

# Developmental Clinical Sciences: Does GM-CSF restore effective neutrophil function in critically ill patients?

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<b>Registration date</b> 26/06/2012	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 11/07/2017	<b>Condition category</b> Other	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Despite the introduction of multiple preventative measures, rates of hospital-acquired infection (HAI) in the intensive care unit remain high. New approaches to tackling this problem are required. A type of white blood cell called the neutrophil is the key cell fighting bacterial and fungal infection in the body. This study group has shown that the majority of patients on intensive care have neutrophils which don't eat germs effectively and are therefore less able to fight off infection. These patients, whose white blood cells don't work properly in this way, are much more likely to develop a second infection whilst in hospital (HAI). These patients can be identified by measuring the levels of a specific receptor on the surface of the neutrophils by a simple blood test. Previous work carried out by this research group has also shown that by adding a drug called granulocyte macrophage-colony stimulating factor (GM-CSF) to a sample of blood from such patients in the laboratory, it is possible to restore the ability of the neutrophils to eat bacteria and fight infection. This study, therefore, tests whether it is possible to restore the eating ability of critically ill patients' white blood cells, in real life, by giving them GM-CSF as an injection while they are on intensive care. If the study demonstrates a clear effect for GM-CSF in improving the function of patients neutrophils, the way would be paved for future studies determining whether GM-CSF can prevent HAI in future, larger studies. Currently, no good drug treatments preventing HAI in the ICU are available.

### Who can participate?

Participants aged 18 or over recruited via four ICUs across North East England

### What does the study involve?

The study involves two parts. The first part aims to establish the best dose of GM-CSF that should be used in order to improve the function of neutrophils in critically ill patients. Patients with faulty neutrophils who are enrolled into this part of the study are randomly allocated to receive one of two doses of GM-CSF for 4 or 7 days. The eating capacity of their neutrophils is measured before and after the injections to see which dose is the most effective in improving their function. At the same time the patients' blood tests and clinical condition are monitored to look for any unwanted side effects of treatment. The best dose (i.e., the one which produces the

greatest benefit without significant side effects) is selected for use in the second part of the study.

The second part of the study will again enroll patients on intensive care whose white blood cells don't work properly in this way. Patients who take part in this part of the study are randomly allocated to receive either an injection of the drug (GM-CSF) or an injection of a solution which has no effect (placebo or dummy drug), to see whether those patients who receive the GM-CSF injection have an improvement in the function of their neutrophils compared to those who don't. Participants are followed up for a maximum of 30 days.

As well as looking at whether or not the white blood cells work properly, the study also looks at whether there is a difference in the rates of infection picked up in hospital between the two groups and also whether there is any difference in their clinical outcomes such as length of stay in hospital, time on a ventilator and survival.

What are the possible benefits and risks of participating?

There are no definite benefits of taking part in the study. However, participants may benefit from GM-CSF injections as GM-CSF is expected to improve the function of the white blood cells during critical illness. Participants should not experience any side effects from the drawing of blood (which in the majority of cases will be from an indwelling line) other than the usual minor discomfort associated with a blood test if their line is moved prior to completion of the study. GM-CSF has been associated with potential minor side effects including mild discomfort and redness at the injection site, fever, aches and pains. All of these side effects usually resolve within a couple of days of completing the injections. GM-CSF does have some reported rare potential serious side effects including blood clots to the heart and lungs and inflammation of the lining around the heart. These side effects have only ever been reported at doses far higher than those which will be received during the study. The dose received has been associated with a good safety profile. The placebo injection should not be associated with any side effects other than mild discomfort at the injection site.

Where is the study run from?

1. Newcastle upon Tyne Hospitals Foundation Trust (UK)
2. Gateshead Foundation Trust (UK)
3. Sunderland Royal Hospital (UK)

When is the study starting and how long is it expected to run for?

July 2012 to April 2015

Who is funding the study?

Medical Research Council (MRC) (UK)

Who is the main contact?

1. Prof. John Simpson (Chief Investigator)
  2. Ms Jennie Parker (Trial Manager)
- jennie.parker@ncl.ac.uk

## Contact information

**Type(s)**

Scientific

**Contact name**

Ms Jennie Parker

**Contact details**

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United Kingdom  
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**Additional identifiers****Clinical Trials Information System (CTIS)**

2011-005815-10

**ClinicalTrials.gov (NCT)**

NCT01653665

**Protocol serial number**

12337

**Study information****Scientific Title**

Developmental Clinical Sciences: Does GM-CSF restore effective neutrophil function in critically ill patients?

**Study objectives**

Despite the introduction of multiple preventative measures rates of hospital acquired infection in the intensive care unit remain high. New approaches to tackling this problem are required. The neutrophil (a type of white blood cell) is the key cell fighting bacterial and fungal infection in the body. This research group has already shown that the majority of patients on intensive care have neutrophils which don't ingest germs effectively and are therefore less able to fight infection. These patients, whose white blood cells don't work properly, are much more likely to develop a second infection whilst in hospital (hospital acquired infection).

Previous work done by this group has shown that by adding a drug called granulocyte macrophage colony stimulating factor (GM-CSF) to a sample of blood from these patients in the lab, it is possible to restore the ability of the white blood cells to ingest bacteria and fight infection.

This study will test whether it is possible to restore the capacity of patients' white blood cells to eat germs by giving them GM-CSF as an injection while they are on intensive care.

Patients taking part in the study will receive an injection, under the skin, of either the drug, GM-CSF, or a solution which will have no effect (placebo). We will compare whether those patients who have received the GM-CSF injection have an improvement in the function of the white blood cells compared to those who don't.

As well as looking at the function of the white blood cells we will also study whether there is a difference in the rates of infection picked up in hospital between the two groups.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

NRES Committee Yorkshire & The Humber - Leeds West, 14/02/2012, ref: 12/YH/0083

**Study design**

Randomised; Interventional; Design type: Treatment

**Primary study design**

Interventional

**Study type(s)**

Treatment

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

Topic: Generic Health Relevance and Cross Cutting Themes; Subtopic: Generic Health Relevance (all Subtopics); Disease: Critical Care

**Interventions**

Patients taking part in the study will receive an injection, under the skin, of either the drug, GM-CSF, or a placebo.

Leukine (Sargramostim), a granulocyte macrophage-colony stimulating factor, will be administered at either 3ug/kg/day or 6ug/kg/day for either 4 or 7 days; Study Entry : Registration and One or More Randomisations

**Intervention Type**

Drug

**Phase**

Not Applicable

**Drug/device/biological/vaccine name(s)**

Sargramostim

**Primary outcome(s)**

Current primary outcome measures as of 20/05/2014:

Neutrophil phagocytic capacity 2 days after administration of GM-CSF/placebo (as measured by the percentage of neutrophils ingesting  $\geq 2$  zymosan particles ex vivo).

Previous primary outcome measures:

Neutrophil phagocytic capacity 2 days after GM-CSF injection

**Key secondary outcome(s)**

Current secondary outcome measures as of 20/05/2014:

1. All-cause mortality 30 days post randomisation
2. Number of days of mechanical ventilation
3. Incidence of ICU acquired infections as defined by Hospitals in Europe Link for Infection Control Surveillance (HELICS) criteria

4. Length of ICU stay
5. Safety over the course of the study, during treatment and follow-up
6. Sequential neutrophil phagocytic capacity over the duration of treatment for each participant, possibly either 4 or 7 days
7. Sequential organ failure assessment score (SOFA)

Previous secondary outcome measures:

1. 30 day mortality, for up to 30 day post-injection follow up
2. Duration of mechanical ventilation during the course of the study, for treatment and follow-up
3. Incidence of ICU acquired infections for the duration of time the participant is on the study (treatment and follow-up)
4. Length of ICU stay for the duration of time the participant remains in follow-up; other measures of neutrophil function
5. Safety over the course of the study, during treatment and follow-up
6. Sequential neutrophil phagocytic capacity over the duration of treatment for each participant, possibly either 4 or 7 days
7. Sequential organ failure assessment score (SOFA) for the duration of time the participant remains on study (treatment and follow-up)

### **Completion date**

30/04/2015

## **Eligibility**

### **Key inclusion criteria**

Current inclusion criteria as of 20/05/2014:

1. Male and female, aged  $\geq 18$  years
2. Patients admitted to intensive care unit within the last 72 hours
3. Fulfill criteria for systemic inflammatory response syndrome (SIRS)
4. Has required support of one or more organ systems (invasive ventilation, inotropes or haemofiltration) during current ICU stay
5. Survival over next 48 hours deemed most likely outcome by responsible ICU clinician
6. Neutrophil phagocytic capacity  $< 50\%$

Previous inclusion criteria:

1. Male and female, aged  $\geq 18$  years
2. Patients admitted to intensive care unit within the last 48 hours
3. Fulfill criteria for systemic inflammatory response syndrome (SIRS)
4. Require exogenous support of one or more organ systems (invasive ventilation, inotropes or haemofiltration)
5. Predicted to require organ support for further 48 hours or more
6. Survival is considered to be the most likely outcome by the attending clinician at the time of enrolment
7. Neutrophil CD88 expression is low (i.e. corresponding to  $< 50\%$  neutrophil phagocytic capacity)

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

## **Age group**

Adult

## **Lower age limit**

18 years

## **Sex**

All

## **Key exclusion criteria**

Current exclusion criteria as of 20/05/2014:

1. Absence/refusal of informed consent
2. Current prescription of a colony stimulating factor
3. Any history of adverse reaction/allergy to GM-CSF
4. Total white cell count  $>30 \times 10^9/\text{litre}$  at the time of screening
5. Haemoglobin  $<7.5\text{g/dl}$  at the time of screening
6. Age  $<18$  years
7. Pregnancy or lactation
8. Known in-born errors of neutrophil metabolism
9. Known haematological malignancy and/or known to have  $>10\%$  peripheral blood blast cells
10. Known aplastic anaemia or pancytopenia
11. Platelet count  $<50 \times 10^9/\text{litre}$
12. Chemotherapy or radiotherapy within the last 24 hours
13. Solid organ or bone marrow transplantation
14. Use of maintenance immunosuppressive drugs other than maintenance corticosteroids (allowed up to prednisolone  $10\text{mg/day}$  or equivalent)
15. Known human immunodeficiency virus (HIV) infection
16. Active connective tissue disease (eg rheumatoid disease, systemic lupus erythematosus) requiring active pharmacological treatment
17. ST segment elevation myocardial infarction, acute pericarditis (by ECG criteria) or pulmonary embolism (radiologically confirmed) in the previous week
18. Involvement in any study involving an investigational medicinal product in the previous 30 days

Previous exclusion criteria:

1. Absence/refusal of informed consent
2. Current prescription of a colony stimulating factor
3. Any history of adverse reaction/allergy to GM-CSF
4. Total white cell count  $>20 \times 10^9/\text{litre}$  at the time of screening
5. Haemoglobin  $<8.5\text{g/dl}$  at the time of screening
6. Age  $<18$  years
7. Pregnancy or lactation
8. Known in-born errors of neutrophil metabolism
9. Known haematological malignancy and/or known to have  $>10\%$  peripheral blood blast cells
10. Known aplastic anaemia or pancytopenia
11. Platelet count  $<50 \times 10^9/\text{litre}$
12. Known history of cancer (unless undergone curative resection or treatment)
13. Solid organ or bone marrow transplantation
14. Use of maintenance immunosuppressive drugs other than maintenance corticosteroids (allowed up to prednisolone  $10\text{mg/day}$  or equivalent)
15. Known human immunodeficiency virus (HIV) infection

- 16. Active connective tissue disease (eg rheumatoid disease, systemic lupus erythematosus) requiring active pharmacological treatment
- 17. ST segment elevation myocardial infarction, acute pericarditis (by ECG criteria) or pulmonary embolism (radiologically confirmed) in the previous week
- 18. Involvement in any study involving an investigational medicinal product in the previous 30 days

**Date of first enrolment**

02/07/2012

**Date of final enrolment**

30/04/2015

## **Locations**

**Countries of recruitment**

United Kingdom

**Study participating centre**

Newcastle upon Tyne Hospitals Foundation Trust  
NE7 7DN

**Study participating centre**

Gateshead Foundation Trust  
NE9 9SX

**Study participating centre**

Sunderland Royal Hospital  
SR4 7TP

## **Sponsor information**

**Organisation**

Newcastle upon Tyne Hospitals NHS Trust (UK)

**ROR**

<https://ror.org/05p40t847>

## **Funder(s)**

**Funder type**

Research council

**Funder Name**

Medical Research Council (MRC) (UK)

**Alternative Name(s)**

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

## Results and Publications

**Individual participant data (IPD) sharing plan**

The datasets generated during and/or analysed during the current study are not expected to be made available due to the use of anonymous participant level data being made available not being specified in the participant information sheet or consent form during the trial.

**IPD sharing plan summary**

Not expected to be made available

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Abstract results</a>	results	15/05/2016		No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes