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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
Registration date	**Overall study status**	[X] Statistical analysis plan
19/11/2009	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
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
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Contact information

Type(s)
Scientific

Contact name
Prof Kathryn Rowan

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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, goal-directed, 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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

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

Secondary outcome measures
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

Overall study start date
15/02/2011

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 x 10^9 l or greater than or equal to 12 x 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

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
1260

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
31/12/2013

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Intensive Care National Audit and Research Centre (ICNARC)
London
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Sponsor information

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

Sponsor details
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Sponsor type
Government

Website
https://www.icnarc.org/

ROR
https://ror.org/057b2ek35

Funder(s)

Funder type
Government

Funder Name
NIHR Health Technology Assessment Programme - HTA (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

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?
Statistical Analysis Plan	statistical analysis plan	01/12/2013		No	No
Results article	results	02/04/2015		Yes	No
Results article	results	01/11/2015		Yes	No