SepTiC Protocol Summary

SepTiC is a Phase IV multicentre pragmatic randomised, multi-factorial, open-label trial with an embedded randomised double-blind, placebo-controlled, parallel group trial.

This research looks to answer three important questions through three separate trials:-:

1) Diagnostic Trial

Is it better for patients if we use rapid microbiology tests to allow antibiotics to be changed early? Current tests to find the cause of infection take several days and broad-spectrum antibiotics are used to cover many possible infections for many days, which can lead to antibiotic resistance over time. This means antibiotics become less effective.

2) Fluid Trial

Is it better for patients with sepsis to have less fluid than current standard care?
Fluid is used to help maintain blood flow to the body's organs but there is uncertainty of how much to give and when to administer it. Some studies suggest standard care gives too much fluid and that it might be better, after treating any early lack of fluid, to only give extra if there are clear signs that patients need more and to use diuretics to remove excess fluid.

3) GM-CSF Trial

Does it help to give the sickest patients with sepsis and low white blood cell counts a growth stimulating factor?
Some patients with sepsis have leukocyte dysfunction which affects the immune response. Leukocytes can be stimulated by GM-CSF which may help recovery and prevent new infections.

Participants can be included in all three trials(they could also be included in just trials 1 and 2, or neither of these and just the GM-CSF trial). There will be three randomisations. In the first two trials, eligible patients with sepsis will be randomised on inclusion to:-

(i) a guided antibiotic therapy or normal standard of care (Diagnostic Trial)

(ii) a conservative fluid treatment strategy or normal standard of care (Fluid Trial)

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, this intervention will be blinded (GM-CSF Trial).

Enrolment and randomisation will be performed using the OpenClinica database.

By answering three important research questions at the same time, we will receive quick results and be more cost-effective. Because these treatments would normally be given together to treat sepsis and they all work in different ways, we can study them at the same time without them affecting each other.

Inclusion criteria

- 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).
- Receiving intravenous antibiotics for suspected sepsis
- According to local clinical judgement, patient has received adequate initial early fluid resuscitation

Additional inclusion criteria for the GM-CSF trial only (can be after initial trial entry):

- Intubated and mechanically ventilated and expected to continue for another 24 hours
- **Or** requiring two organ support (i.e. vasopressors or renal replacement therapy)
- An absolute lymphocyte count < 1.2 $x10^9$ /L on two consecutive calendar days at least 12 hours apart, with no values >1.2 $x10^9$ /L in between.

Exclusion criteria

- More than 24 hours since ICU admission (this does **NOT** apply for intervention 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.
- Previously admitted to ICU due to sepsis on this hospital admission
- Not expected to survive 90 days, due to pre-existing chronic (end-stage) disease
- Not expected to survive initial resuscitation (24 hours)
- Neutropaenia (<0.5 neutrophils $x10^9$ /L) due to chemotherapy/malignancy (but not due to sepsis)
- 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)
- Diabetic ketoacidosis (DKA) or hyperglycaemic hyperosmolar state (HHS)
- Within 21 days of a spontaneous subarachnoid haemorrhage
- Diabetes Insipidus
- Weight <40Kg

Additional exclusion criteria for GM-CSF trial only*:*

- 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, anaphylaxis or previous adverse reaction to GM-CSF or yeast-derived products
- Known to be pregnant or breastfeeding
- Known recent (required treatment within the last 5 years) haematological malignancy
- Solid organ or bone marrow transplantation
- Patient weight >125kg

Our trial will include 3758 patients with sepsis who are admitted to Critical Care over 3 years.

For questions 1 and 2, one quarter of patients will get standard care, half of patients will have one of the two interventions and one quarter will have both interventions. Then amongst the most ill patients, half will receive the immune stimulation drug (question 3).

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 6 months after randomisation to complete questionnaires about the quality of their life at 6 months (EQ-5D-5L) and problems with memory and thinking (MOCA-Blind). Vital status will be checked via the medical records at day 90 and 1 year after randomisation.