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SepTiC: Sepsis Trials in Critical Care

Submission date 23/03/2023	**Recruitment status** Recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 03/11/2023	**Overall study status** Ongoing	
Last Edited 19/03/2025	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims
SepTIC is a pragmatic, open-label trial with an embedded randomised (like flipping a coin) double-blind (neither the doctor nor the participants know whether the drug or the placebo was administered), placebo-controlled, parallel group trial that will take place in up to 60 ICUs within the UK.

Who can participate?
Adults (at least 16 years of age) admitted to ICU due to suspected sepsis and expected to stay for at least two calendar days

What does the study involve?
Participants can be included in all three trial arms (can do both 1 and 2, neither and included in 3 if eligible). There will be three randomisations. In the first two, eligible patients with sepsis will be randomised on inclusion to:
1. A guided antibiotic therapy or normal standard of care (trial 1)
2. A conservative fluid treatment strategy or normal standard of care (trial 2)
3. In an eligible subset of more severely ill patients (~35% of the total trial population) the third randomisation will allocate patients to the addition of GM-CSF (treatment for stimulating the immune system) or placebo (trial 3), this intervention will be blinded.
Enrolment and randomisation will be performed using an online system.
There will be an internal pilot study to check the rates of patient recruitment and adherence to the study protocol. The internal pilot will run for the initial 8 months of recruitment (~350 patients) and run seamlessly into the main trial.
Patients will be followed up for the duration of their stay in ICU, to hospital discharge. Patients will be contacted for follow up and to complete a quality of life and cognitive function questionnaires 6 months from initial randomisation. Vital status will be checked via the medical records at day 90 and 1 year after randomisation.

What are the possible benefits and risks of participating?
Benefits:
There may not be any direct benefits of participating in the study, but the results may help future patients and assist doctors in the future in treating people with sepsis more effectively and successfully.
Risks:

he main ethical issue arise from the fact that the treatment for sepsis in an ICU is a medical emergency. Evidence from previous studies suggests that earlier treatment improves outcomes. Therefore, to ensure there is no delay to treatment, it is imperative that patients are randomised as soon as they become eligible on ICU. Delays to treatment could affect the scientific validity of the trial, making the results less generalisable to usual practice. Due to their critical illness, most eligible patients for the study will have a reduced level of consciousness and will be unable to give consent at that time. Hence treatment with the study drugs will need to be started in most cases without prospective consent in place. The specific nature of usual supportive care measures (which includes administration of antibiotics and other routinely administered interventions in critical care) are seldom discussed with their families and are presented to patients and their families as a "package deal" when time persists (in contrast to surgical procedures, which are more likely to be discussed in detail). As this is an emergency situation it is not possible to identify eligible patients in advance of them losing the capacity to provide consent. In addition, relatives are likely to be distressed by the patient´s illness and admission to critical care at the point the patient is eligible for the trial – and are unlikely to have capacity to make a decision in the short time-frame available. The minimisation of further distress has been a priority when deciding on the proposed consent process. The process has been based on qualitative work with family members in similar studies regarding the preferred timing and way of approach for consent. This process has also been used in a number of other similar critical care research studies. After randomisation, the clinical team will identify the next-of-kin (family / relative / friend) recorded in the patients clinical notes and they will be approached by a member of the clinical research team and asked if they would be happy to provide Personal Legal Consent. The trial will be explained to them, they will be given an information sheet about the trial and they will be asked to give an opinion on the patient´s participation in the trial. If a Personal Legal Representative cannot be contacted in an adequate timeframe (approximately 2 hrs) a Professional Legal Representative will be approached. This will be a doctor in the hospital who is not part of the research team (i.e. not on the research delegation log). They will be informed about the trial and asked to give an opinion on the patient´s participation in the trial. Once patients regain capacity in the hospital, they will be approached by a member of the clinical research team, the trial explained to them, including their participation and that the study was discussed with their Personal or Professional Legal Representative while they lacked capacity. They will then be given the patient information sheet and asked to consent for the continuation of the study. All patients in critical care units are monitored closely and clinical/research staff in this setting are very experienced in assessing mental capacity.
Admission of adult patients to ICUs with sepsis will be linked to existing healthcare-related registries and databases in the UK. The following data may be obtained by data linkage with death registries and hospital discharge coding databases in the UK:
• Hospital readmissions, and diagnoses and procedures carried out during readmissions
• Mortality after discharge from the index hospitalization
We will seek consent from patients to collect this data. ICNARC will use patient identifiable data (NHS number, date of birth, post code and sex) which is already collected as part of the CMP national clinical audit to link data with other routinely collected data sets. This allows the research objectives to be achieved in an efficient manner and allows for the best possible follow up of longer term survival for patients. This is not possible without patient identifiable data. The CMP national clinical audit has section 251 approval for use of patient identifiable data for audit.
In trial 3, (GM-CSF), the patients may experience some uncommon side effects, for example: - redness at the site of injection; allergic reaction; these will be listed in the consent form.
Patients in all groups will be closely monitored for adverse events that may be related to trial interventions, which will be reported to the Sponsor, and where relevant, to oversight committees and the regulatory authority.
Confidentiality: Minimal patient identifiable data will be required to enable the trial team to link

data to routine data sources.
Use of tissues in future research: a total of 30mls of blood will be collected for future research, all samples will be stored at the Imperial Tissue Bank for analysis in other ethically approved studies.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
March 2023 to April 2027

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
septic@imperial.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Janis Best-Lane

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1005848

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
A4-1- 22SM8039, IRAS 1005848, CPMS 57737

Study information

Scientific Title
Sepsis Trials in Critical Care

Acronym
SepTiC

Study objectives
Primary objectives:
To assess the clinical effectiveness and cost-effectiveness of:
1. Rapid PCR-based microbiological diagnostics combined with procalcitonin (in the Diagnostic trial)
2. Conservative fluid therapy with an active fluid de-resuscitation strategy (in the Fluids trial)
3. GM-CSF, using an enrichment strategy to both identify patients at higher risk of mortality (prognostic enrichment) and who are more likely to respond to treatment (predictive enrichment) (in the GM-CSF trial).

Secondary objectives:
To collect blood samples from recruited patients to be stored in the Imperial Tissue Bank for use in later ethically approved studies

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 31/08/2023, Seasonal REC (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 20 7104 8057; seasonal.rec@hra.nhs.uk), ref: 23/LO/0339

Study design
Interventional double blind randomized parallel group placebo controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Sepsis

Interventions
Intervention 1:- Diagnostic Trial
Research Question:- Do rapid PCR-based microbiological diagnostics combined with

procalcitonin improve outcomes and antibiotic stewardship compared to standard care in patients admitted to intensive care (ICU) with sepsis?
Intervention Arms:- PCR test and procalcitonin result or Standard of Care
If randomised to intervention a PCR test and Procalcitonin check will be completed. A blood sample will be taken after randomisation for rapid PCR-based pathogen testing, which will be sent to the study laboratory. Procalcitonin (PCT) will be measured on the day of inclusion and the next calendar day. If randomised to standard of care patients will be prescribed antibiotics according to the local antibiotic prescribing guidelines and using standard microbiology sampling, culture and sensitivity testing.

Intervention 2:- Fluid Trial
Research Question:- Does conservative fluid therapy with active removal of accumulated fluid (de-resuscitation) improve outcomes compared to standard care in patients admitted to ICU with sepsis?
Intervention Arms:- Conservative fluid therapy with de-resuscitation or Standard of Core
If randomised to intervention, conservative fluid strategy will be followed as soon as possible after randomisation. From Day 2 – 5 patients will be assessed for cardiovascular stability. If cardiovascularly stable and there are signs of fluid overload, deresuscitation will be given. Deresuscitation will consist of combination diuretic therapy . If randomised to standard care will be prescribed fluids according to usual care, at the discretion of the treating clinicians.

Intervention 3:- GM-CSF Trial
Research Question:- Does GM-CSF compared to placebo improve outcomes in a high-risk subset of patients admitted to ICU with sepsis?
If randomised to intervention, GM-CSF 250-500 µg will be given subcutaneously once a day for up to 8 days. If randomised to standard care a matching placebo will be given.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Sargramostim (Leukine)

Primary outcome measure
90-day mortality combined with clinical state (in-hospital with organ support, in-hospital without organ support, discharged from hospital) over time

Secondary outcome measures
1. Duration of mechanical ventilation, shock, renal replacement therapy up to 90 days
2. Length of stay in ICU and hospital up to 90 days
3. Antibiotic use (defined daily doses per 1000 occupied bed days) up to 90 days
4. Infection relapse / recurrence or secondary infection requiring further antibiotic treatment up to 90 days
5. Adverse events and adverse drug reactions (including antibiotic related adverse events) up to 90 days
6. Health-related Quality of Life (EQ-5D-5L) and cognitive function (MoCA-Blind) at 6 months
7. 1-year mortality

Overall study start date
21/03/2023

Completion date
30/04/2027

Eligibility

Key inclusion criteria
1. Adults (≥16 years of age) admitted to ICU due to suspected sepsis and expected to stay for at least two calendar days (i.e. expected to still to be in ICU the day after tomorrow).
2. Receiving intravenous antibiotics for suspected sepsis
3. According to local clinical judgement, patient has received adequate initial early fluid resuscitation

The following inclusion are for intervention 3 only (can be after initial trial entry):
1. Intubated and mechanically ventilated and expected to continue for another 24 hours
2. Or requiring two organ support (i.e. vasopressors or renal replacement therapy)
3. An absolute lymphocyte count < 1.2 x109 /L on two consecutive calendar days at least 12 hours apart, with no values >1.2 x10^9 /L in between.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
3,758

Key exclusion criteria
1. More than 24 hours since ICU admission (this does NOT apply for trial 3, GM-CSF). Note: As early intervention in sepsis is important, the aim should be to enrol eligible patients as soon after ICU admission as is practically possible.
2. Previously admitted to ICU due to sepsis on this hospital admission
3. Not expected to survive 90 days, due to pre-existing chronic (end-stage) disease
4. Not expected to survive initial resuscitation (24 hours)
5. Neutropaenia (<0.5 neutrophils x109 /L) due to chemotherapy/malignancy (but not due to sepsis)
6. A source of infection that will require a prolonged course of antibiotics, for greater than 21 days (e.g. infective endocarditis, osteomyelitis, hepatic or cerebral abscess, tuberculosis)
7. Diabetic ketoacidosis (DKA) or hyperglycaemic hyperosmolar state (HHS)
8. Within 21 days of a spontaneous subarachnoid haemorrhage
9. Diabetes Insipidus
10. Weight <40Kg

The following additional criteria relate to intervention 3 only:
1. More than 120 hours since ICU admission
2. Already receiving G-CSF or GM-CSF
3. A total white blood cell count >50 x10^9 /L
4. Allergy or previous adverse reaction to GM-CSF
5. Known to be pregnant or breastfeeding
6. Known recent (required treatment within the last 5 years) haematological malignancy
7. Solid organ or bone marrow transplantation
8. Patient weight >125kg
9. Known anaphylaxis to GM-CSF or yeast-derived products

Date of first enrolment
02/01/2023

Date of final enrolment
30/04/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Imperial College London

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Sponsor type
University/education

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ROR
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Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Publication on website
Other publication
Submission to regulatory authorities
The results of the trial will be made publicly available via the trial website, institutional websites and also through charity/patient groups (e.g. ICU Steps, Intensive Care Foundation).
Participants will not routinely be given results as this is a trial that is unlikely to offer individual patients or their doctors any information that will be of relevance to their ongoing or future clinical care.

Intention to publish date
30/04/2028

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Prof Anthony Gordon, septic@imperial.ac.uk, one year after the primary trial results have been published. Any applications should include an explanation of what data is required and what for what purpose, with a supporting rationale. Any request will be reviewed by a scientific access committee and data sharing decisions will be made subject to scientific merit, suitable data sharing agreement, as well as any applicable ethical or legal restrictions.

IPD sharing plan summary

Available on request, Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.1	22/08/2023	19/03/2025	No	No