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Protocol for fever control using external cooling in mechanically ventilated patients with septic shock: SEPSISCOOL II randomised controlled trial

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ABSTRACT

Introduction Fever treatment is commonly applied in patients with sepsis but its impact on survival remains undetermined. Patients with respiratory and haemodynamic failure are at the highest risk for not tolerating the metabolic cost of fever. However, fever can help to control infection. Treating fever with paracetamol has been shown to be less effective than cooling. In the SEPSISCOOL pilot study, active fever control by external cooling improved organ failure recovery and early survival. The main objective of this confirmatory trial is to assess whether fever control at normothermia can improve the evolution of organ failure and mortality at day 60 of febrile patients with septic shock. This study will compare two strategies within the first 48 hours of septic shock: treatment of fever with cooling or no treatment of fever.

Methods and analysis SEPSISCOOL II is a pragmatic, investigator-initiated, adaptive, multicentre, open-label, randomised controlled, superiority trial in patients admitted to the intensive care unit with febrile septic shock. After stratification based on the acute respiratory distress syndrome status, patients will be randomised between two arms: (1) cooling and (2) no cooling. The primary endpoint is mortality at day 60 after randomisation. The secondary endpoints include the evolution of organ failure, early mortality and tolerance. The target sample size is 820 patients.

Ethics and dissemination The study is funded by the French health ministry and was approved by the ethics committee CPP Nord Ouest II (Amiens, France). The results will be submitted for publication in peer-reviewed journals.

Trial registration number NCT04494074.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Study feasibility tested in a pilot trial.
⇒ Use of adaptive randomisation to control group comparability.
⇒ Use of conditional power at interim analysis to determine the probability of obtaining a positive result.
⇒ Stratification based on the presence of acute respiratory distress syndrome to detect different response to treatment.

INTRODUCTION

Background and rationale

Sepsis is a common syndrome responsible for multiple organ failure and septic shock, which lead to a high mortality rate.[1] Patients with septic shock typically experience a disproportionate host response to infection so that fever may contribute to excessive inflammation and worsen organ failure. Fever has a high metabolic cost, so cooling febrile critically ill patients reduces their heart rate, cardiac output and oxygen consumption.[2] The deleterious effects of fever on inflammation have mostly been shown in experimental models of acute lung injury.[3–6] Because experiments have also reported protective effects of heat stress on host defences and lung inflammation, the controversy persists.[7] It remains unclear whether fever or the physiological

response to fever causes morbidity, and whether management of fever with pharmacological agents or physical cooling confers benefit. The benefit-to-risk ratio of fever treatment may be favourable in the presence of severe infection.[8 9] Fever is associated with worse disease evolution in patients with acute respiratory distress syndrome (ARDS).[10] Reducing oxygen demand, cardiac output, right-to-left lung shunt and carbon dioxide CO2 production can increase partial pressure of oxygen PaO2 and allow more protective ventilation strategies.[11 12] As trials have reported harmful effect of induced hypothermia in sepsis, avoiding hypothermia represents an important goal when controlling fever.[13 14]

The SEPSISCOOL-I (SC-I) pilot study focused on febrile patients with septic shock and compared a strategy of fever control using external cooling to no fever treatment.[15] Cooling significantly improved organ function and decreased mortality on day 14 with an adjusted OR of 0.36 (95% CI 0.17 to 0.76). There were no significant adverse events (AEs) observed in the cooling group. Of note, the need for sedation had to be included to limit the risk of shivering and to produce a metabolic benefit.[2] There was a trend towards a higher incidence of early acquired nosocomial infection in the cooling group. Discrepant results regarding the risk of acquired infection when using fever control have been reported.[16 17]

Only six randomised controlled trials (RCTs) assessing fever treatment in intensive care unit (ICU) patients with infection have reported mortality. Four of these RCTs used pharmacological intervention and two used external cooling.[15 18–22] The efficacy in controlling fever was higher when using cooling.[23] Two meta-analyses in adult ICU patients, with or without sepsis, concluded that active temperature management neither increases nor decreases the mortality risk.[24 25] Drewry *et al*[24] reported a relative risk (RR) of 0.93 (95% CI 0.77 to 1.13) and Dallimore *et al*[25] reported an RR of 1.01 (95% CI 0.81 to 1.28). The wide CIs indicate uncertainty in the estimate of the treatment effect. The authors of these meta-analyses did not take into account the severity of the treated patients. An individual personal data meta-analysis assessed fever control in adult ICU patients according to their baseline characteristics.[23] The RR of reducing death using fever control was the largest (22%) among patients requiring invasive mechanical ventilation and vasopressor (OR 0.72, 95% CI 0.50 to 1.04); the CI includes a potential clinically important benefit of fever control in this subgroup of the most severe patients.

OBJECTIVES AND OUTCOMES

Primary objective and outcome

The study hypothesis is that a strategy of fever control at normothermia using external cooling will significantly reduce mortality at day 60 after randomisation compared with no fever treatment.

Secondary objectives and outcomes

The following secondary outcomes will be examined:

1. Evolution of organ failure assessed by organ-support-free days on day 28 and evolution of the Sequential Organ Failure Assessment (SOFA) score.
2. Acute kidney injury (AKI, based on the creatinine Kidney Disease Improving Global Outcomes criteria)[26] up to day 7, criteria to initiate renal replacement therapy (RRT)[27] and to start new RRT up to day 28.
3. ARDS acquired after randomisation up to day 3.[28]
4. Mortality at day 28 after randomisation.
5. Incidence of secondary ICU-acquired nosocomial infections through day 28.
6. Tolerance of the two strategies:
   - The number of patients with shivering through 48 hours.[29]
   - The number of patients with seizures through 72 hours, clinically documented and/or proven by electroencephalography.
   - The number of patients with hypothermia through 72 hours defined by a core body temperature below 36°C.
   - The number of patients with >1 new episode of supraventricular or ventricular cardiac arrhythmia through 72 hours.

Study design

SEPSISCOOL-II is an investigator-initiated, pragmatic, multicentre, open-label, randomised controlled, superiority trial. Primary outcome across two parallel groups in a 1:1 ratio is assessed on statistical difference. After stratification based on the presence of ARDS, adaptive randomisation and an adaptive multistage population-enrichment design will be used.[30 31] Inclusions started on October 2022. We complied with the SPIRIT 2013 checklist (https://www.spirit-statement.org/spirit-statement/) recommendations for this protocol draft (see online supplemental material 1) and provided all WHO Trial Registration Data Set (see online supplemental material 2).

Rationale for adaptive study design

To test the hypothesis that patients with ARDS will benefit the most from fever control

Determining groups of patients who are more likely to benefit from treatments represents an important goal for individualised medicine.[32 33] Heterogeneity decreases the likelihood that studies will show treatment benefits. The same intervention can benefit one group but worsen another.[34 35] A multistage population-enrichment design has been proposed to adapt the study design in the presence of different treatment effects among groups of patients.[30] Two prespecified strata of patients according to the presence or the absence of ARDS will be identified at randomisation.[30 31] According to data from the pilot study, half of the included patients are expected to present with ARDS.[15]

To ensure balance at interim and final analyses

The trial intervention is not masked for the investigators, healthcare workers and patients, as blinding of cooling is not feasible. This increases the risk of a selection bias of the included patients, resulting in non-comparable groups. Increasing the number of patients reduces the risk of imbalance. Notably, interim analyses are performed on necessarily small populations, but balance in important predictors is required to permit confident decisions. Adaptive randomisation based on predictors of mortality would ensure balance at interim and final analyses, helping to make adequate decisions on study continuation and interpretation of the final results.[36]

To warrant adequate power

Available outcome data on febrile patients with the Sepsis-3 criteria are limited.[37] An adaptive design with sample size reassessment at interim analysis based on the conditional power (CP) observed between the cooling and no cooling group will ensure the study has sufficient power.

METHODS AND ANALYSIS

Eligibility criteria

Patients with septic shock defined by the Sepsis-3 definition will be screened for enrolment.[37] Only patients requiring invasive mechanical ventilation and sedation will be included. Sedative treatments are mandatory to avoid induction of shivering. There is no consensus regarding the definition of fever; the same threshold applied in the pilot study will be used—that is, 38.3°C.

There is no maximal delay for inclusion after the start of vasopressor. Fever can occur later when a patient comes from the operating room or is hypothermic at the initial phase of shock. However, at the time of inclusion and randomisation patient must still need vasopressor.

Patients with other indications for temperature control will not be included (table 1).

Intervention

Fever management

Interventions for fever management is applied by the ICU team similarly to the sepsiscool-I trial.[15] In the experimental group, fever is controlled by external cooling during the first 48 hours following randomisation. The objective of cooling is to maintain normothermia at 36.5°C–37°C over 48 hours. Cooling is applied by automated surface methods according to the technique available in each centre. The temperature target is set at 36.7°C.

In the control arm, no cooling must be applied. No intervention switch is allowed within the trial. Antipyretic methods are not allowed except when fever surpasses 41°C. A subject may be discontinued from allocated intervention at any time if the investigator or the sponsor feels that it is not in the subject's best interest to continue. If a subject is withdrawn from allocated intervention due to an AE, the subject will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilised.

Other interventions in the two groups

Septic shock management is let at the discretion of clinical staffs according to usual centre practices. Weaning of vasopressors is performed according to the algorithm used and published in the sepsiscool-I pilot trial.[15] Management of ARDS is performed according to French expert guidelines.[38]

Table 1 Eligibility criteria

Inclusion criteria	► Documented or suspected infection, either community or hospital acquired ► Ongoing antimicrobial treatment and/or intervention for infection source control (eg, surgical drainage) ► Septic shock defined by the need for vasopressors (epinephrine or norepinephrine) to maintain mean arterial pressure >65 mm Hg and lactate >2 mmol/L despite adequate fluid resuscitation ► Patients under invasive mechanical ventilation ► Core body temperature >38.3°C ► Intravenous sedation or opioids ► Attending physician confirms clinical equipoise without substantial risk if the patient participates in the trial ► Consent of the patient or the family or the next of kin before inclusion or inclusion in emergency procedure by the investigator
Exclusion criteria	► Cardiac arrest within the previous 7 days ► Acute brain injury within the previous 7 days ► Extensive burns or epidermal necrolysis ► <18 years ► Core body temperature >41°C ► Under legal guardianship ► No affiliation with the French healthcare system ► Pregnancy ► Patient already recruited in the trial ► Participation in another interventional study with mortality as the primary endpoint ► An investigator's decision not to resuscitate

Sample size calculation

Justification of estimations

The Sepsis-3 definition of septic shock will select patients with a higher mortality risk than those reported in older studies.[35 39] The expected mortality has been extracted from the results of the pilot study and from the databases of two RCTs performed in France (ie, 'HYPER2S' and 'SEPSISPAM') among patients meeting the Sepsis-3 criteria (n=698 patients).[15 40 41] Half of the patients had ARDS and the observed mortality was 54%; mortality was similar among patient with and without ARDS.

In a meta-analysis of personal data, the RR of death using fever control among patients requiring mechanical ventilation and vasopressors was 22% (OR 0.72, 95% CI 0.50 to 1.04).[23] The RR difference estimation in large RCTs comparing two treatments for sepsis was 22% in the 'HYEPR2S', 'SEPSISPAM', 'CASS' and 'APROACCHSS' studies. The RR difference estimations in large RCTs comparing treatments for ARDS were 19% in the 'PETAL' study and 33% in 'EPVent-2' study.[13 40–44]

Hypotheses

An expected mortality of 52% with an expected RR of death of 19% is assumed. The hypothesis is to reduce mortality at day 60 from 52% to 42%. For a two-sided alpha of 5%, a power of 80% and a cooling-to-no cooling ratio of 1:1, 780 evaluable patients are needed. Due to lost to follow-up or other reasons, the final sample size of 820 patients is planned. The calculation was performed using the nQuery V.8 software (PTT0).

Randomisation

ICU medical investigators complete the process of informed consent and randomise the patients during their ICU stay. The treatment arm allocation will be provided by an interactive web response system (IWRS). After randomisation, cooling will be initiated immediately in patients allocated to the experimental group (figure 1). Allocation will be performed by stratification based on ARDS and by covariate-adaptive procedures. The ARDS criteria and the following patient characteristics—known to be strong predictors of mortality—will be recorded and added to the IWRS at randomisation to power the algorithm and ensure to the groups are balanced:

- Immunosuppression (ie, cancer chemotherapy, HIV, corticosteroids >1 mg/kg and/or >1 month, solid organ transplant, bone marrow transplant, immunosuppressant drugs for autoimmune disease).
- Arterial oxygen partial pressure to fractional inspired oxygen PaO_2/FiO_2 ratio (≤4 hours before randomisation).
- Lactate level (≤4 hours before randomisation).
- Age.
- Vasopressors (epinephrine+norepinephrine).
- Clinical centre of randomisation.

The aforementioned characteristics are routinely monitored: their real-time availability guarantees the feasibility and the robustness of the real-time successful randomisation. These variables will be monitored and recorded in the study database. Hence, the distribution of covariates will be continually updated as the trial progresses.

Dynamic hierarchical randomisation will be used to tackle the challenges of balancing a large number of stratification variables.[45] The minimal sufficient balance randomisation method developed by Zhao *et al*[46] will be implemented. As recommended by regulators, a random component will be incorporated to reduce

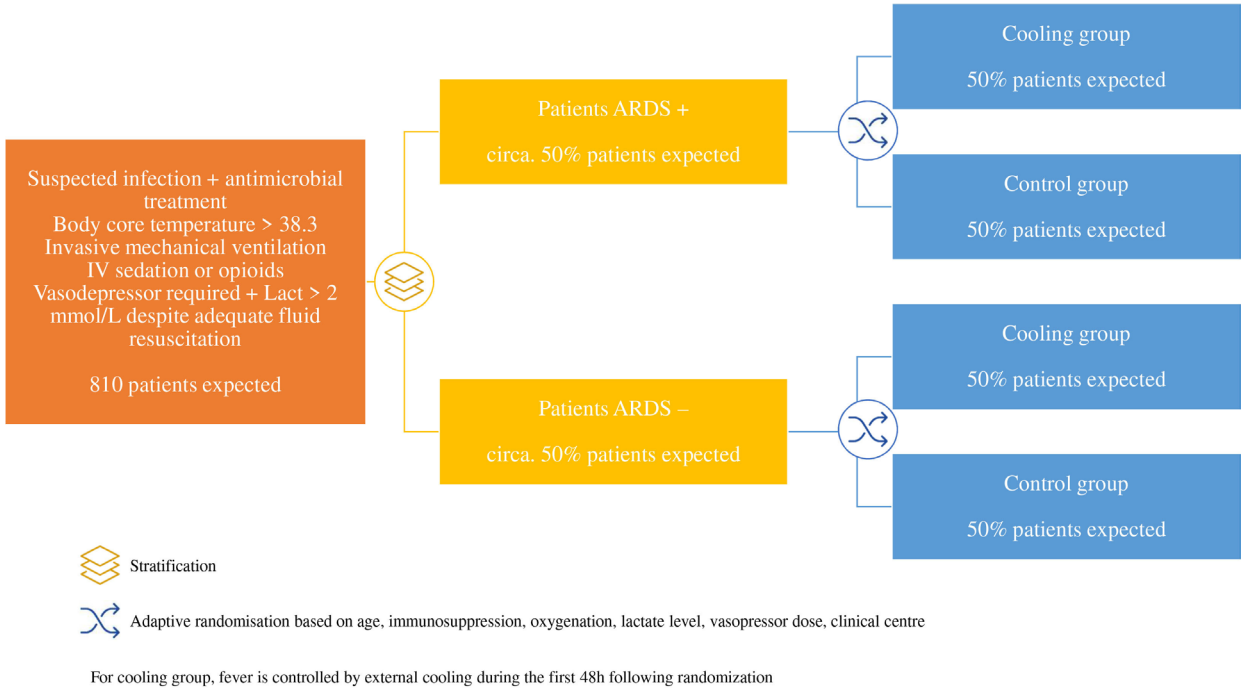

Figure 1 SEPSISCOOL-II trial design. ARDS, acute respiratory distress syndrome.

the predictability of the allocation.[47 48] The imbalance control limit will be set to p≥0.3 for all covariates, and the covariate-adaptive allocation procedure will start after 20 patients have been randomised in each ARDS stratum.[46] For each covariate (either continuous or categorical), a vote is conducted to decide whether this covariate should be selected for the randomisation and how to reach balance. The algorithm then allocate the definitive arm, with a predefined probability, according to the results of the votes for the selected covariates. This process is performed for each new participant.

Development and test of the algorithm

The proposed algorithm for randomisation has been tested internally and widely on simulated data (>10 000 datasets simulated). Nineteen scenarios were computed and included worst-case and best-case schemes. Once we will have fully implemented the randomisation in this study, a separate research paper will provide a comprehensive overview of all relevant developments (ie, simulations and real-world data) used for assessing and validating the performances of the proposed algorithm.

Blinding

As blinding of cooling is not feasible, the trial intervention is not masked for investigators, healthcare workers and patients. Several methodological aspects limit the risk of bias. First, adaptive randomisation precludes the risk of allocation expectation. Second, interim and final statistical analyses will be performed by independent statistician. At interim analysis, the need for a blind break is let at the discretion of the data monitoring committee (DMC). Third, the primary endpoint of the study, that is, mortality, is unlikely to be influenced by the lack of blinding. Fourth, the majority of secondary endpoints are specifically recorded for the study according to strict definitions. However, they are not validated by an endpoint adjudication committee.

Data collection

All information on data collection methods and management can be found in the protocol version V.3.0 dated 8 June 2023.

Method and timing

Data will be collected on an electronic case report form (CRF) by a trained investigator or research technician among 27 French hospitals (see exhaustive list in online supplemental material 3). Research assistants will regularly monitor all centres on site to attest to protocol adherence and the accuracy of the recorded data. The details of the recorded data are indicated in online supplemental material 4.

Quality control

A plan for quality control will be established prior to the beginning of the study. This plan of monitoring, tailored to the specific human subject protection and data integrity risks of the study, will describe the strategy, methods, responsibilities of all parties involved, and requirements for monitoring the study.

Statistical methods

Except where mentioned otherwise, for all analyses (primary, secondary and interim), two-sided p<0.05 will be considered statistically significant. The strategy for design, analysis and report will be made in compliance with the Consolidated Standards of reporting Trials CONSORT statement (http://www.consort-statement.org/). Any modification of the presented statistical analysis strategy will be indicated in the final publication.

Compliance with the protocol and study treatment

Protocol deviations will be described prior to database lock in a blinded fashion regarding either the use of cooling or antipyretic drugs in the control group or no cooling performed in the experimental group. This step will lead to establishing the populations (randomised and treated per protocol).

Demography and clinical characteristics at baseline

Demographic and clinical characteristics of patients at baseline (H0) will be compared between the two groups according to standard statistical tests: Student's t-test or the non-parametric Wilcoxon test for quantitative parameters (based on the variable's distribution) and the χ^2 test or Fisher's exact test for qualitative parameters. The results will be presented as mean±SD if the parameter follows a normal distribution and median (IQR) if the parameter follows another distribution.

Primary analysis

Principal analysis on primary endpoint

The difference in the proportion of deceased patients through day 60 after randomisation will be compared using logistic regression in the randomised population according to the intention-to-treat principle.[49] The following hypotheses will be tested:

- H0: $p_{cooling} - p_{no\ cooling} = 0$.
- H1: $p_{cooling} - p_{no\ cooling} \neq 0$.

The results will be presented overall (pooled ARDS strata) as the absolute difference and 95% CI (unbiased estimates). After programming, closed testing together with the p value combination function will be performed to control for type I errors.

Sensitivity analysis on primary endpoint

The model used for the primary analysis will be challenged at the end of the study with the following (but not limited to) sensitivity analyses:

- The analysis will be repeated on the per-protocol population, that is, all randomised patients without any major protocol deviation.
- An analysis based on the 'worst-case scenario' may be considered for patients with missing vital status information at day 60.
- A survival analysis will be conducted using Kaplan-Meier curves and the associated log-rank test.

Secondary analyses

Evolution of organ failure

Evolution of the SOFA score between day 0 and day 7 will be analysed using a mixed model for repeated measures, with a random patient effect (subject's intercept) and an interaction term time×patient (subject-specific evolution).

Organ-support-free days—that is, ventilator, vasopressors and RRT from randomisation to day 28—will be assessed as proposed by Yehya *et al*.[50] The number of free days between the two treatment groups will be compared by Student's t-test or the non-parametric Wilcoxon test for quantitative parameters (based on the variable's distribution).

The proportions of patients with AKI through day 7 and the proportion of patients who develop ARDS after randomisation through H72 will be compared using a logistic regression as described for the primary analysis.

Day 28 mortality

Day 28 mortality will be compared between the two treatment groups using logistic regression as described for the primary analysis.

Expected AEs

The proportion of patient with shivering hypothermia, new cardiac arrhythmia through 48 hours and seizure through 72 hours will be compared between the two treatment groups using a logistic regression as described for the primary analysis.

The incidence of secondary ICU-acquired nosocomial infections through day 28 will be reported for 1000 ICU days and compared by Poisson or negative-binomial regression according to overdispersion and zero-inflation of the data.[15] The definitions used for nosocomial infections are indicated in online supplemental material 5.

Preplanned subgroup analysis

The effect of cooling on all-cause mortality at day 60 (primary endpoint) will be assessed among the subgroups of:

- ARDS status.
- Immunosuppressed patients.
- Patients not receiving treatment potentially influencing temperature evolution, that is, steroids and RRT.
- Patients randomised less than 12 hours after vasopressor start.

Interim analyses

A first interim analysis will be performed after enrolment of 200 patients for safety assessment only. Exploratory outcomes, mortality at day 28, the Simplified Acute Physiology III score and variables used in the algorithm for adaptive randomisation will be provided to the DMC. Data will be presented for four groups according to the ARDS strata and study arms (ARDS YES with cooling YES, ARDS YES with cooling NO, ARDS NO with cooling YES, ARDS NO with cooling NO) in a blinded fashion. No statistical test will be performed between groups; the decision to stop the study for safety reason will be let at the discretion of the DMC.

A second interim analysis is planned after enrolment of 50% of patients. In addition to the data listed above, the number of patients receiving antipyretics in the no cooling group and mortality at day 60 will be provided. Interim analysis will be performed by a blinded independent statistician. The sponsor and all investigators will be kept blinded to the data and the interim analysis results. The decision for breaking the randomisation code will be let to the discretion of the DMC.

Statistical criteria for termination of the study at the second interim analysis

Because of the limited number of subjects at interim analysis, early stop for efficacy may strongly increase the type I error.[51] The stopping rules are planned for futility only.

For each ARDS stratum, the CP (ie, the probability of rejecting the null hypothesis at the final stage of the trial, given the current data) calculated by the method proposed by Metha and Pocock, applying stochastic curtailment. The calculation will be made according to (a) the observed difference of the primary endpoint between the experimental and control group at the interim step and the interim information level computed as a function of (b) the observed number of patients in each treatment group at the interim step and (c) the average of primary endpoint expected in the experimental and in the control groups in the original trial planning .[30 52 53] In the absence of an ARDS stratum effect (CP similar in the two strata), then we will compute a unique CP by pooling the strata (figure 2A); else if the CP is different between the two strata, then we will make two separate decisions depending on the CP of each stratum (figure 2B,C). Three zones for CP-based decision-making are defined as follows:

- Unfavourable: CP<CP_{min}, the CP_{min} cut-off value will be set at 10%.
- Promising: CP_{min}<CP < 80% (1–β).
- Favourable: CP>80%.

If CP falls in the unfavourable zone, the stratum or study will be stopped. If the CP falls in the promising zone, the sample size will be re-estimated based on the considered ARDS strata or whole population. If the CP falls in the favourable zone, the stratum or study will continue with the initial sample size estimation. The decision-making process is summarised in the figure 2. Depending on the inferential statistical results at this interim analysis, the DMC will make one of the following recommendations:

- To continue the trial to the final step with both ARDS strata (initial sample size prevails).
- To continue the trial with enrichment for both ARDS strata after sample size reassessment.
- To continue the trial to the final step for one ARDS strata (initial sample size prevails) with enrichment for the other strata after sample size reassessment.

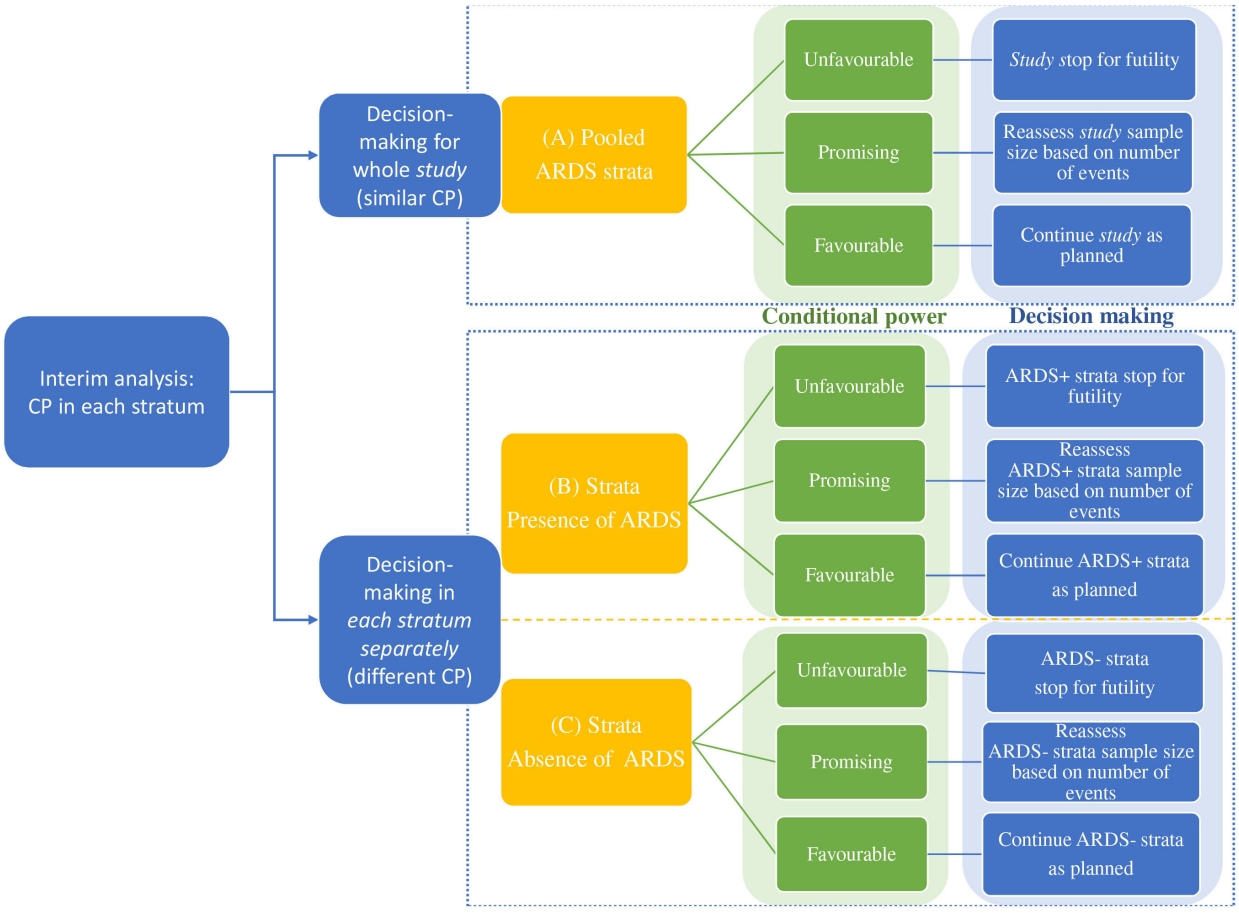

Figure 2 Interim analyses and rules for decision-making. See the text for the definition of conditional power. (A) Absence of the acute respiratory distress syndrome (ARDS) stratum effect; (B) effect of cooling in favour of ARDS; (C) effect of cooling in favour of no ARDS. CP, conditional power.

- To stop one ARDS strata and to continue the trial without enrichment for the other strata (initial sample size prevails).
- To stop one of the two ARDS strata and to continue the trial with enrichment for the other strata after sample size reassessment.
- To completely stop the study.

For strong control of the familywise error rate at the set alpha level, the use of the closed testing principle is planned at the very end of the study (any elementary hypothesis must be rejected alone, but all intersections that contain this elementary hypothesis must also be rejected) together with a p value combination function to combine the p values observed at each stage of the sequential design.[30 54 55]

Missing data management

During data management, invalid data will be considered missing data. Except when stated otherwise, no imputation is planned for either the primary or secondary analyses.

Data monitoring

Data monitoring committee

The DMC comprises three clinicians and one statistician (see composition in online supplemental material 6). Collectively, they have experience in the conduct, monitoring and analysis of RCTs. None of the members are directly involved in the study. DMC membership is restricted to individuals free of conflict of interest, and each member has signed a conflict of interest form. The DMC has approved the study protocol and the operating charter (further details in version v1–0 dated 23 December 2020).

At interim analysis, the committee will monitor the rate of inclusion and recorded expected adverse effects and will make the final decision to terminate the study or not. Results of interim analysis on day 60 mortality will be provided as well as the incidence of expected adverse effects. Patients' characteristics recorded at randomisation for treatment allocation will be also provided. Because the study is at minimal risks, no rules will be defined to stop the study for safety reasons but early stop for safety reasons will be left at the discretion of the DMC.

Monitoring of AEs

This study will not test drugs, devices or human products, which has been classified by the ethics committee as a trial exposing patients to minimal risks and constraints. Patients with septic shock are at high risk for developing complications no matter the strategy of fever

management. Therefore, serious AEs will not be recorded as an entity. The most important AEs will be captured in the exploratory outcome measures: death, seizure, shivering, nosocomial infections, cardiac arrhythmia and skin lesions related to surface cooling. The list was validated by the DMC.

ICU patients are closely monitored 24 h a day by expert nurses and physicians allowing rapid detection of AEs.

According to the French law, in study at minimal risks and constrains, vigilance and safety reporting will correspond to those performed in usual care. AEs will be reported to the corresponding agency 'pharmacovigilance', 'materiovigilance' or 'biovigilance'. A monitoring of expected adverse effects will be specifically performed for the study. The following known and expected adverse effects will be notified in the CRF but not reported to the sponsor (Article R1123-49): death, seizure, shivering, nosocomial infections, cardiac arrhythmia, skin lesions related to surface cooling.

Data availability statement

According to the Best Clinical Practice, the coordinating investigator permits the direct access to the trial documentation to any authorised party to examine, analyse, verify and reproduce any records and reports for evaluation of a clinical trial.

The sponsor and the clinical research unit of Assistance Publique Hôpitaux de Paris APHP–Hôpital Européen Georges Pompidou, in charge of the statistical analyses, will have access to the final trial dataset. Datasets and statistical code are not publicly available but request on access may be submitted to the corresponding author or to the sponsor (clinical research unit, Centre Hospitalier Intercommunal de Créteil, 40 avenue de Verdun, 94 000 Créteil, France).

No additional data are available at this date.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

DISCUSSION

The SEPSISCOOL-II trial was developed to provide evidence on the beneficial effect of fever control at normothermia by external cooling in a selected population of severe patients expected to benefit the most from this treatment.

Strengths

The hypothesis tested in the SEPSISCOOL-II trial comes from current evidence reported prior to study development in systematic reviews. The feasibility has been tested in a pilot RCT.[15] The design is an adaptive multicentre, randomised controlled, superiority trial allowing adaptations for collected evidence. Interim analyses are key to refine the effect of cooling in patients with ARDS. We will conduct an interim analysis after 50% of the participants have been followed for 60 days to allow early identification of the treatment response according to whether ARDS is present and to adapt the study continuation according to strict rules. The confidence in making the decision will be increased assuming between-group comparability. When validating the algorithm, imbalance across clinical centres and heterogeneity based on randomisation variables have typically been studied and did not lead to considerable impact on randomisation process.

Several methods of adaptation in randomisation have been described, but few have been tested in the reality of a clinical trial. This trial will use the method of Zhao *et al*,[46] which has been applied in a large RCT (NCT04494074) to control the between-group balance in a population at risk for heterogeneity, as regularly observed in studies on septic shock.

Limits

To construct the randomisation algorithm, we selected a priori variables previously found to be associated with mortality in patients with septic shock. The drawback of this approach is the need to include variables that are trustworthy and easily available at the time of randomisation and at each clinical site. This is the reason why we did not select calculated predictive scores. Other factors influencing the primary endpoint could lead to imbalances between the groups. Sensitivity analysis with adjustment is planned to limit that risk.

The trial intervention is not masked for investigators, healthcare workers and patients, as blinding of cooling is not feasible. Hence, there is an increased risk of bias. However, our primary outcome on mortality is unlikely to be affected by the lack of blinding.

Participants may be subjected to protocol violations, expected to occur more frequently in the no cooling group. To maximise protocol compliance, the inclusion criteria include the investigator's agreement with equipoise for fever treatment.

ETHICS AND DISSEMINATION

Ethics

The clinical research unit of the Centre Hospitalier Intercommunal de Créteil is the sponsor of the trial. The patients will be not able to provide informed consent; therefore, a process of deferred consent will be applied. Their next of kin or other designated persons available at screening will be requested to express their wishes to include the patient and to sign an informed consent form. As soon as possible, a definitive post hoc consent form will be obtained from each patient to continue to participate in the study.

The protocol, informed consent forms and subject information sheet have been reviewed and approved (no: 20.11.27.66122) by a French ethics committee (Comité de Protection des Personnes Nord Ouest II (Amiens, France)). For any major change in the protocol, the

sponsor will request the approval of the ethic committee (article L. 1123-9), inform the French health authority (ANSM), the investigators and the DMC, and update trial registry ClinicalTrials.gov.

The data will be recorded and managed in compliance with the French Data Protection Act and with the European Data Protection Regulation before, during and after the study. All original records will be archived at the trial sites for 15 years.

This manuscript corresponds to V.3.0 dated 8 June 2023.

Dissemination

Communications and scientific reports corresponding to this study will be carried out under the responsibility of the coordinating investigator (Frédérique Schortgen) with the agreement of all investigators. Publications will be approved by the statistician of the clinical research unit of Assistance Publique Hopitaux de Paris APHP–Hopital Européen Georges Pompidou (Armelle Guénégou-Arnoux), the coordinating investigator and all the investigators. The coordinating investigator, the statistician and the investigators of trial sites with at least one inclusion will be granted one authorship. Publication rules will follow international recommendations.[56] Participants will be informed of the overall results of the study, if wished (Article L1122-1). We do not intend to use professional writers at this date.

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Contributors AA, SK and FS designed the study in collaboration with the REVA network and obtained funding. AA, JMu and SK wrote the statistical analysis plan and estimated the sample size. SB developed the eCRF and implemented the randomisation algorithm. CJ planned and conducted the work reported here. JA, JDu, NA, PA, JBa, DC, BC, JBo, ADe, JDe, ND, GD, ADu, J-BL, SL, CG, CJ-N, J-PQ, J-CL, JMa, AM, BM, PP, GP, J-CR, AR, CS and LVPV contributed to the writing and revising the paper and approved the final submission.

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Competing interests FS is a member of the executive committee of the French Intensive Care Society (SRLF). All other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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SUPPLEMENTARY MATERIAL 1

SPIRIT 2013 Checklist

Section/item	Item No	Description	Addressed on section or page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Section Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	Suppl Material 2
Protocol version	3	Date and version identifier	Section Footnotes, subsection Roles and responsibilities
Funding	4	Sources and types of financial, material, and other support	Section Fundings
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 + Section Footnotes, subsection Contributors
	5b	Name and contact information for the trial sponsor	Section Data availability statement

	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	Section Footnotes, subsection Roles and responsibilities
	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)	Section Footnotes, subsection Roles and responsibilities
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Section Background and rationale
	6b	Explanation for choice of comparators	Section Background and rationale
Objectives	7	Specific objectives or hypotheses	Section Objectives and outcomes
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)	Section Study design
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Section Data Collection, subsection Method and timing + Suppl Material 3
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)	Section Methods and analysis Subsection Eligibility Criteria + Subsection Intervention
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Section Intervention subsection Fever management
	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)	Section Intervention subsection Fever management
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Section Data collection, subsection Method and timing
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Section Intervention
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	Section Objectives and outcomes

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)	Section Method and timing + Table 2
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	Section Sample size calculation
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Section Randomization + Section Interim analyses + Section Footnotes subsection Newsletter
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Section Randomization
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	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Section Randomization

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Section Data collection + subsection Method and timing + subsection Quality control
	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	Section Data collection + subsection Method and timing + subsection Quality control + Section Intervention
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	Section Data collection + subsection Method and timing + subsection Quality control
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	Section Statistical methods

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Section Statistical methods, subsection Pre-planned subgroup analysis
	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)	Section Statistical subsections Compliance - …) + Section Statistical methods, subsection Missing data management
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Section Data Monitoring, subsection DMC + Section Statistical analyses, subsection Interim analyses; DMC charter v1-0 December 23th, 2020 (in French)
	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	Section Statistical analyses, subsection Interim analyses; DMC charter v1-0 December 23th, 2020 (in French)

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	Section Data monitoring, subsection Monitoring adverse events
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Section Ethics
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Section Ethics
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Section Ethics
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Section Ethics
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Section Footnotes, subsection Competing interests

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	Section Data availability statement
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
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	Section Dissemination
	31b	Authorship eligibility guidelines and any intended use of professional writers	Section Dissemination
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Section Data availability statement
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Separate documents
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	NA

SUPPLEMENTARY MATERIAL 2

WHO Trial Registration Data Set (Version 1.3.1):

1) Primary Registry and Trial Identifying Number: RCB N°2020-A3201-38
2) Date of Registration in Primary Registry: July 28th, 2020.
3) Secondary Identifying Numbers: NCT04494074; PHRC-19-0046.
4) Source(s) of Monetary or Material Support: the French National "Programme Hospitalier de Recherche Clinique 2019".
5) Primary Sponsor: clinical research unit of the Centre Hospitalier Intercommunal de Créteil.
6) Secondary Sponsor(s): NA.
7) Contact for Public Queries: AA (see page 1).
8) Contact for Scientific Queries: AA (see page 1).
9)-10) Public-Scientific Title: Protocol for Fever Control Using External Cooling in Mechanically Ventilated Patients with Septic Shock: SEPSISCOOL II Randomised Controlled Trial.
11) Countries of Recruitment: France
12) Health Condition(s) or Problem(s) Studied: febrile patients with septic shock in ICU.
13) Intervention(s): Routinely applied, external cooling (intervention) or no-cooling (control) strategy for fever management during the first 48 hours following randomisation.
14) Key Inclusion and Exclusion Criteria: Inclusion criteria: Documented or suspected infection, either community or hospital acquired; Ongoing antimicrobial treatment and/or intervention for infection source control (e.g., surgical drainage); Septic shock; Patients under invasive mechanical ventilation; Core body temperature > 38.3°C; Intravenous sedation or opioids; Attending physician confirms clinical equipoise without substantial risk if the patient participates in the trial. Exclusion criteria: Cardiac arrest within previous 7 days; Acute brain injury within previous 7 days; Extensive burns or epidermal necrolysis; Core body temperature ≥ 41°C; pregnancy; Participation in another interventional study with mortality as the primary endpoint; investigator's decision not to resuscitate
15) Study Type: interventional randomized open-label controlled parallel group phase IV trial. Covariate-balance adaptive allocation.
16) Date of First Enrolment: October 12th, 2022.
17) Sample Size: Planned to enrol 820 participants. Currently enrolled: 25 participants (April 28th, 2023).
18) Recruitment Status: Recruiting.
19) Primary Outcome(s): Mortality at day 60 after randomisation.
20) Key Secondary Outcomes: evolution of organ failure on day 28; evolution of Sequential Organ Failure Assessment score at day 28; acute kidney injury up to day 7, criteria to initiate renal replacement therapy (RRT) and to start new RRT up to day 28; ARDS acquired after randomisation up to day 3.; mortality at day 28; incidence of secondary ICU-acquired nosocomial infections through day 28; tolerance of the two strategies up to day 90.
21) Ethics Review: Approved Februray 4th, 2021 by the French Comité de Protection des Personnes Nord Ouest II (Amiens, France).
22) Completion date: NA.
23) Summary Results: NA.
24) IPD sharing statement: upon request to the sponsor.

SUPPLEMENTARY MATERIAL 3

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SUPPLEMENTARY MATERIAL 4

Schedule of enrolment, interventions and data collection

				Hours from randomisation						Days from randomisation		
Intervention	**Inclusion**	**Pre-randomisation**	**Randomisation**	**0–24**	**24**	**24–48**	**48**	**48–72**	**72**	**7**	**28**	**60**
Informed consent	----------											
Eligibility criteria	X											
Variables for stratification and randomisation			X									
Allocation			X									
Baseline characteristics, comorbidities, infection, severity score, organ supports, delay from vasopressor start		X										
Study treatment				----------								
Vital signs, vasopressor dose, RASS			X	X	X	X	X	X	X			
Biological analyses: arterial blood gazes, lactate, creatinine					X		X		X			
Safety events: shivering, skin lesions, seizure, new cardiac arrhythmias, secondary acquired ARDS				X	X	X	X	X	X			
SOFA score					X		X		X	X		
AKI				----------								
Organ support: vasopressors, mechanical ventilation, RRT				----------								
ICU-acquired infection				----------								
Vital status											X	X

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment. RASS: Richmond agitation sedation scale.

SUPPLEMENTARY MATERIAL 5

Definitions of nosocomial infections

Nosocomial infections are diagnosed by clinical teams after 48 hours of inclusion. NI are defined according to the ECDC criteria applied routinely in French surveillance systems (https://www.ecdc.europa.eu/en/publications-data/surveillance-healthcare-associated-infections-and-prevention-indicators-european). Recorded infections are ventilator acquired pneumonia (VAP), blood stream infection (BSI), catheter related blood stream infection, urinary tract infection (UTI) and surgical site infection.

VAP is defined in accordance with clinical criteria (X-ray, fever >38 °C, leucocytosis >12 000 white blood cells (WBC)/mm3, purulent sputum) and microbiological confirmation among: 1- minimally contaminated lower respiratory tract sample with quantitative culture (104 colony-forming units (CFU)/ml for BAL, 103 CFU/ml for protected brush samples or distal protected aspirate); 2- non-protected sample (endotracheal aspirate, ETA) with quantitative culture (106 CFU/ml); 3- alternative microbiological criteria (e.g. positive blood culture, multiplex PCR test);

BSI is defined as a positive blood culture of a recognized pathogen or the combination of clinical symptoms (fever >38 °C, chills, hypotension) and two positive blood cultures of a common skin contaminant from two separate blood samples drawn within 48 hours.

UTI is defined as either a microbiologically confirmed symptomatic UTI with a positive urine culture ≥105 microorganisms per ml of urine requiring antibiotics

Venous catheter -related BSI was defined as a BSI occurring 48 hours before or after catheter removal, and a positive culture with the same microorganism of either a) quantitative CVC

culture ≥ 103 CFU/ml or differential delay of positivity of blood cultures, or positive culture with the same microorganism from pus from insertion site.

Surgical site infection within 30 days after surgery: deep incisional or organ.

SUPPLEMENTARY MATERIAL 6

Members of the independent endpoint adjudication committee:

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