Protocolised Management In Sepsis:
A multicentre randomised controlled trial of the clinical and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock
Methodological co-investigators

- Kathy Rowan (Chief Investigator)
- David Harrison (Statistical analysis)
- Richard Grieve (Economic evaluation)
Clinical co-investigators

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ICNARC CTU Trial Team

- Paul Mouncey (ProMISe Trial Manager)
- Tiffany Osborn (ProMISe Trial Clinician)
- Sarah Corlett (Trials Office Administrator)
- TBA (Trials Data Manager)
- Rachael Scott (Trials Office Manager)
Background/rationale

• Rivers *et al* 2001, reported results of single centre trial in the US
• Compared six hours of early, goal-directed, protocolised resuscitation with usual resuscitation
• Reduction of in-hospital mortality from 46.5% to 30.5%
• Shortened hospital length of stay for survivors
Background/rationale

• Increasing incidence of severe sepsis in UK
  – 31,000 critical care episodes per year

• Approx. 21% present at ED with hospital mortality 35%

• Mean stay - 9 days critical care and 14 days hospital
Primary objectives...

- To estimate the effect of early, goal-directed, protocolised resuscitation compared with usual resuscitation on mortality at 90-days.

- To compare incremental cost-effectiveness of early, goal-directed, protocolised resuscitation compared with usual resuscitation at one year.
Secondary objectives...

To compare:

- requirement for, and duration of, organ support in critical care unit
- emergency department, critical care unit and acute hospital length of stay
- mortality, health-related quality of life and resource use/costs at 90-days and one year
- estimate lifetime incremental cost-effectiveness
Patient flow through the trial

1. Initial assessment
2. Consent
3. Randomisation
   - Early, goal-directed, protocolised resuscitation
   - Usual resuscitation
   - 90 days post randomisation
   - 1 year post randomisation
Progress (i)...

- Re-contracted start date with funder from 1 November 2009 to 1 April 2010 (48 months) - H1N1...!
- ProMiSe Trial Meeting - 16 March 2010 - attendance from 54 NHS hospitals
- Clinical Trial Protocol development completed
- Edwards Lifesciences negotiations
- CLRN negotiations
- Liaison with international colleagues (ProCESS/ARISE)
Progress (ii)...

- Ethics approval - 2 August
- CSP global checks completed (October)
- Site sign-up - local R&D process started
Sites registered...
Patient flow through the trial

- Initial assessment
- Consent
- Randomisation
  - Early, goal-directed, protocolised resuscitation
  - Usual resuscitation
- 90 days post randomisation
- 1 year post randomisation
Patient flow through the trial

Initial assessment
Inclusion criteria

- Eligibility - up to SIX* hours from ED presentation (met in ANY order):

  - Infection
    - Presumed/Known

  - SIRS - two of
    - Temperature (≥38°C or ≤36°C)
    - Heart rate (≥90 beats min⁻¹)
    - WBC (≤4 × 10⁹ l⁻¹ or ≥12 × 10⁹ l⁻¹ or ≥10% immature neutrophils)
    - Respiratory rate / Hyperventilation (≥20 breaths min⁻¹ / PaCO₂ ≤4.3 kPa / acute mechanical ventilation)

  - Hypoperfusion
    - Lactate (4 mmol l⁻¹ or higher)
    - Or Hypotension
      - SBP less than 90 mmHg / MAP less than 65 mmHg (after minimum one litre fluid challenge within 60 minutes)
      - IV antibiotics
        - Commenced

*Average time to meet eligibility criteria in ARISE (Australasia) is 1.6 hours
Exclusion criteria (i)

- Age less than 18 years
- Known pregnancy
- Primary diagnosis of:
  - an 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
- Haemodynamic instability due to active gastrointestinal haemorrhage
Exclusion criteria (ii)

- Immunosuppressive agents for uncured cancer or immunosuppression for organ transplantation or from systematic disease
- Requirement for immediate surgery
- Known history of AIDS
- Do-Not-Attempt-Resuscitation (DNAR) status
- Advanced directives restricting implementation of the resuscitation protocol
- Contraindication to central venous catheterization
- Contraindication to blood transfusion
- Attending clinician deems aggressive resuscitation unsuitable
- Participating in another interventional study
- Transferred from another in-hospital setting
- Not able to commence resuscitation protocol within one hour of randomisation or complete resuscitation protocol within six hours of commencing
Patient flow through the trial

Initial assessment → Consent
Consent

• Up to **TWO** hours from becoming eligible to consent and randomise
• Mental capacity of the patient established
• If patient has mental capacity, approach
• If patient does not have mental capacity, approach Personal/Professional Consultee (if available)
• If no Consultee(s), emergency consent to randomise
• Seek retrospective consent on regaining mental capacity
Patient flow through the trial

1. Initial assessment
2. Consent
3. Randomisation
Randomisation

- Dedicated 24/7 telephone randomisation service
- Randomisation stratified by recruiting site
- ProMISE Trial Clinician or clinical co-investigator available 24/7 for any queries
Timings

- Up to six hours to meet inclusion criteria
- Up to two hours to consent/randomise
- Protocolised resuscitation commenced/usual resuscitation continued as soon as possible
Patient flow through the trial

Initial assessment → Consent → Randomisation

Early, goal-directed, protocolised resuscitation
Early goal-directed protocolised resuscitation

- Protocol:
  - three elements
  - performed in series or simultaneously to attain minimum goals at the discretion of treating clinician(s)
Line insertion

- Central Venous Catheter with ScvO2 monitoring capability
- Arterial line at discretion of treating clinician(s)
Central Venous Pressure (CVP)

<table>
<thead>
<tr>
<th>Minimum goal</th>
<th>Achieved</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>CVP 8 mmHg</td>
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- Fluid type (crystalloid/colloid) and rate may be adjusted based on patient requirements at the discretion of the treating clinician(s)

No

500 ml fluid bolus every 30 minutes

Yes

To next element - SBP/MAP
Systolic Blood Pressure (SBP) or Mean Arterial Pressure (MAP)

Minimum goal  Achieved  Action

- SBP 90 mmHg Or MAP 65 mmHg

  No  Vasopressor agents

  Yes  To next element - ScvO₂

- If MAP greater than 90mmHg, consider vasodilator
- Vasopressor/vasodilator type and use at the discretion of the treating clinician(s)
Central venous oxygen saturation ($\text{ScvO}_2$)

Minimum goal: $\text{ScvO}_2$ 70%

- **Achieved**
  - Yes: To next element - CVP
  - No:
    - If Hb <10 g dl$^{-1}$ after clear fluid resuscitation then give Packed Red Blood Cells
      - If Hb $\geq$10 g dl$^{-1}$ give dobutamine
      - If goal still not met, consider ventilation with sedation/paralysis
    - No action taken, reassess every 30 minutes

Reassess every 30 minutes
Timings

- Up to six hours to meet inclusion criteria
- Up to two hours to consent/randomise
- Protocolised resuscitation commenced (or usual resuscitation continued) as soon as possible
- Six hours of protocolised resuscitation
Patient flow through the trial

- Initial assessment
- Consent
- Randomisation

Early, goal-directed, protocolised resuscitation
Usual resuscitation
Usual resuscitation

- Sites to continue to resuscitate patients as deemed appropriate by the treating clinician(s)
Patient flow through the trial

1. Initial assessment
2. Consent
3. Randomisation
   - Early, goal-directed, protocolised resuscitation
   - Usual resuscitation

4. 90 days post randomisation
5. 1 year post randomisation
At 90 days

- Mortality (primary outcome)
- Health-related quality of life
- Resource use and costs

At one year

- Mortality
- Health-related quality of life
- Resource use and costs
Trial design...

• Multi-centre, open, parallel group, randomised controlled trial
• 1260 adult patients presenting in the ED with emerging septic shock
• Recruit patients from 48 NHS EDs
Sample size...

- Rivers *et al.* ARR 16% (46.5 to 30.5%) in hospital mortality
- Aim to achieve 80% power to detect ARR 8% in 90-day mortality from 40% to 32% (P<0.05)
- Require 630 patients per arm (1260 total) including refusals/lost to follow-up
- Excess of 99% power to detect ARR of magnitude observed in Rivers *et al.*
Recruitment rate...

- 14 patients per hospital per year (ICNARC Case Mix Programme Database suggests 22 patients/hospital/year)
- Previous UK studies:
  - 13 per centre per year\(^1\)
  - 75 per centre per year\(^2\)
  - 600 per centre per year\(^3\)
- Recruitment period 26 months
Trial data collection...

Timepoints

- Baseline
- End of six hours of treatment
- 24 & 72 hours post randomisation
- Adverse Events up until 30 days post-randomisation
- Acute hospital stay data
Resources...

- **Staffing**
  - CLRN resources for NHS support costs
  - ProMISe resources for local co-ordination

- **Equipment**
  - Vigileo Monitor, training and 24/7 support provided by Edwards Lifesciences Ltd

- **Other**
  - Start-up funds for sites
  - Ongoing support from ICNARC CTU and
Timelines from here...

- Site sign-up
- Local R&D process
- First site initiation/set-up meeting (23 November, 2010)
- Start patient recruitment (December 2010)
- Subsequent site initiation/set-up meetings (December 2010 to March 2011)
Governance - TSC/DMEC

- TSC Chair: Professor Steve Goodacre
- DMEC Chair: Professor Jon Nicholl
International trials

• **ProCESS**
  Protocolised Care for Early Septic Shock
  1935 patients / 40 sites
  Opened: March 2008

• **ARISE**
  Australasian Resuscitation In Sepsis Evaluation
  1600 patients / 32 sites
  Opened: October 2008
Contact...

Please contact the ProMISE Trial Team at the ICNARC CTU if you have any questions

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