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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Section Background and rationale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

Centres list

Trial centres	Name of PI	E-mail of PI	Address
CHI Créteil, Medical ICU	Frédérique SCHORTGEN	Frederique.schortgen@chicreteil.fr	40 avenue de Verdun 94000 Créteil
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CH Le Mans, Medical ICU	Christophe GUITTON	cguitton@ch-lemans.fr	194 avenue Rubillard 72000 Le Mans
CHU Angers, Medical ICU	Pierre ASFAR	PiAsfar@chu-angers.fr	4 Rue Larrey 49933 Angers
CHU Nantes, Medical ICU	Jean Baptiste LASCARROU	jeanbaptiste.lascarrou@chu-nantes.fr	1 place Alexis Ricordeau 44093 Nantes
CHU Nice, Medical ICU	Clément SACCHERI	saccheri.c@chu-nice.fr	151 Route St Antoine Ginestière 06202 Nice
APHP, Hôpital Lariboisière, Medical ICU	Nicolas DEYE	Nicolas.deye@aphp.fr	2 rue Ambroise Paré 75010 Paris
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APHP, Mondor, Medical ICU	Armand MEKONTSO-DESSAP	armand.dessap@aphp.fr	51 Avenue du Maréchal de Lattre de Tassigny 94010 Créteil
CHU Amiens, Medical ICU	Julien MAIZEL	maizel.Julien@chu-amiens.fr	Avenue Professeur Cabrol 80054 Amiens Cedex
CHD Vendée, la Roche sur Yon, Medical ICU	Jean Claude LACHERADE	jean-claude.lacherade@chd-vendee.fr	Boulevard Stéphane Moreau 85925 La Roche sur Yon
CHU Dijon, Medical ICU	Jean Pierre QUENOT	jean-pierre.quenot@chu-dijon.fr	14 rue Paul Gaffarel 21079 Dijon

APHM, Hôpital de la Timone, Department of Emergency ICU	Jeremy BOURENNE	Jeremy.bourenne@ap-hm.fr	264 rue Saint Pierre 13005 Marseille
G.H.R. Mulhouse Sud Alsace, Medical ICU	Anne-Florence Dureau	anne-florence.dureau@ghrmsa.fr	20 avenue du Docteur René Laennec 68100 Mulhouse
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APHP, CHU Bicetre, Medical ICU	Nadia ANGUEL	nadia.anguel@aphp.fr	78 rue du Général Leclerc 94270 Le Kremlin Bicêtre
CH Victor Dupouy Argenteuil, ICU	Gaetan PLANTEFEVE	gaetan.plantefeve@ch-argenteuil.fr	69 rue du Lieutenant Colonel Prudhon 95100 Argenteuil
Hôpital nord Franche Comté, Medical ICU	Julio BADIE	Julio.BADIE@hnfc.fr	100 route de Moval 90015 Belfort Cedex
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CH de TARBES, Medical ICU	Philippe PETUA	ppetua@ch-tarbes-vic.fr	Boulevard de Lattre de Tassigny 65013 Tarbes
GH Nord, Hôpital de la Croix-Rousse, Medical ICU	Jean-Christophe RICHARD	j-christophe.richard@chu-lyon.fr	103 grande Rue de la Croix-Rousse 69004 Lyon
CH Cholet, Medical ICU	Julien DUPEYRAT	julien.dupeyrat@ch-cholet.fr	1 rue Marengo 49300 Cholet
CHU Michallon, Medical ICU	Guillaume DUMAS	dumas.guillaume1@gmail.com	Bd de la Chantourne 38700 La Tronche
CHU Pasteur 2, Medical ICU	Alexandre ROBERT	robert.a@chu-nice.fr	30 voie Romaine 06001 Nice

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:

Pr Claude Guerin: Medical ICU Hôpital Edouard Herriot, Lyon, Université de Lyon, and Institut Mondor de Recherches Biomédicales, INSERM 955, CNRS ERL 7000, Créteil, France

Pr Charles Edouard Luyt: Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Medical Intensive Care Unit, Paris and Sorbonne Université, 27063, UPMC Univ Paris 06, INSERM, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, Paris, France

Pr Alain Cariou: Assistance Publique-Hôpitaux de Paris, Medical Intensive Care Unit, Cochin University Hospital, Paris and Paris Cité University – Medical School, Paris, France

Dr Lucie Biard: Assistance Publique-Hôpitaux de Paris, Department of Biostatistics and Medical Information, Université Paris Cité, Saint-Louis Hospital, Paris and INSERM U1153 Team ECSTRRA, F-75010 Paris, France

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