22 exercise your right to complain directly to the CNIL (for more information on this subject, please visit www.cnil.fr). 23 24 10) How is this research supervised? 25 26 AP-HP has taken all the measures necessary to carry out this research in compliance with the public health regulations 27 applicable to research involving human volunteers. 28 29 AP-HP has taken out an insurance policy (number 0100518814033 200013) with its insurance broker BIOMEDICINSURE, 30 whose address is Parc d'Innovation, Bretagne Sud C.P.142 56038 Vannes Cedex, to cover its civil liability and that of all its 31 collaborators. 32 33 AP-HP has been approved by the Ethics Committee (CPP Sud-Ouest et Outre-Mer III) on [29/07/2020] and by the Agence 34 Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) on 21/02/2020. 35 36 11) What are your rights ? 37 38 39 Your participation in this research is free and voluntary. Your decision will not affect the quality of care and treatment you 40 receive. 41 42 Before you agree to take part in this research, you will undergo an appropriate medical examination, the results of which will be 43 reported to you. 44 45 Throughout the study, and at any time, you can ask your investigator for further information about your health and explanations 46 of the research process. 47 48 You can withdraw from the research at any time without explanation, without any impact on your treatment or the guality of care 49 you receive, and without any impact on your relationship with your doctor. After this withdrawal, you may be followed by the 50 same medical team. In this case, the data collected up to the time of withdrawal will be used to analyse the research results. 51 52 Your medical file will remain confidential and can only be consulted under the responsibility of the doctor in charge of your 53 treatment, as well as by the health authorities and persons authorised by AP-HP for research and bound by professional 54 confidentiality. 55 56 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 57 the study. 58 59 60 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 from at the tend of this doctiment. At the tend of this doctiment.

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CONSENT FORM

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8					
9	I, the undersigned, Mrs, M	Vr [delete as appropriate] (first	t name, surname)		agree to voluntarily
10	participate in the study ent	itled			
11	"Comparison of three ma	anagement strategies for de r	novo supraventricular ar	rhythmias in s	eptic shock: a randomised
12	controlled trial." sponsor	red by Assistance Publique -	Hôpitaux de Paris and I	was informed !	by Dr./Pr. (name, surname,
13	telephone)	· · · · ·	investigator o	of this study.	
14			,	· · · · · · ,	
15	- I have read the Invitation	to Participate version 3.0 dated	1 19 6 2023 (4 nages) whi	ch explains the	purpose of this study how
16	it will be conducted and w	bat my participation will entail.	a 10.0.2020 (1 pagoo), wiii		purpose of the study, now
17	I will keep a copy of the i	nvitation to participate and the i	nformed consent form:		
18	- I will keep a copy of the li	answere to all my questione:			
19	- I have received adequate	answers to an my questions,			
20	- I have had enough time t	ticination is free of charge and	that I am atom my northeir	nation of any fir	as without any lightlifty and
21	- I understand that my par	licipation is nee of charge and	that I can stop my particip	Jation at any tin	he without any hability and
22	without affecting the quality	y of care i receive;	and was be used for all		that I want altient to this at
23	- I have been informed that	at the data collected in the rese	earch may be used for oth	er studies and	that I may object to this at
24	any time;				1 2 0
25	- I understand that my part	icipation may also be interrupte	ed at any time by the docto	r, who should e	xplain the reasons;
20	- I have undergone a medi	cal examination appropriate to	the research prior to taking	g part in this res	search, the results of which
27	have been communicated	to me;			
28	- I am aware that, in order	to participate in this research,	I must be affiliated to or a	beneficiary of a	a social security scheme. I
29	confirm that this is the case	e;	6		
21	- I have been informed that	at my participation in this resea	arch will last for 28 days, d	luring which tim	ie I cannot consider taking
22	part in any other research	without informing the investigat	ing physician in charge of	my case in this	study,
22	- My consent does not in a	any way relieve the doctor follo	wing me in the research o	r AP-HP of any	responsibility, and I retain
31	all the rights guaranteed to) me by law.			
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38	Signature of the participa	ating person	Signature of	f the doctor	
39					
40	First name, Surname:		Fist name, Si	urname:	
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43	Date:	Signature:	Date:		Signature:
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53	This document must be produ	ced in three copies: one copy must	be kept by the investigator fo	r 15 years, the sec	cond given to the consenting
54	person, and the third sent to A	IF-HP III a sealed envelope at the en	iu or the study.		
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Standard Protocol Items: Recommendations for Interventional Trials

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

Section/item	ltemNo	Description	Repored on page NO
Administrative inf	formation		27-28-29
Title		Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Frial 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

1 2 3 4 5 6 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
8 9		6b	Explanation for choice of comparators	7
10 11	Objectives	7	Specific objectives or hypotheses	8
12 13 14 15 16 17 18	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
20	Methods: Participa	nts, inter	rventions, and outcomes	
22 22 23 24 25 26	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
27 28 29 30 31 32	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
33 34 35 36	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
37 38 39 40 41 42		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
43 44 45 46		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
47 48 49 50 51		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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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: Assignme	ent of in	terventions (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

1 2 3 4 5		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
6 7	Methods: Data coll	ection, n	nanagement, and analysis	
8 9 10 11 12 13 14 15 16 17 18 19	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
20 21 22 23 24		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
25 26 27 28 29 30 31 32 33	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
34 35 36 37 38	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
39 40 41 42		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14,15
42 43 44 45 46 47		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
48 49	Methods: Monitorir	ng		
50 51 52 53 54 55 56 57 58 59 60	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

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		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	1	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 a	and dissem	ination		
Researd approva	ch ethics Il	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protoco amendn	l nents	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
Consen	t 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
Confide	ntiality	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
Declara interests	tion of S	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 trial care	y and post- e	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			
1	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 recomme Explanation & Elabor protocol should be transformed by the Group under the Cre license.	nended t ration for acked an ative Cor	hat this checklist be read in conjunction with the SPI important clarification on the items. Amendments to ad dated. The SPIRIT checklist is copyrighted by the mmons " <u>Attribution-NonCommercial-NoDerivs 3.0 Ur</u>	RIT 2013 the SPIRIT nported"