SepTiC

Sepsis Trials in Critical Care

Confirming Eligibility

V2.0 30-JAN-2024

Sponsor: Imperial College London

Funder: NIHR

IRAS ID: 1005848

REC ref: 23/LO/0339

Chief Investigator: Prof Anthony Gordon

Study Coordination Centre:

Imperial Clinical Trials Unit

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FUNDED BY NIHR | National Institute for Health Research

Coordinating Centre / Trial Management Team

- Trial coordinated by Imperial Clinical Trials Unit
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Introduction to SepTiC

+ A multi-centre, pragmatic, multi-factorial, open-label randomised controlled trial, with an embedded randomised, double-blind, parallel group trial.

Research questions

1. Do rapid PCR-based microbiological diagnostics plus procalcitonin improve outcomes and antibiotic stewardship compared to standard care in patients admitted to ICU with sepsis?
2. Does conservative fluid therapy with active removal of accumulated fluid (de-resuscitation) improve outcomes compared to standard care in patients …with sepsis?
3. Does GM-CSF compared to placebo improve outcomes in a high-risk subset of patients …with sepsis?
4. What is the relative cost-effectiveness of each of these interventions compared to current standard of care?

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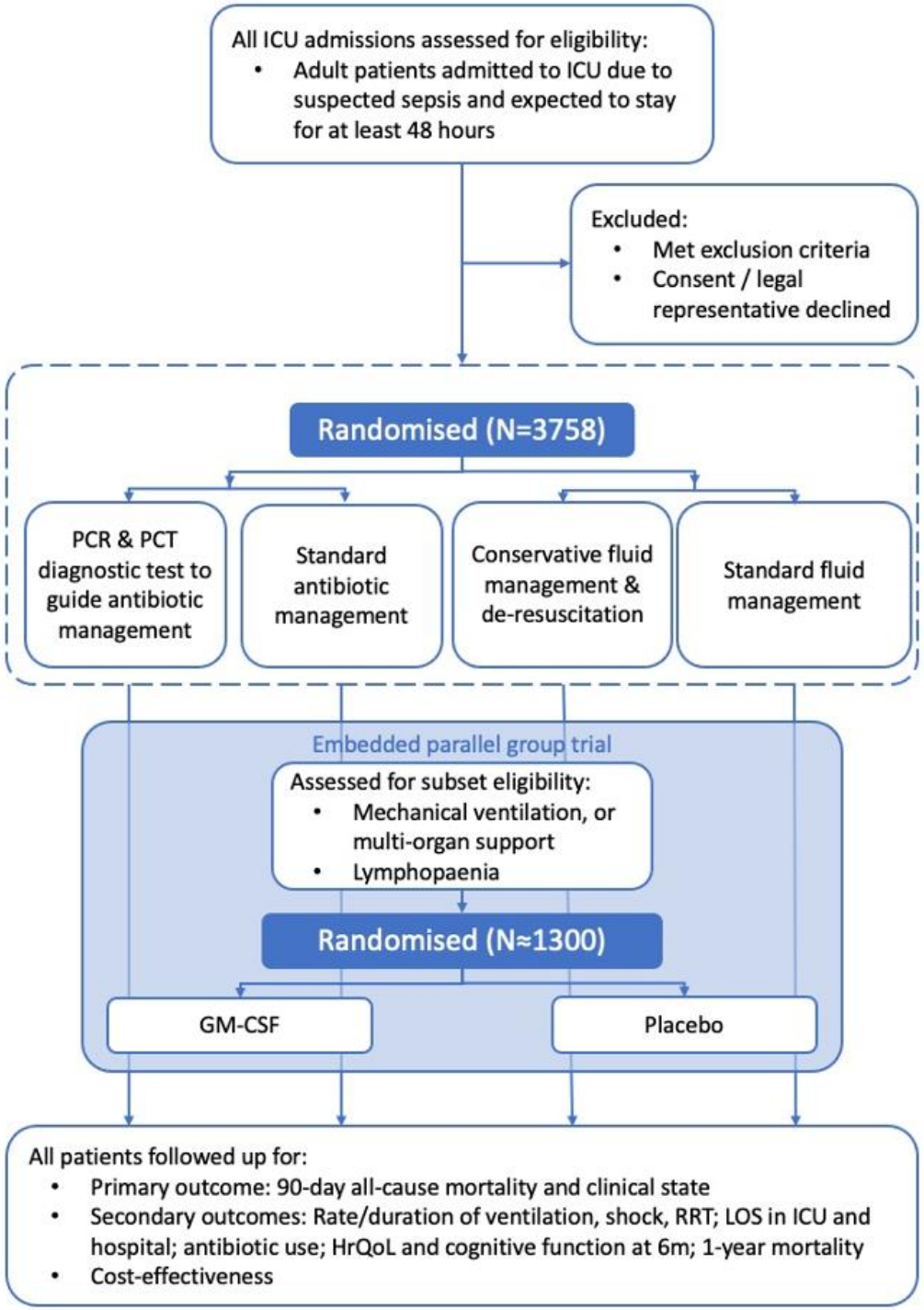
Confirming Eligibility

- As per MHRA requirements only a clinician is able to confirm whether a patient is eligible for the trial.
- The clinician confirming eligibility **is** required to be listed on the delegation log and **must be** listed on the Eligibility Check log so that the study has oversight of those clinicians who have received this training and are qualified to confirm eligibility.
- Eligibility should be confirmed for the trials the patient is eligible for, i.e. they may be eligible for trials 1+2 first and 3 (GM-CSF) later, therefore eligibility should be checked for trial 3 (GM-CSF) when the patient is eligible. This needs to be documented in the medical records.
- Please ensure a 'Eligibility Form' is completed for each eligible patient and filed in their medical records.

Study Flowchart



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Inclusion Criteria – All participants

+ Adult patients (≥16 yrs) 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)

+ Receiving intravenous antibiotics for suspected sepsis

+ According to local clinical judgement, patient has received adequate initial early fluid resuscitation

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Exclusion Criteria – All participants

+ More than 24 hours since ICU admission *(not for GM-CSF arm, see next slide)*
+ Previously admitted to ICU due to sepsis on this hospital admission
+ Not expected to survive 90 days, due to pre-existing chronic disease
+ Not expected to survive initial resuscitation (24 hours)
+ Neutropaenia due to chemotherapy / malignancy (but not due to sepsis)
+ A source of infection that will require a prolonged course of antibiotics, for >21 days (e.g. infective endocarditis, osteomyelitis, hepatic or cerebral abscess, tuberculosis)
+ DKA / HHS / DI / SAH (in last 21 days)
+ Weight <40Kg

GM-CSF Trial - Inclusion criteria

The patient may not be eligible for the GM-CSF trial now, but please check again if the patient becomes more unwell.

+ Intubated, mechanically ventilated & expected to continue for another 24 hours

Or

+ Two organ support (Vasopressors, RRT)

AND

+ An absolute lymphocyte count <1.2 x10^9 /L on two consecutive calendar days

(at least 12 hrs apart with no values >1.2 x10^9 /L in between)

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Additional Exclusion criteria – GM-CSF

+ More than 120 hours (5 days) since ICU admission
+ Already receiving G-CSF or GM-CSF
+ A total white blood cell count (WBC) >50 $x10^9$ /L
+ Allergy or adverse reaction to GM-CSF or yeast-product
+ Known to be pregnant or lactating
+ Known active haematological malignancy *(treated within last 5 years)*
+ Solid organ or bone marrow transplantation
+ Patient weight >125kg

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Good Clinical Practice (GCP)

+ International, ethical and scientific quality standard to which all research involving human participants is conducted
+ Comprised of 13 core principles & applies to all clinical investigations that could affect safety and well-being of human participants, providing international assurance that:
  - Data and reported results of clinical investigations are credible and accurate
  - Rights, safety and confidentiality of participants in clinical research are respected and protected
- You are encouraged to obtain GCP certification, such as that available through NIHR: https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm

Principles of Good Clinical Practice (GCP)

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approval/favourable opinion.

Principles of Good Clinical Practice (GCP)

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice(GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.