# The clinical and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock

Submission date Recruitment status [X] Prospectively registered 18/11/2009 No longer recruiting [ ] Protocol [X] Statistical analysis plan Registration date Overall study status 19/11/2009 Completed [X] Results [ ] Individual participant data **Last Edited** Condition category 20/04/2016 Infections and Infestations

#### Plain English summary of protocol

Background and study aims

Each year in the UK, about 31,000 people are admitted to critical care with severe sepsis, a syndrome where the body has an uncontrolled inflammatory response to infection which leads to damage to and subsequently failure of organs such as the lungs, heart and kidneys. Around one third of these patients die before discharge from hospital. Identifying these patients early and applying a strict protocol to control the amount of fluids, blood and drugs given may reduce the number of deaths and also the amount of time patients spend in hospital. However, we do not know whether this approach would be as successful if applied across all hospitals in the NHS. We aim to compare this protocol to the usual care delivered in NHS emergency departments and medical/surgical admissions units to establish the best approach to managing these patients.

Who can participate?

Patients aged 18 or over with the early signs of severe sepsis

What does the study involve?

Participants are randomly allocated either to be treated according to the new protocol or to receive the usual care. We assess the number of deaths within 90 days and the costs of each approach to determine whether the protocols offer good value for money to the NHS.

What are the possible benefits and risks of participating? Not provided at time of registration

Where is the study run from?

Intensive Care National Audit and Research Centre (ICNARC) (UK)

When is the study starting and how long is it expected to run for? February 2011 to December 2013

Who is funding the study?

NIHR Health Technology Assessment Programme - HTA (UK)

Who is the main contact? Prof Kathryn Rowan kathy.rowan@icnarc.org

# Contact information

#### Type(s)

Scientific

#### Contact name

Prof Kathryn Rowan

#### Contact details

Intensive Care National Audit and Research Centre (ICNARC) Napier House 24 High Holborn London United Kingdom WC1V 6AZ

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## Additional identifiers

#### Protocol serial number

HTA 07/37/47; ICNARC/01/01/09

# Study information

#### Scientific Title

A multicentre, randomised controlled trial of the clinical and cost-effectiveness of early, goaldirected, protocolised resuscitation for emerging septic shock

#### Acronym

**ProMISe** 

#### Study objectives

Current hypothesis as of 04/01/2013:

To evaluate a resuscitation protocol, with pre-determined haemodynamic goals, compared with usual resuscitation

Previous hypothesis until 04/01/2013:

To evaluate a resuscitation strategy with pre-determined haemodynamic endpoints compared to usual care for patients with severe sepsis or septic shock.

More details can be found at: http://www.nets.nihr.ac.uk/projects/hta/073747 Protocol can be found at: http://www.nets.nihr.ac.uk/ data/assets/pdf file/0014/51800/PRO-07-37-47.pdf

#### Ethics approval required

Old ethics approval format

#### Ethics approval(s)

Not provided at time of registration

#### Study design

Prospective multicentre randomised controlled trial

#### Primary study design

Interventional

#### Study type(s)

Treatment

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

Severe sepsis/septic shock

#### **Interventions**

Intervention arm: Early goal-directed protocolised resuscitation; targeting of specific haemodynamic goals including central venous pressure, mean arterial pressure and central venous oxygen saturation.

Control arm: Usual care

Patients admitted to Emergency Departments with severe sepsis or septic shock will undergo 6 hours of the intervention arm post-randomisation. For the control arm patients will be treated via usual care for these 6 hours. After this patients will be treated with standard care.

Patients will be followed up for a year post-admission to hospital. This will include assessments at 28 days, 90 days and 1 year. This trial is not classed as a CTIMP.

#### Intervention Type

Other

#### Phase

Not Applicable

## Primary outcome(s)

- 1. Mortality at 90 days
- 2. Incremental cost-effectiveness at one year

#### Key secondary outcome(s))

Current secondary outcome measures as of 04/01/2013:

- 1. To compare:
- 1.1. Mortality at one year
- 1.2. Health-related quality of life at 90 days and one year
- 1.3. Resource use and costs at 90 days and one year
- 1.4. Requirement for, and duration of, critical care unit organ support
- 1.5. Length of stay in the ED, critical care unit and acute hospital
- 2. To estimate:
- 2.1. Lifetime incremental cost-effectiveness

Previous secondary outcome measures until 04/01/2013:

- 1. Duration of survival
- 2. Mortality at 28 days
- 3. Mortality at discharge from critical care and discharge from hospital
- 4. Mortality at one year
- 5. Sequential Organ Failure Assessment (SOFA) score at 6 hours and 72 hours (adjusted for baseline)
- 6. Requirement for, and duration of, monitoring and support of specific organ systems (CCMDS)
- 7. Duration of ED, critical care unit and hospital stay
- 8. Health-related quality of life (EQ-5D) at 90 days and one year
- 9. Resource use and costs at 90 days and one year
- 10. Lifetime incremental cost-effectiveness

#### Completion date

31/12/2013

# Eligibility

#### Key inclusion criteria

- 1. Greater than or equal to 18 years of age, either sex
- 2. Known or presumed infection
- 3. Two or more systemic inflammatory response syndrome (SIRS) criteria:
- 3.1. Core temperature less than or equal to 36°C or greater than or equal to 38°C
- 3.2. Heart rate greater than or equal to 90 beats/min
- 3.3. Respiratory rate greater than or equal to 20 breaths/min (or hyperventilation indicated by partial pressure of carbon dioxide in arterial blood [PaCO2] 4.3 kPa or mechanical ventilation for an acute process)
- 3.4. White blood cell count less than or equal to  $4 \times 10^9$  l or greater than or equal to  $12 \times 10^9$  l (or the presence of greater than 10% immature neutrophils "bands")
- 4. Refractory hypotension or hypoperfusion:
- 4.1. Hypotension is confirmed by the presence of systolic blood pressure less than 90 mmHg despite an intravenous (IV) fluid challenge of at least 20 ml/kg within 30 minutes of Emergency Department (ED) arrival (including IV fluids administered by pre-hospital/Emergency Medical Services [EMS] personnel)
- 4.2. Hypoperfusion is confirmed by a blood lactate concentration greater than or equal to 4 mmol/L)
- 5. First dose of IV antimicrobial therapy commenced prior to randomisation

#### Participant type(s)

Patient

#### Healthy volunteers allowed

No

#### Age group

Adult

#### Lower age limit

18 years

#### Sex

Αll

#### Key exclusion criteria

Current exclusion criteria as of 04/01/2013:

- 1. Age less than 18 years
- 2. Known pregnancy
- 3. Primary diagnosis of:
- 3.1. an acute cerebral vascular event
- 3.2. acute coronary syndrome
- 3.3. acute pulmonary oedema
- 3.4. status asthmaticus
- 3.5. major cardiac arrhythmia (as part of primary diagnosis)
- 3.6. seizure
- 3.7. drug overdose
- 3.8. injury from burn or trauma
- 4. Haemodynamic instability due to active gastrointestinal haemorrhage
- 5. Requirement for immediate surgery
- 6. Known history of AIDS
- 7. Do-Not-Attempt-Resuscitation (DNAR) status
- 8. Advanced directives restricting implementation of the resuscitation protocol
- 9. Contraindication to central venous catheterization
- 10. Contraindication to blood transfusion
- 11. Attending clinician deems aggressive resuscitation unsuitable
- 12. Transferred from another in-hospital setting
- 13. Not able to commence resuscitation protocol within one hour of randomisation or complete six hours of protocol treatment from commencement

#### Previous exclusion criteria until 04/01/2013:

- 1. Aged less than 18 years
- 2. Known pregnancy
- 3. Primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary oedema, status asthmaticus, major cardiac arrhythmia (as part of primary diagnosis), seizure, drug overdose, injury from burn or trauma
- 4. Haemodynamic instability due to active gastrointestinal (GI) haemorrhage
- 5. Immunosuppressive agents including chemotherapy for uncured cancer, immunosuppression for organ transplantation or from systematic disease
- 6. Requirement for immediate surgery
- 7. Do not resuscitate status
- 8. Advanced directives restricting implementation of the protocol
- 9. Contraindications to central venous catheterisation
- 10. Contradiction to blood transfusion (i.e. Jehovah's Witness)
- 11. Attending physician deems aggressive care unsuitable
- 12. Participation in another interventional study
- 13. Transferred from another in-hospital setting
- 14. Not able to start within 1 hour of randomisation or finish within 6 hours

#### Date of first enrolment

15/02/2011

#### Date of final enrolment

# Locations

#### Countries of recruitment

United Kingdom

England

Study participating centre
Intensive Care National Audit and Research Centre (ICNARC)
London
United Kingdom
WC1V 6AZ

# Sponsor information

#### Organisation

Intensive Care National Audit and Research Centre (ICNARC) (UK)

#### **ROR**

https://ror.org/057b2ek35

# Funder(s)

### Funder type

Government

#### **Funder Name**

NIHR Health Technology Assessment Programme - HTA (UK)

# **Results and Publications**

Individual participant data (IPD) sharing plan

## IPD sharing plan summary

Not provided at time of registration

## Study outputs

Output type	Details	Date created Date added	Peer reviewed?	Patient-facing?
Results article	results	02/04/2015	Yes	No
Results article	results	01/11/2015	Yes	No
Participant information sheet	Participant information sheet	11/11/2025 11/11/2025	No	Yes
Statistical Analysis Plan	statistical analysis plan	01/12/2013	No	No