NIHR HTA Programme

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639

email: hta@hta.ac.uk
web: www.hta.ac.uk

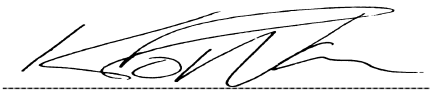
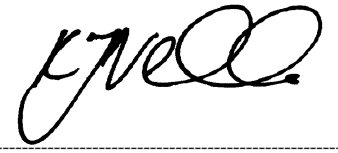
icnarc | intensive care national audit & research centre

HTA

ProMISe

Protocolised Management In Sepsis (ProMISe):
a multi-centre, randomised controlled trial of the clinical and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock

REC number:	**10/H0722/42**
Trial Sponsor:	**ICNARC**
Trial Sponsor reference:	**ICNARC/01/01/09**
Trial Funder:	**NIHR HTA Programme**
Funder reference:	**07/37/47**
ISRCTN number:	**ISRCTN36307479**
NIHR CRN Portfolio ID number:	**9820**
CSP reference:	**39113**
Protocol version:	**Version 2.3**
Protocol version date:	**31 August 2012**

Role, name and position:	Signature:	Date:
Chief Investigator: Prof Kathryn Rowan Director, ICNARC		31 August 2012
For the Sponsor: Keryn Vella Operations Director, ICNARC		31 August 2012

Please note: This protocol should not be applied to patients treated off trial. The trial will be monitored for adverse events and ICNARC can only ensure that active trial investigators are updated of any amendments to the protocol.

Trial management:

For general queries, supply of trial documentation and central data management, please contact the Intensive Care National Audit & Research Centre (ICNARC) Clinical Trials Unit (CTU) at:

ICNARC
Napier House
24 High Holborn
London
WC1V 6AZ

Trial Manager: Mr Paul Mouncey, ICNARC
Tel: +44 (0) 20 7269 9277
Fax: +44 (0) 20 7831 6879
Email: promise@icnarc.org

Clinical Advisor: Dr Tiffany M. Osborn
Email: promise@icnarc.org

Trial Statistician: Ms Sarah Power, ICNARC
Senior Statistician: Dr David Harrison, ICNARC

Chief Investigator: Prof Kathryn Rowan, Director
Address: ICNARC
Napier House
24 High Holborn
London
WC1V 6AZ

Clinical Management:

For any urgent clinical support please contact the 24 hours/seven days per week telephone number below.

Clinical support 24/7 telephone number: 020 7269 9295

Lead Clinicians: Prof Derek Bell, Professor of Acute Medicine,
Chelsea and Westminster Hospital, London

Prof Tim Coats, Professor of Emergency Medicine,
Leicester Royal Infirmary

Prof Mervyn Singer, Professor of Intensive Care Medicine,
University College Hospital, London

Co-applicants: Prof Julian Bion, Professor of Intensive Care Medicine,
Queen Elizabeth Hospital, Birmingham

Col. Tim Hodgetts, Honorary Professor of Emergency Medicine & Trauma,
Queen Elizabeth Hospital, Birmingham

Dr Duncan Young, Consultant and Senior Clinical Lecturer in Anaethetics and Critical Care, John Radcliffe Hospital, Oxford

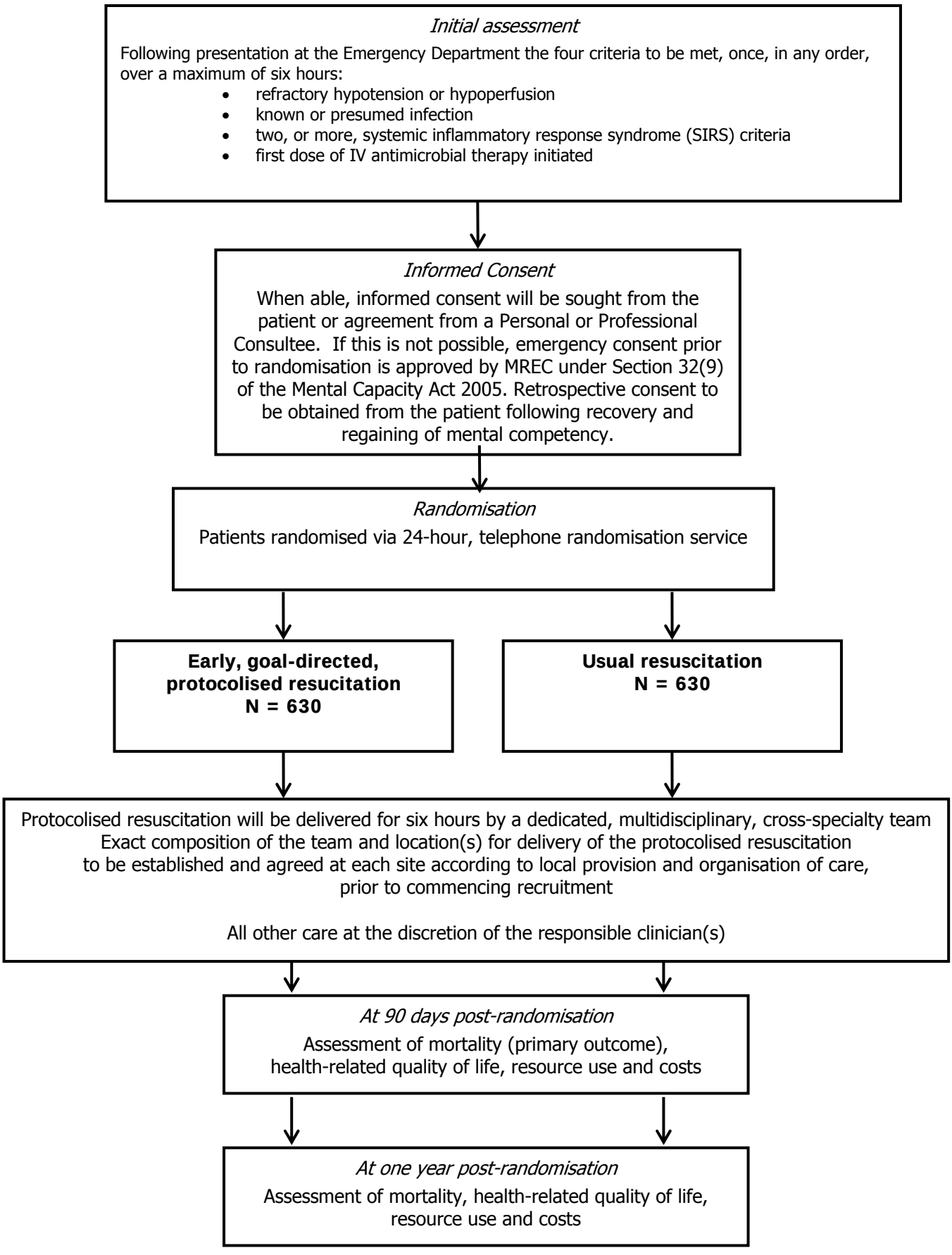
Contents

1.0 Protocol summary

1.1 Summary of trial design

Title:	A multicentre, randomised controlled trial of the clinical and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock
Short Title/acronym:	Protocolised Management In Sepsis/ProMISe
REC number:	10/H0722/42
Sponsor name and reference:	ICNARC and ICNARC/01/01/09
Funder name and reference:	NIHR HTA Programme and 07/37/47
ISRCTN number:	36307479
NIHR CRN Portfolio ID number:	9820
CSP reference:	39113
Design:	An open, prospective, multicentre randomised controlled trial
Overall aim:	To evaluate a resuscitation protocol, with pre-determined haemodynamic goals, compared with usual resuscitation
Primary endpoints:	90-day all cause mortality Incremental cost per QALY gained at one year
Secondary endpoints:	To compare: mortality at one year; health-related quality of life at 90 days and one year; resource use at 90 days and one year; requirement for and duration of critical care organ support; length of stay in the Emergency Department, critical care unit and acute hospital. To estimate : lifetime incremental cost-effectiveness.
Target accrual:	1260
Inclusion criteria:	Following presentation at the Emergency Department, the four criteria to be met, once, in any order, over a maximum of six hours: refractory hypotension or hypoperfusion known or presumed infection two, or more, systemic inflammatory response syndrome (SIRS) criteria first dose of IV antimicrobial therapy initiated
Exclusion criteria:	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 Requirement for immediate surgery Known history of AIDS Do-Not-Attempt-Resuscitation (DNAR) status Advanced directives restricting implementation of the protocol Contraindication to central venous catheterization Contraindication to blood transfusion Attending physician deems aggressive care unsuitable Transferred from another in-hospital setting Not able to commence protocol within one hour of randomisation or complete six hours of protocol treatment from commencement
Planned number of sites:	Minimum 48
Treatment summary:	Early, goal-directed, protocolised resuscitation versus usual resuscitation
Anticipated duration of recruitment:	26 months
Duration of patient follow up:	For one year post-initiation of resuscitation or until death
Definition of end of trial:	The end of the trial will be when the final patient has completed their one year follow-up

1.2 Trial schema



2.0 Introduction

2.1 Background

2.1.1 Emerging septic shock is a major public health problem

Severe sepsis is a syndrome characterised by a systemic inflammatory response to infection that leads to rapid acute organ failure and, potentially, rapid decline to death. In 2006, ICNARC reported an increasing incidence of severe sepsis in UK adult critical care units, rising from 50 to 70 cases per 100,000 population per year over the last decade. This now represents approximately 31,000 patient episodes per year.[1] Similarly, high incidence rates have been reported elsewhere.[2]

Patients with emerging severe sepsis and septic shock (sepsis with hypoperfusion and sepsis with persistent hypotension after a one litre fluid bolus) presenting in the Emergency Department (ED) are an important subgroup of these patients. Analysis of the ICNARC Case Mix Programme Database (CMPD), a national database of over 600,000 admissions to critical care units, indicates that 21% of all severe sepsis cases (approximately 6,500 patients per year) are admitted to the critical care unit via the ED. In-hospital mortality for these patients is 35%. They spend a mean of 9 days in the critical care unit and a further 14 days in acute hospital culminating in an average cost of around £19,000 per patient or a total annual cost for the NHS in excess of £100 million per annum.

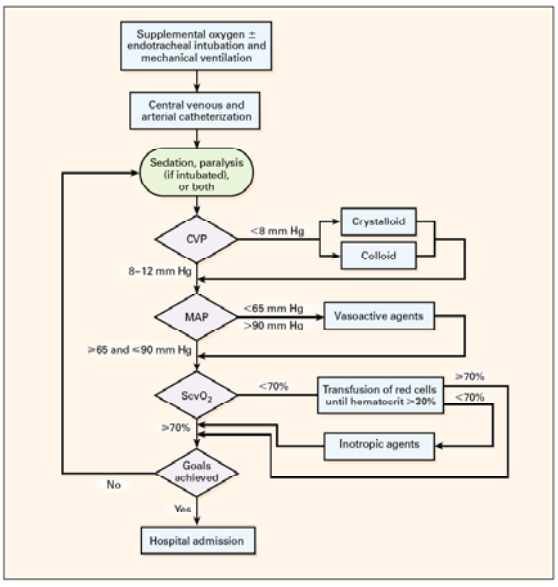
Efforts to improve care for these patients are hampered by multiple factors including limited evidence regarding the timing and delivery of therapies. It has been suggested that, there are "golden hours" in the initial management of emerging septic shock where prompt, rigorous, protocolised care may reduce unwanted consequences and improve clinical outcomes.[3]

2.1.2 Early, goal-directed, protocolised resuscitation for emerging septic shock

In 2001, Rivers *et al.* [4] reported the results of a single-centre, randomised controlled trial (RCT), which took place in the United States (US). This trial was investigating the delivery of six hours of early, goal-directed, protocolised resuscitation (with pre-determined haemodynamic goals) to patients presenting at an ED with emerging septic shock. Early protocolised resuscitation, compared with usual resuscitation, significantly reduced hospital mortality (from 46.5% to 30.5%) and shortened hospital length of stay for survivors.

The rationale for this approach is that many patients with emerging septic shock have global tissue hypoxia that is not adequately identified using traditional resuscitation endpoints and rapid correction of occult tissue hypoxia leads to improved survival. Accordingly, early, goal-directed, protocolised resuscitation incorporates the invasive measurement of central venous haemoglobin oxygen saturation ($ScvO_2$) to detect occult global tissue hypoxia. By improving $ScvO_2$, tissue perfusion may be optimised rapidly. The primary goal is to correct the oxygen debt by restoring and maintaining $ScvO_2$ equal to, or above, 70%.

Figure 1. Early goal-directed resuscitation protocol used in the Rivers *et al.* trial.



Other direct and indirect evidence for early, goal-directed, protocolised resuscitation includes:

animal models of sepsis demonstrating improved survival with aggressive fluid resuscitation;[5] decreased mortality in a meta-analysis of ten, single-centre, non-randomised, before and after studies using historical controls (see: Appendix 2); decreased mortality in a single-centre, RCT in a critical care population;[6] and evidence from other critically-ill patient subgroups (e.g. myocardial infarction and trauma) where mortality has been reduced following the introduction of early, goal-directed, protocolised resuscitation.[7;8]

2.1.3 Early, goal-directed, protocolised resuscitation for emerging septic shock in the UK

The plausible biological rationale for early, goal-directed, protocolised resuscitation, combined with the results of the single-centre, US trial and some observational studies, has led to its recommendation for initial management of all patients with severe sepsis in the internationally, professionally-endorsed Surviving Sepsis Campaign's (SSC) Guidelines for resuscitation and management of severe sepsis.[9;10] However, adoption and compliance with these SSC resuscitation and management bundles remains limited.

Current resuscitation practice in the UK, though not standardised across hospitals, usually involves intravenous fluid and vasoactive drug administration with the intensity of resuscitation typically being determined by clinical assessment. Therapeutic strategies to improve $ScvO_2$ are not routinely employed during resuscitation in UK hospitals.

Several surveys and studies have reported barriers to the implementation of early, goal-directed, protocolised resuscitation for emerging septic shock. These include: recognition of patients; time required to deliver the protocol; local staffing and functioning of the ED; available resources; concerns about the invasiveness/aggressiveness; requirement for collaboration across specialities (emergency medicine, acute medicine and critical care medicine); and equipoise over the current evidence. A recent survey of 173 English EDs (2007) indicated that only 19% perform some form of early, goal-directed, protocolised resuscitation but that a further 10% were in some phase of planning this.[11] Only two publications have evaluated the SSC resuscitation bundle in a UK setting - one, an audit of a hospital implementing the SSC resuscitation bundle and the other, a non-randomised trial in two NHS acute hospitals. These demonstrated an association between compliance with the SSC resuscitation bundle, or a modified version (without invasive monitoring), and reduced mortality in a predominantly ward based patient population[12].

Reports of successful implementation of early, goal-directed, protocolised resuscitation have identified important enablers including: leadership (local champion); communication, education and training; buy-in to the protocol; provision for protocol transition from ED to the critical care unit; and locally determined delivery.

2.1.4 The need for a UK multi-centre trial

Despite the promising results, the US, single-centre Rivers *et al* trial can only be considered "proof of concept" and it is necessary to establish whether these results are generalisable to the NHS. The sample size was small (n=263 patients) and single-centre studies often reflect local, and sometimes unique, processes of care. Results of single-centre studies may not be replicated in larger, multi-centre studies and important examples of this have recently been reported in the critical care literature.[13]

Both the National Institute for Health and Clinical Excellence (NICE) and the National Patient Safety Agency (NPSA) have recently highlighted the need for a rapid response to acute deterioration of patients in hospital, including those in the ED.[14;15] The delivery of early, goal-directed, protocolised resuscitation may be usefully integrated into such rapid response systems.

Given both the need to reduce mortality and the existence of Level 2 evidence that early, goal-directed, protocolised resuscitation may be an effective treatment not currently used in UK hospitals, a well designed phase III trial to examine the effect of this in UK patients is imperative. The findings will aid patients, families, clinicians and policy-makers and will immediately affect care of critically ill patients.

Currently, multi-centre RCTs of early, goal-directed, protocolised resuscitation for emerging septic shock are open in the US (ProCESS – Protocolised Care for Early Septic Shock) and in Australasia (ARISE – Australasian Resuscitation in Sepsis Evaluation). However, these trials alone are unlikely to change practice in the UK due to differences in the case mix and service delivery and organisation of emergency and critical care.

2.2 ProMISe

The aim of ProMISe is to compare early, goal-directed, protocolised resuscitation for patients presenting with early signs of severe sepsis/septic shock. The trial design is an open, multi-centre, parallel group RCT.

Patients are randomised between early, goal-directed, protocolised resuscitation and usual resuscitation. The intervention arm is delivery of the early, goal-directed, resuscitation protocol (with pre-determined haemodynamic goals). The control arm is delivery of usual resuscitation i.e the care the patient would usually receive if they were not recruited into ProMISe.

2.2.1 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 at one year of early, goal-directed, protocolised resuscitation versus usual resuscitation

2.2.2 Secondary objectives

To compare:

- mortality at one year;
- health-related quality of life at, 90 days and one year ;
- resource use and costs at 90 days and one year;
- requirement for, and duration of, critical care unit organ support;
- length of stay in the ED, critical care unit and acute hospital.

To estimate:

- lifetime incremental cost-effectiveness.

2.3 Trial activation

The ICNARC CTU will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating ProMISe:

- Research Ethics Committee (REC) approval;
- adequate funding for central coordination;
- confirmation of sponsorship; and
- adequate insurance provision.

3.0 Selection of sites / Site investigators

3.1 Site selection

In this protocol **"Site"** refers to the hospital where ProMISe is conducted.

Sites must be able to comply with:

- all responsibilities as stated in the ProMISe Clinical Trial Site Agreement;
- trial treatments, follow-up schedules and all requirements of the trial protocol;
- Research Governance Framework;
- data collection requirements; and
- International Conference on Harmonisation Good Clinical Practice.

ProMISe requires a minimum of 48 sites. Central grant funding, available for 48 grant funded sites, includes the secondment of the equivalent of sixteen ProMISe dedicated Research Nurses throughout the trial. Each hospital should be allocated the equivalent of 0.33 full-time equivalent Research Nurse time. These resources can also be distributed regionally across a group of hospitals if it is determined to be advantageous locally.

3.1.1 Selection of site investigators

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site and ethics committee to lead and coordinate the work for ProMISe on behalf of the site. PIs must have experience in treating sepsis. Each site must identify emergency medicine, critical care medicine, and acute medicine (where available),"champions".

3.2 Site initiation and activation

3.2.1 Inclusion criteria at the site level

The following criteria must be met for a site to participate in ProMISe – a site must:

- identify and sign-up local investigators ("champions") from, at least, emergency medicine and critical care medicine;
- not be providing early, goal-directed, protocolised resuscitation as part of standard resuscitation practice;
- identify a dedicated ProMISe Research Nurse (to be funded, or part-funded, centrally);
- agree to incorporate ProMISe into routine ED activity particularly highlighting the importance of screening at ED presentation;
- agree to adhere to randomisation and to ensure compliance;
- agree, where possible, to recruit all eligible patients to ProMISe and to maintain a ProMISe Screening Log to include reasons why eligible patients were screened and not recruited;

All screened and eligible patients will be recorded to establish an unbiased case selection and full reporting according to the CONSORT statement.[24]

On agreement to participate, and having met all site level inclusion criteria, a ProMISe Research Nurse should be identified and seconded. Unless $ScvO_2$ measurement is consistently part of a site's standard resuscitation, the site will be eligible to participate in ProMISe.

3.2.2 Site initiation

Site initiation will be performed by at least one of the following:

- site visit;
- teleconference with site; or
- investigator meetings.

The following documentation must be in place prior to a site being opened to recruitment by the ICNARC CTU:

- ProMISe Site Research Staff Contact Form;
- ProMISe Delegation of Trial Duties Log;
- all relevant institutional approvals (e.g. local R&D);
- a fully signed ProMISe Trial Agreement with ICNARC;
- confirmation of Electro-Biomedical Engineering testing;
- indemnity form completed for equipment on loan.

3.2.3 Site activation

Once the ICNARC CTU have confirmed that all documentation is in place, a site activation e-mail will be issued to the PI, at which point, the site may start to screen for eligible patients.

Once the site has been activated, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol;
- all relevant site staff are trained in the protocol requirements;
- all trial staff are trained appropriately, including GCP trained;
- appropriate recruitment and care for patients in the trial;
- timely data entry; and
- prompt notification of all adverse events (as specified in Section 11).

The PIs, other investigators and all local staff involved in the conduct of the trial at the site must be identified on the ProMISe Site Research Staff Contact Form and ProMISe Delegation of Trial Duties Log, held at site, and copied to the ICNARC CTU when any changes are made, to be authorised.

4.0 Informed consent

4.1 Obtaining informed consent from participants

Once eligibility has been confirmed and, if the patient is competent to give informed consent, then authorised staff (as per the ProMISe Delegation of Trial Duties Log) will describe ProMISe, supplementing the oral information with the Patient Information Sheet (PIS). Patients will be made aware of the potential risks and benefits. After the doctor or nurse has checked that the PIS and Consent Form are fully understood, the doctor or nurse will invite the patient to sign the form and will then add their own name and countersign it.

Previous work on informed consent in critically-ill patients, conducted by ICNARC alongside the PAC-Man Study (a randomised controlled trial of 1014 patients in 65 critical care units), indicated that only a minority (2.5%) may be able to provide informed consent.[16] While the proportion of patients able to give informed consent is likely to be considerably higher in this trial, it will still be essential to have robust plans in place for situations in which informed consent is not possible.

4.2 Proposed action where fully informed consent is not possible

The Mental Capacity Act 2005 allows consent through this method when:

a) the research is related to the impairing condition that causes the lack of capacity or to the treatment of those with that condition; or
b) the research cannot be undertaken as effectively with people who have the capacity to consent to participate.

ProMISe fulfils the criteria (a) and (b) presented, as the severe sepsis/septic shock will be the cause of the incapacity and, due to the very low numbers of those having capacity to give consent, ProMISe cannot be restricted solely to patients with capacity (who would not be representative of the reference population).

Also the Mental Capacity Act 2005 states that the research:

c) will be likely to be of benefit to the person lacking capacity, either directly (i.e. by improving her/his personal circumstances) or indirectly (by improving the quality of treatment or care more generally), and that this benefit is in proportion to any burden on that person caused by taking part; or
d) will serve to increase knowledge of the cause, treatment or care of people with the same or similar condition and that the risks to participants will be negligible, with no significant interference with their privacy or freedom of action.

The hypothesis is that there will be a reduction from 40% to 32% in 90-day mortality in the early, goal-directed, protocolised resuscitation arm. Rivers e*t al* also demonstrated a reduction in hospital length of stay, and fewer complications for early goal-directed protocolised resuscitation arm.[4] ProMISe will answer the question as to whether early, goal-directed, protocolised resuscitation is beneficial to other people with the same or similar conditions. All risks associated with the treatment are stated in Appendix 4 with no interference to their privacy or freedom of action.

4.2.1 Consultation

If the patient is not competent to give informed consent and there is a Personal Consultee present to advise on the presumed wishes on the patient, authorised staff will describe ProMISe to the patient's Personal Consultee, supplementing the oral information with the Consultee Patient Information Sheet (CPIS). After the doctor or nurse has checked that the CPIS and Consultee Agreement Form are understood, the doctor or nurse will invite the Personal Consultee to sign the form and will then add their own name and countersign it.

If there is no Personal Consultee present agreement can be obtained via the telephone. If agreement is obtained via the telephone the doctor or nurse will complete the Consultee Telephone Agreement Form.

If there is no Personal Consultee present, then the patient will be provided with, if in place at the hospital, a Professional Consultee (Independent Mental Capacity Advocate) appointed by the Trust, if immediately available. Agreement will be addressed in the same manner as for the Personal Consultee. Copies of the signed Consultee Agreement Form or Consultee Telephone Agreement Form and CPIS will be placed in the hospital notes.

If a patient or their Consultee (Personal or Professional) refuses to agree to the patient taking part in the trial, the patient will receive usual care as defined by the clinician responsible for the care of the patient.

If there is neither a Personal or Professional Consultee immediately available, then the doctor or nurse will proceed with Emergency Consent, using the process detailed below in Section 4.2.2 under Section 32(9) of the Mental Capacity Act 2005.

4.2.2 Emergency Consent

It is likely that, due to the emergency nature of the patients' condition with immediate intervention necessary, and there may be no Consultee (Personal or Professional) available. If this is the case, then an independent doctor will be consulted and, if the independent doctor agrees, the researcher will recruit the patient into the trial. This can be done in person or via the telephone. Once Emergency Consent is obtained, the doctor or nurse will complete the Emergency Consent Form.

4.2.3 Retrospective Consent

If the patient recovers and subsequently becomes able to give consent, then a Retrospective Consent Form will be completed. All consent procedures will adhere to the Mental Capacity Act 2005. This procedure will be the same as if the patient was approached prior to randomisation but using a specific Retrospective Patient Information Sheet. If a site later becomes aware that the patient has a pre-exisiting medical condition meaning that they could never regain sufficient mental capacity to provide informed Retrospective Consent (unknown but present prior to randomisation), the site should obtain agreement from the Personal Consultee to use the patient's data. If any patient refuses Retrospective Consent or if any patient or their Consultee (Personal or Professional) withdraws their consent/agreement at any time during the trial, then that patient's data will be locked on the secure, dedicated, ProMISe web data entry system and the patient will continue to receive usual treatment as defined by the clinician(s) responsible for the care of the patient.

5.0 Selection of patients

5.1 Pre-randomisation evaluation

All patients presenting at the ED, at each participating hospital, will be first assessed by the treating ED clinical team and receive standard care in accordance with the current best practice. The treating ED clinical team will then contact the dedicated ProMISe Research Nurse for their hospital.

Standard care should include the following assessments or procedures that are required to evaluate the suitability of patients for the trial:

- in patients with suspected or confirmed infection this should include having arterial or venous blood lactate measurement to assess for the presence of hypoperfusion;
- a first dose of intravenous (IV) antimicrobial therapy commenced prior to randomisation.

Additional investigations and evaluation of the suspected infection will occur as part of standard clinical management.

It is also expected that a minimum IV fluid challenge of one litre fixed bolus within sixty minutes, will be given as part of standard resuscitation for patients with suspected or confirmed infection and evidence of hypotension.

5.2 ProMISe Screening Log

The ProMISe Screening Log will be supplied by the ICNARC CTU and maintained by the site in the Investigator Site File. This should record each patient who meets all the inclusion criteria but was not randomised and each patient who meets all the inclusion criteria and one of more of the exclusion criteria. Details of why the patient was not randomised should be recorded. The ProMISe Screening Log should be sent to the ICNARC CTU, when requested, with patient identifiers removed prior to sending.

5.3 Delivery at site

Whereas the content of the early, goal-directed, resuscitation protocol to be evaluated will be identical across all sites, delivery of the protocol will be locally determined (i.e. pragmatic) and implementation will be delegated to the local investigators to suit their local NHS setting. Delivery of the protocol includes the ability to transition from the ED to another location within the hospital, during the six-hour protocol time frame, where clinically indicated.

5.4 Patient eligibility

Once a potential patient is identified, it is imperative that the following four criteria are satisfied, as soon as possible, and in any order following presentation at the ED, within a maximum of six hours.

5.4.1 Inclusion criteria

1) Refractory hypotension **or** hypoperfusion
    a. Refractory hypotension is confirmed by the presence of a systolic blood pressure of less than 90 mmHg or a mean arterial pressure of less than 65 mmHg, despite a minimum IV fluid challenge of one litre fixed bolus within sixty minutes (including IV fluids administered by pre-hospital personnel)

    or

    b. Hypoperfusion is confirmed by a blood lactate concentration of 4mmol l^{-1} or greater
2) Known or presumed infection
3) Two or more Systemic Inflammatory Response Syndrome (SIRS) criteria:
    a) core temperature of 36°C or less or of 38°C or more;
    b) heart rate of 90 beats min^{-1} or more;
    c) respiratory rate of 20 breaths min^{-1} or more(or hyperventilation indicated by either a $PaCO_2$ less than 4.3 kPa or mechanical ventilation for an acute process); or
    d) white blood cell count of $4x10^9$ l^{-1} or less or of 12×10^9 l^{-1} or greater (or the presence of greater than 10% immature neutrophils (bands)).
4) First dose of IV antimicrobial therapy initiated prior to randomisation.

Eligibility needs to be confirmed as soon as possible. Each inclusion criterion needs to be met once over a maximum time period of six hours. After this time, resuscitation is no longer considered to be early and the patient is not eligible for entry into ProMISe.

5.4.2 Exclusion criteria

1) Age less than 18 years
2) Known pregnancy
3) 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
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

N.B. If during screening, a patient is found to be participating in another interventional study/trial, then please contact the ICNARC CTU on 020 7269 9295 to discuss their participation in ProMISe.

6.0 Randomisation procedures

The approaching, consenting and randomisation procedures must be completed within two hours of confirmation of eligibility.

6.1 Randomisation and allocation

A dedicated, 24 hours/seven days per week, telephone randomisation service will be available. In addition, during recruitment, the ProMISe Clinical Advisor, or one of the clinical co-investigators, will be available 24 hours/seven days per week to address any emergency recruitment/randomisation issues.

Randomisation telephone number:	020 8099 7784
Emergency 24/7 telephone number:	020 7269 9295

Allocation to one of the two arms will be by randomised permuted blocks (with variable block lengths of 4, 6 and 8), stratified by recruiting site. As this is a large, multi-centre trial, the risk of chance imbalance in prognostic factors is low and the need to randomise patients during a very short time-window mandates that the randomisation process be as simple as possible. For these reasons, we have elected not to stratify the randomisation process on additional prognostic factors.

Patient randomisation must be performed prior to commencement of any trial intervention.

Following pre-randomisation evaluations (as detailed in Section 5.1), confirmation of eligibility and consent of a patient at a site, the ProMISe Randomisation - Eligibility Form must be fully completed prior to telephoning the randomisation service. The eligibility criteria will be reviewed during the randomisation telephone call. A ProMISe Trial Number and treatment allocation will be assigned, and time of randomisation and date/time of T1 (end of the 'golden' hour) will be stated at the end of the call. These must be recorded at the site by the caller on the ProMISe Randomisation – Eligibility Form.

The telephone randomisation service is provided by Sealed Envelope (http://www.sealedenvelope.com/)

6.2 Trial materials

6.2.1 Central venous oxygenation catheter and monitor

Continuous $ScvO_2$ measurement will be undertaken via the PreSep™ central venous oximetry catheter. The PreSep™ catheter is manufactured by Edwards Lifesciences Limited and is commercially available, and licensed for this purpose, in the UK. The catheter is a 20cm 8.5 French triple lumen central venous catheter (CVC), and has two 18-gauge lumens and a single 15-gauge lumen. In addition, the PreSep™ has a fibreoptic bundle used for oximetric $ScvO_2$ monitoring. When the fibreoptic port is connected to a calibrated Edwards Vigilance or Vigileo monitor, the catheter is capable of providing a continuous $ScvO_2$ reading. The catheters and monitor will be supplied to sites for ProMISe and used only for those patients randomised to receive the early, goal-directed, resuscitation protocol.

The monitor is provided on loan free-of-charge to all sites participating in the trial for the duration of the trial period.

There is a 24 hours/seven days per week support to address any emergency technical issues with the trial equipment.

Edwards Lifesciences support telephone number:	0800 756 0802

6.2.2 Trial equipment

Trial equipment will be stored on a ProMISe trolley. When a patient is randomised to receive the early, goal-directed, protocolised resuscitation, this trolley will be used.

The equipment will include:
- PreSep™ $ScvO_2$ catheter;
- Edwards Vigileo monitor;
- early, goal-directed, resuscitation protocol.

6.3 Modification of early, goal-directed, protocolised resuscitation

Patients will be continuously monitored during the six hours of the delivery of early, goal-directed, protocolised resuscitation. At any time during the six-hour resuscitation period and, if clinically indicated, individual elements of the early, goal-directed, resuscitation protocol can be modified or discontinued at the clinical discretion of the treating clinician(s) for patient safety. For example, the protocol may be modified due to the development of: acute pulmonary oedema; an arrhythmia resulting in cardiovascular instability; or a blood transfusion reaction.

Ultimate responsibility for the safe and effective implementation of the early, goal-directed, protocolised resuscitation remains with the participating trial site.

Patients who do not receive any or all of the elements of the early, goal-directed, protocolised resuscitation will be followed up, according to the trial follow-up schedule, and analysed according to the intention-to-treat principle.

7.0 Trial treatment

7.1 Summary

It is necessary that patients are randomised, as soon as possible, and within two hours of meeting the eligibility criteria.

Eligible patients will be randomised to receive either:

- six hours of early, goal-directed, protocolised resuscitation;

or

- usual resuscitation (standard UK resuscitation practice).

For patients randomised to early, goal-directed, protocolised resuscitation, the clinical protocol will be commenced immediately following randomisation and within "one hour" ("one hour" to be defined as up to the end of the following hour i.e. if the patient is randomised at 9:24 am they have to start early, goal-directed, protocolised resuscitation by 11:00 am). Simple protocol guides will be provided. Patients randomised to usual resuscitation will continue as usual.

7.1.1 Early, goal-directed, protocolised resuscitation

If not already initiated, supplemental oxygen is to be administered, with intubation and mechanical ventilation as needed, to achieve a pulse oximeter reading of 93% or greater. The following elements of the resuscitation protocol may be administered in series or simultaneously, depending on the clinical assessment of the patient's requirements. For example, if a patient is in extremis, the clinical team may decide to administer IV fluids in conjunction with vasopressors. Each element of the protocol should be initiated, if there are no potential condraindication(s), and should be delivered at the discretion of the treating clinician(s) dependent upon patient requirements.

Line insertion

Line insertion involves both the PreSep^{TM}, a CVC with continuous oximetric monitoring capability, inserted either into the subclavian or internal jugular vein, and an arterial line. The CVC with continuous oximetric monitoring capability is inserted using standard techniques for central access and calibrated to achieve a $ScvO_2$ reading. All CVCs will be inserted and managed according to the guidelines of the CVC Care Bundle (*NHS Saving Lives High Impact Intervention: Number 1*[17]).

Fluid resuscitation

Fluid boluses in half-litre, or equivalent increments, are given every thirty minutes until a minimum central venous pressure (CVP) of 8 mmHg is reached. Type of fluid used is at the discretion of the treating clinician(s). The rate may be adjusted, based upon individual patient requirements, at the discretion of the treating clinician(s). Additionally, if the treating clinician(s) discerns a risk to patient safety, a lower CVP may be used.

Blood pressure management

An arterial line is recommended for continuous blood pressure monitoring. If either mean arterial pressure (MAP) is less than 65 mmHg or systolic blood pressure (SBP) is less than 90 mmHg, after fluid resuscitation to a minimum CVP of 8 mmHg, vasopressors are administered and titrated to a minimum MAP of 65 mmHg or a minimum SBP of 90 mmHg. All sites are expected to use such therapies based on best current evidence. Thus, treating clinician(s) may administer their vasopressor of choice, deemed most appropriate based upon the current evidence, patient requirement and local practice.

If MAP is greater than 90 mmHg, afterload reduction can be initiated to lower MAP to within 65-90 mmHg. The vasodilator agent used is at the discretion of the treating clinician(s). If the treating clinician(s) determines a MAP in excess of 90 mmHg is required, due to patient safety concerns such as a known baseline SBP or MAP in excess of the protocol goals, then the patient should be treated accordingly and recorded on the relevant CRF.

$ScvO_2$ management

Once the CVP is a minimum of 8 mmHg and either the MAP is a minimum of 65 mmHg or SBP is a minimum of 90 mmHg, the third goal is a minimum $ScvO_2$ of 70%.

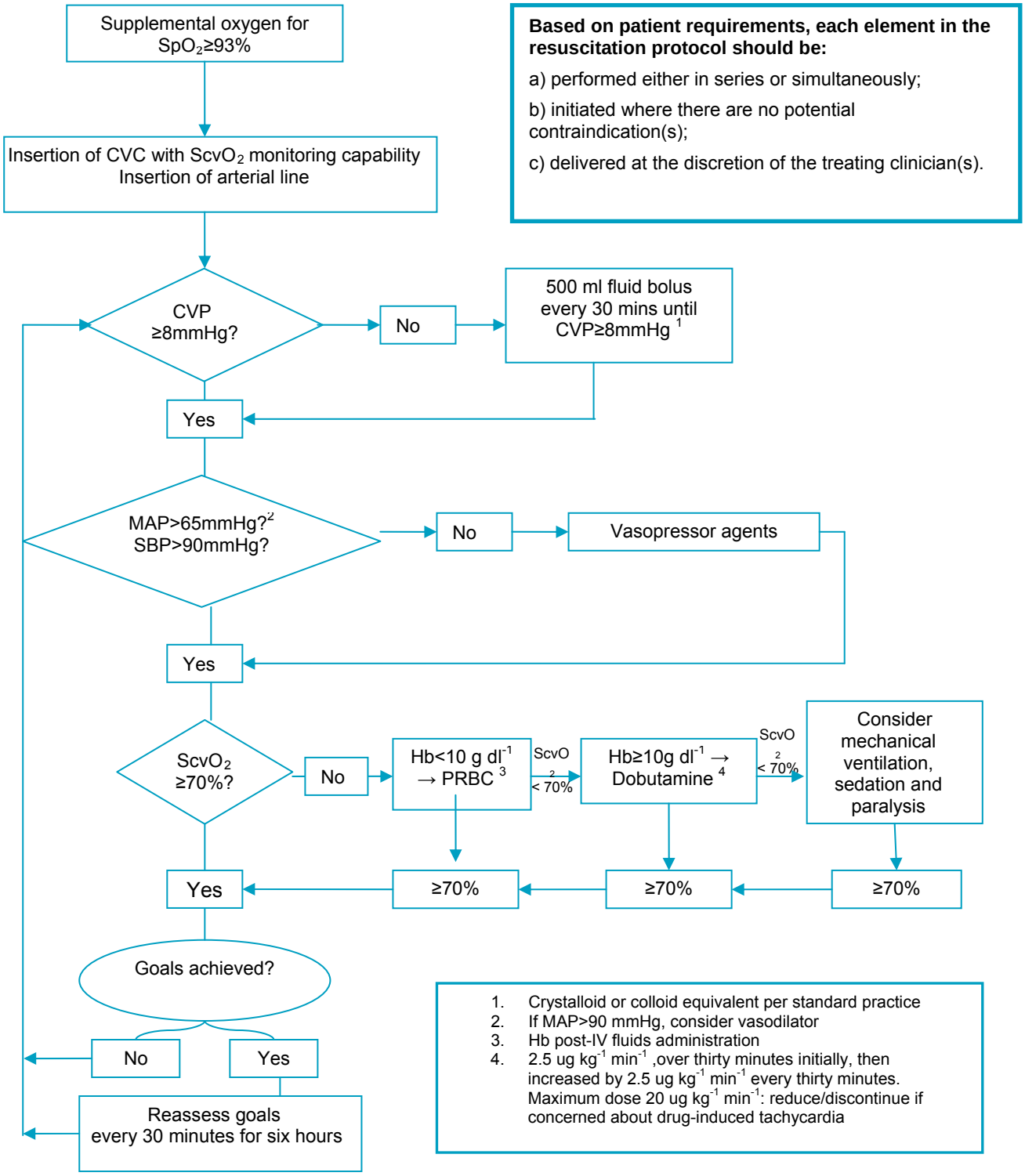
If the $ScvO_2$ is less than 70% and the post-fluid resuscitation haemoglobin is less than 10g dl^{-1}, then packed red blood cells are transfused. Once the haemoglobin is 10g dl^{-1} and, if the $ScvO_2$ is still less than 70%, then inotropic support is initiated with dobutamine. Dobutamine dosing is 2.5 ug kg^{-1} min^{-1}, over thirty minutes initially, then increased by 2.5 ug kg^{-1} min^{-1} every thirty minutes until the $ScvO_2$ is 70% or greater. Dobutamine should be reduced/discontinued, at the discretion of the treating clinician(s), if there is concern about a likely, drug-induced tachycardia, arrhythmia, or if a maximum dose of 20 ug kg^{-1} min^{-1} is attained.

If the $ScvO_2$ remains low, then the patient may be intubated, sedated and paralysed, if not done previously to decrease oxygen consumption.

Post-goal monitoring

Once all goals are met, the patient is monitored continuously for the remainder of the intervention period (a total of six hours). If an end-point subsequently falls below its goal, then the early, goal-directed, resuscitation protocol re-cycles. At the end of six hours, the patient returns to standard care and continuous $ScvO_2$ monitoring is no longer mandated.

Figure 2. ProMISe early, goal-directed, resuscitation protocol



7.1.2 Usual resuscitation

For patients randomised to usual resuscitation, all investigations, monitoring and treatment will be instituted, as considered appropriate, by the treating clinician(s). For these patients, the ProMISe early, goal-directed, resuscitation protocol and associated intervention arm equipment will not be provided. As soon as practicable, and according to local practice, patients should be admitted for in-patient care and transferred to an appropriate hospital location.

7.1.3 Co-interventions

All patients may receive additional treatments beyond those prescribed in the resuscitation protocol including antimicrobial agents, steroids and appropriate surgical intervention. All co-interventions will be left to the discretion of the treating clinician(s) and recorded, as per usual practice, in the patient's medical record.

Note that, in keeping with best practice, it is essential that antimicrobial therapy is administered as soon as practicable.

7.2 Management after trial treatment withdrawal

If patients are withdrawn from trial treatment, then they will receive usual resuscitation and care, as per the treating clinician(s) discretion.

8.0 Assessments

Patient details
- Identifiers
- Sociodemographics
- Co-morbidities

Recruitment data
- Date and time of ED presentation
- Inclusion/exclusion criteria
- Date and time met inclusion/exclusion criteria
- Organ dysfunction and illness severity score
- Date and time randomised

Resuscitation data
- Date and time commenced (if randomised to early, goal-directed, protocolised resuscitation arm)
- Line insertion
- Hourly for six hours
    - Physiological goals
    - Interventions (amount and type)
- At end of six hours
    - Organ dysfunction

24 hours from randomisation
- Organ dysfunction
- Interventions (amount and type)

72 hours from randomisation
- Organ dysfunction
- Interventions (amount and type)
- Infection data

Critical care data
- Critical care organ support

Hospital data
- Date and time of location change within the hospital
- Date and time of discharge from the hospital
- Discharge location

30 days from randomisation
- Safety monitoring data

90 days from randomisation
- Survival status
- Health related Quality of Life (HRQoL)
- Resource use and cost data

1 year from randomisation

- Survival status
- HRQoL
- Resource use and cost data

8.1 Follow-up after initial hospital discharge

All patients surviving to discharge from an acute hospital will be checked against death registrations on the NHS Central Register (NHSCR) for subsequent reporting of mortality data. This will be achieved through regular application of the 'list cleaning' service offered by the Medical Research Information Service (MRIS).

Following randomisation into the trial, the ICNARC CTU will write to each patient's General Practitioner to inform them of the patient's participation in the trial, including a brief description of the trial and a request that the General Practitioner notifies the ICNARC CTU of any events of note.

Patients recorded on the NHSCR as being alive at 90 days and at one year post-randomisation will receive questionnaires to record their health-related quality of life, subsequent hospital admissions and use of personal health services. Questionnaires will be sent with a personally signed letter, a pen enclosed, and a stamped addressed envelope.[18]

Health-related quality of life will be measured by the EuroQol (EQ-5D) measure (see: Appendix 3).[19] EQ-5D is a widely-used generic quality of life measure that can be combined with survival data to calculate Quality-Adjusted Life Years (QALYs). Information on subsequent hospital admissions and the use of personal health services will be recorded on separate healthcare resource use questionnaires.[20]

9.0 Data management guidelines

The ProMISe Team, at each site, should attend and document the early, goal-directed, protocolised resuscitation or abstract retrospectively the recorded data, as necessary.

For both arms, organ dysfunction is evaluated by the SOFA score[21] at baseline, 6 hours and 72 hours, irrespective of location.

All data will be abstracted onto ProMISe paper CRFs. Data are to be entered onto a secure, dedicated, ProMISe web data entry system. The ICNARC CTU will work closely with staff at participating sites to ensure accurate (complete, valid and reliable) data. Extensive completeness, range and consistency checks will further enhance the quality of the data.

Where appropriate, data collection for ProMISe will be piggybacked onto the Case Mix Programme (CMP). Support for the collection and use of patient identifiable data has been approved for the CMP by the Patient Information Advisory Group (PIAG) under Section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001) – Approval Number: PIAG 2-10(f)/2005. Section 251 support is reviewed annually by PIAG and covers all aspects of data management including data security. ICNARC is also registered under the Data Protection Act.

9.1 Data collection

All data must be transcribed onto the ProMISe paper CRFs prior to entering onto the secure, dedicated, ProMISe web data entry system. The original ProMISe paper CRFs must be kept at site. All entries must be clear and legible. The use of abbreviations and acronyms must be avoided. The PI is responsible for the accuracy of all data reported in the ProMISe paper CRF. All ProMISe paper CRFs must be completed and signed by staff listed on the ProMISe Trial Delegation Log and authorised by the PI to perform this duty.

Security of the dedicated, ProMISe web data entry system is maintained through user names and frequently updated passwords. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 1998.

9.2 Corrections

Any corrections made to a ProMISe paper CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The amended ProMISe paper CRF must be retained securely at site. These changes must also be made on the secure, dedicated, ProMISe web data entry system.

9.3 Queries

Data entered onto the secure, dedicated, ProMISe web data entry system will be checked centrally at the ICNARC CTU for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to sites. Sites are required to resolve any queries and update the relevant ProMISe paper CRF and data on the secure, dedicated,

ProMISe web data entry system as required. The amended version of the ProMISe paper CRF must be retained at site.

9.4 Timelines for data entry

Web based data entry must be entered at site, from the ProMISe paper CRFs as soon as possible. The ProMISe paper CRFs need to be kept at site for quality assurance, and monitoring purposes in a secure location.

Sites that persistently do not enter data within a timely manner may be suspended from recruiting further patients into the trial by the ICNARC CTU.

10.0 Trial monitoring and oversight

10.1 Monitoring

Sites must agree to allow trial-related monitoring and audits by providing direct access to source data/documents, as required. Patients' informed consent for this will also be obtained.

10.1.1 On-site monitoring

Members of the ICNARC CTU will be carrying out on-site monitoring. Sites will be contacted with details regarding this prior to the on-site monitoring visit.

10.1.2 Monitoring report

Following the monitoring visit, the ICNARC CTU will provide the site with a monitoring report, which will summarise the documents reviewed, along with any findings. The PI at each site will be responsible for ensuring that the findings from the monitoring visit are addressed.

10.1.3 Central monitoring

Data entered onto the secure, dedicated, ProMISe web data entry system will be checked at the ICNARC CTU for completeness, accuracy and consistency of data. Data queries will be issued to the site. Sites are required to resolve any queries and update the relevant ProMISe paper CRF and data on the secure, dedicated, ProMISe web data entry system as required. The amended version must be retained at site. The ICNARC CTU will send reminders for any overdue data or query.

Sites will also be requested to submit ProMISe Screening Logs and ProMISe Trial Delegation Logs to the ICNARC CTU on a regular basis and these will be checked for consistency and completeness.

10.2 Non-compliance

Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance by a site to important aspect(s) of the trial requirements.

11.0 Adverse Events

11.1 Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC and ICH GCP E6:

Adverse Event
Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with trial treatment. An Adverse Event (AE) can therefore be any unfavourable symptom or disease temporally associated with the use of the trial treatment, whether or not it is related to the trial treatment.

Serious Adverse Event
An AE that:

- results in death;
- is life threatening (the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe);
- requires in-patient hospitalisation or prolongs existing hospitalisation;
- results in persistent or significant disability/incapacity;
- consists of a congenital anomaly or birth defect;
- is otherwise considered to be medically significant by the investigator.

11.2 Recording and Reporting procedures

All patients in ProMISe are critically ill, due to the complexity of the condition, the patients are at increased risk of AEs occurring, many of these events are expected as a result of the patients' medical condition and standard treatment, but may not be related to the trial. Consequently any AEs, not listed in Appendix 4, occurring as a result of the patients' medical condition or standard treatment will not be reported. Pre-existing conditions do not qualify as AEs unless they worsen, these however should be documented in the patient medical notes.

All other AEs that occur between randomisation and 30 days post-the six hours of early, goal-directed, protocolised resuscitation or post-randomisation for those in the usual resuscitation arm must be recorded in the patient medical notes, on the ProMISe paper CRFs and on the secure, dedicated, ProMISe web data entry system. Information regarding date of event onset, severity and relatedness to the trial treatment must be recorded (definitions below). Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to the ICNARC CTU using the trial specific ProMISe SAE Report Form by fax within **24 hours** of observing or learning of the SAE. <u>All sections of the ProMISe SAE Report Form must be completed.</u>

Severity
The site PI or other delegated site investigator(s) must perform an evaluation of severity, for each AE, using the following criteria:

1 = Mild
2 = Moderate
3 = Severe
4 = Life-threatening
5 = Fatal

Relatedness

The site PI or other delegated site investigator(s) must perform an evaluation of relatedness for each AE. This must be determined as follows:

- **None**

There is no evidence of any causal relationship.

- **Unlikely**

There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant medications).

- **Possible**

There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant medications).

- **Probable**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Expectedness

The site PI or other delegated site investigator(s) must perform an evaluation of expectedness for each SAE regardless of causal relationship to the trial procedures. This evaluation must be performed using the list of expected adverse events in Appendix 4. This must be determined as follows:

- **Expected**

The event is listed as an expected AE in Appendix 4 of the ProMISe Protocol.

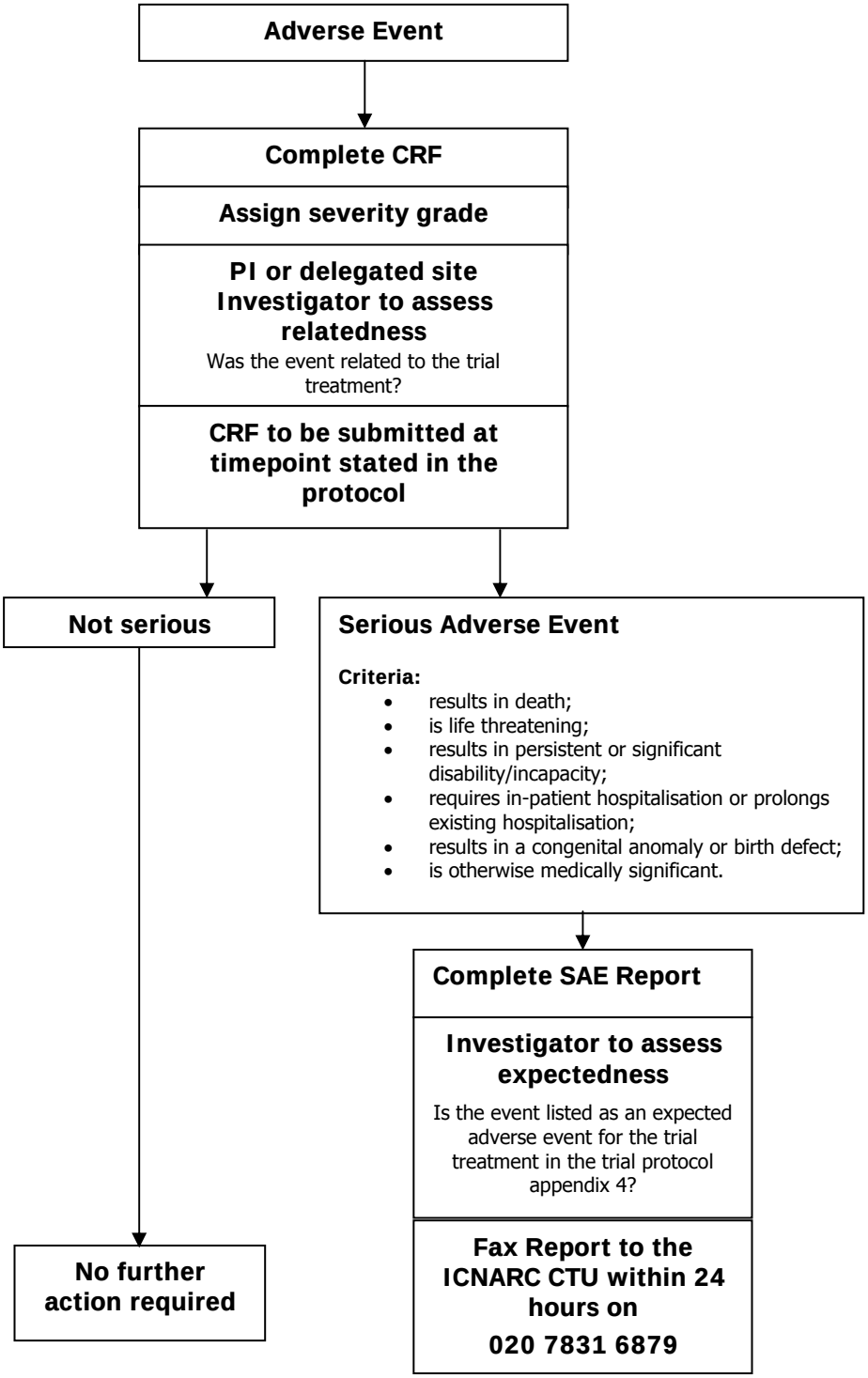
- **Unexpected**

The event is not listed as an expected AE or, the severity of the event is greater than that listed in Appendix 4 of the ProMISe Protocol, for example:

  - the event is life threatening or fatal (unless stated in the protocol Appendix 4 as expected).
  - the patient presents with an event which is considered to be moderate or severe, but only mild is listed as expected in the ProMISe Protocol Appendix 4.

All SAEs must be reported by faxing a completed SAE Report Form within 24 hours of becoming aware of the event to the ICNARC CTU
Fax: 020 7831 6879

Adverse Event reporting flowchart



Serious Adverse Event follow-up reports

All SAEs must be followed-up until resolution. The PI or other delegated site investigator(s) must provide follow-up SAE Report(s) if the SAE had not resolved at the time the initial report was submitted.

Serious adverse event processing at the ICNARC CTU

On receipt of the SAE Report, a clinical member of the ICNARC CTU ProMISe Trial Team, on behalf of the Chief Investigator, will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting. If this is difficult to determine, the Chief Investigator and/or Trial Management Group (TMG) will be consulted for their opinion. In the case of discrepant views, both opinions will be reported.

If the event is evaluated by either the site or a clinical member of the ICNARC CTU ProMISe Trial Team as a related and unexpected SAE, the ICNARC CTU will submit a report to REC within 15 calendar days.

11.3 Clinical review

The ICNARC CTU will provide safety information to the Chief Investigator / TMG / Trial Steering Committee (TSC) / Data Monitoring and Ethics Committee (DMEC) on a periodic basis for review.

11.4 Additional safety monitoring at the ICNARC CTU

The ICNARC CTU will also monitor safety data for any trial related events that are not considered related to the trial treatment. In the event that any trial procedures appear to be resulting in AEs, the Chief Investigator and/or TMG will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, The ICNARC CTU will inform the REC as appropriate.

11.5 Annual progress reports

The ICNARC CTU will submit Annual Progress Reports to the REC. This will commence one year from the date of approval for the trial.

12.0 Withdrawal of patients

In consenting to the trial, patients are consenting to trial treatment, assessments, follow-up and data collection.

12.1 Withdrawal from trial treatment

The treating clinician(s) may withdraw a patient from trial treatment whenever continued participation is no longer in the patient's best interests, but the reasons for doing so must be recorded. In these cases patients remain within the trial for the purposes of follow-up and data analysis according to the treatment arm to which they have been randomised.

If a patient wishes to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used.

12.2 Withdrawal of consent to data collection

If a patient explicitly states their wish not to contribute further data to the trial their decision must be respected and the ICNARC CTU notified in writing. Details should be recorded in the patient's hospital records and no further trial data will be requested.

13.0 Trial closure

13.1 End of trial

The end of the trial will be when the final patient has completed their 1 year follow-up. At which point the Declaration of End of Trial Form will be submitted to the participating ethical committee, as required.

13.2 Archiving of trial documentation

At the end of the trial, the ICNARC CTU will archive securely all centrally held trial related documentation for a minimum of 10 years. Arrangements for its confidential destruction will then be made. It is the responsibility of PIs at each site to keep data and all essential documents relating to the trial held at site for a minimum of 10 years after the end of the trial and in accordance with national legislation and for the maximum period of time permitted by the site, as per local policy.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

If a patient withdraws consent for any data to be used it will be confidentially destroyed.

The ICNARC CTU will notify sites when documentation held at sites may be archived. All archived documents must still be available for inspection and monitoring by appropriate authorities and the the ICNARC CTU upon request.

13.3 Early discontinuation of trial

The trial may be stopped before completion by the Trial Steering Committee (TSC). This can be upon recommendation of the Data Monitoring and Ethics Committee (DMEC). Sites will be informed in writing by the ICNARC CTU of reasons for early closure and the actions to be taken with regard to treatment of patients. Patients should continue to be followed up as per protocol.

13.4 Withdrawal from trial participation by a site

Should a site choose to close to recruitment the PI must inform the ICNARC CTU in writing. Follow up as per protocol must continue for all patients randomised into ProMISe at that site.

Stes that contravene the ProMISe Trial Protocol and the Clinical Trial Site Agreement will be subject to review by the TMG and Sponsor and may be suspended or closed down by the ICNARC CTU.

14.0 Trial management and Trial committees

14.1 Good practice

This trial will be managed according to the Medical Research Council's Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring into Allegations of Scientific Misconduct. The ICNARC CTU has developed its own policies and procedures based on these MRC guidelines, which are adhered to for all research activities at the ICNARC CTU. In addition, the ICNARC CTU has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

14.2 Trial administration

14.2.1 Trial Management Group

All day to day management of ProMISe will be the responsibility of Trial Manager Paul Mouncey and Chief Investigator, Professor Kathryn Rowan. Staff who work on ProMISe will meet regularly to discuss, the progress of the trial and findings from other related research. The TMG includes the central champions from emergency medicine, acute medicine, and critical care medicine.

14.2.2 Trial Steering Committee

The progress of the trial will be monitored and supervised by the TSC. The TSC will be chaired by Professor Steve Goodacre, Professor of Emergency Medicine, University of Sheffield, as an independent chair. It will also consist of two additional independent members and at least one service user representative.

14.2.3 Data Monitoring and Ethics Committee

The DMEC, will be chaired by Professor Jon Nicholl, Director, Medical Care Research Unit, University of Sheffield, as an experienced statistician and trialist with previous data monitoring committee experience. The DMEC will also include experienced clinicians representing the fields of critical care medicine and emergency medicine. All members of the DMEC will be independent of both the trial and the TSC. The DMEC will operate under the DAMOCLES Charter,[40;41] and will report to the TSC, making recommendations on the continuation, or not, of the trial. Safety will be monitored by the DMEC through reporting of SAEs throughout the trial period. The chair of the DMEC will be in contact with their opposite number from the ProCESS and ARISE RCTs to ensure that any important data arising from these studies are made available at the earliest possible opportunity.

14.2.4 Role of the ICNARC CTU

The ICNARC CTU will be responsible for the day to day management and coordination of the trial and will act as custodian of the data. The ICNARC CTU will ensure that all SAEs are appropriately reported to the REC.

15.0 Statistics

15.1 Population for analysis

The target population are adult patients presenting in the ED with early signs of septic shock: systemic inflammatory response, suspected infection and hypotension or hypoperfusion. Subjects will be randomised without regard to race or sex.

15.2 Primary analysis

The primary outcome measure for clinical effectiveness will be 90-day all cause mortality. Patients will be followed to hospital discharge. If discharge from hospital occurs before 90 days, information on subsequent deaths will be obtained through patients' GPs and the NHSCR. The primary outcome measure for cost effectiveness will be the incremental cost per QALY gained at one year.

All analyses will be lodged in a statistical analysis plan, *a priori*, before the investigators are unblinded to any trial outcomes. All analyses will be performed according to the intention to treat principle. Results will be reported in accordance with the CONSORT statement.[24]
Baseline covariates will be compared between the two arms to observe balance and the success of randomisation. These comparisons will not be subjected to statistical testing, as such tests are invalid.[25] The delivery of the protocol will be described in detail.
The primary analysis will test the hypothesis that there is no difference in 90-day mortality for patients randomised to receive early, goal-directed, protocolised resuscitation compared with those randomised to receive usual resuscitation.

The primary analysis will be performed unadjusted using Fisher's exact test. As a supporting analysis, the analysis will be repeated adjusted for baseline covariates using multilevel logistic regression with unit-level random effects. Adjustment for baseline covariates can increase the precision of the estimate of treatment effect, and therefore the power of the trial, and adjust for any bias caused by chance imbalance between the trial arms. The covariates for inclusion in the adjusted analysis will be selected *a priori* based on an established relationship with outcome for patients with severe sepsis and septic shock, and not because of observed imbalance, significance in univariable analyses or by a stepwise selection method.

15.3 Secondary analysis

The secondary outcomes measures will be:

- duration of survival;
- mortality at 28 days;
- mortality at discharge from critical care and discharge from hospital;
- mortality at one year;
- SOFA score at 6 hours and 72 hours (adjusted for baseline);
- requirement for, and duration of, monitoring and support of specific organ systems (CCMDS);
- duration of ED, critical care unit and acute hospital stay;
- health-related quality of life (EQ-5D) at 90 days and one year;
- resource use and costs at 90 days and one year;
- lifetime incremental cost-effectiveness.

Secondary analyses of binary outcomes (mortality, requirement for organ support) will be performed by Fisher's exact test and, where appropriate, adjusted logistic regression. Secondary analyses of continuous outcomes (SOFA score, duration of organ support, duration of ED, critical care and acute hospital stay, health-related quality of life) will be performed by t-tests or ANCOVA (for outcomes measured at baseline) or by nonparametric or bootstrapped alternatives (depending on the distribution of the outcome variable) and, where appropriate, adjusted linear regression. Comparisons of duration of organ support will be performed using the days alive and free of organ support up to 28 days. Duration of ED, critical care unit and acute hospital stay will be compared overall and for survivors and non-survivors separately. Secondary analyses of time-to-event data (duration of survival) will be performed by Kaplan-Meier methods and Cox proportional hazards modelling.

15.4 Subgroup analysis

Subgroup analyses will be performed to test for interactions between the effect of each trial arm and baseline covariates. An important *a priori* subgroup analysis will test whether the effect of early, goal-directed, protocolised resuscitation differs according to the degree of protocolisation of care delivered within usual resuscitation. This will be assessed in each site from the data collected on usual resuscitation patients. In addition, the following covariates will be tested:

- age;
- severity of illness – MEDS score;[26]
- severity of organ failure – SOFA score;[21]
- time from ED presentation to randomisation.

Subgroup analyses of a trial adequately powered on a primary endpoint will inevitably be underpowered, and a non-significant interaction test will not rule out the possibility that a subgroup effect exists. Based on simulation studies, a subgroup analysis of this trial is likely to have around 30% power to detect a subgroup effect of equivalent magnitude to the overall anticipated treatment effect and 80% power to detect a subgroup effect of twice this magnitude.[27] Combining the data from ProMISe with those from the ongoing ProCESS and ARISE RCTs in the US and Australia in an individual patient data meta-analysis will allow greatly increased power for investigation of interaction effects.

15.5 Economic evaluation

Early, goal-directed, protocolised resuscitation uses fluids, vasoactive agents, packed red blood cells and dobutamine to establish adequate CVP and MAP or SBP and $ScvO_2$. It is anticipated therefore that this protocol, utilising invasive monitoring, will be more expensive to deliver than usual resuscitation. However, no robust data exist to establish these costs. Furthermore, any additional costs of delivering early, goal-directed, protocolised resuscitation may be offset by cost savings resulting from reductions in critical care and acute hospital stay.

A full cost-effectiveness analysis (CEA) will be undertaken to assess which strategy (early, goal-directed, protocolised resuscitation versus usual resuscitation) is most cost-effective. Any additional intervention costs associated with early, goal-directed, protocolised resuscitation will be assessed together with any subsequent reduction in morbidity costs, for example from reduced use of critical care. Resource use and outcome data collected as part of the RCT will be used to report cost-effectiveness at one year. The CEA will use the trial data to project the relative cost-effectiveness of each strategy over the lifetime.

The cost analysis will take a health and personal health services perspective.[28] Detailed information will be collected during the first six hours post randomisation on the resource use and costs associated with delivering the protocol and usual resuscitation. Patient-level resource use data will be collected on: the time spent in the emergency department; the time in other intermediate care areas (e.g. assessment wards), the key fluid intake (e.g. blood products); drug use (e.g. IV antibiotics, dobutamine), the use of consumables (e.g. central lines) and equipment (e.g. monitoring by CVC and pressure transducers). The potential opportunity costs associated with any additional staff time required to deliver early, goal-directed, protocolised resuscitation will be recorded on visits to a selection of sites. These resource use data will be combined with unit costs collected from finance departments in individual sites and from national sources.[29;30]

For each patient, the number of days in critical care will be recorded and assigned to a Healthcare Resource Group (HRG) using mandated data collected for the Critical Care Minimum Data Set (CCMDS). The HRG categorisation will recognise the use of high cost interventions for septic shock (e.g. recombinant human activated protein C). These activity data will be combined with unit cost per hospital bed-day (by HRG) from the NHS Payment by Results database.

Readmissions will be recorded on the trial database. The use of personal health services will be recorded by patient questionnaire at one year, and valued using unit costs taken from published sources.[30] Data from the EQ-5D questionnaires at one year will be combined with survival data to report quality-adjusted life years (QALYs).
The CEA will report the mean (95% confidence interval) incremental costs and QALYs at one year, using the same comparators as the main statistical analysis (see above).
The CEA will use a decision-model to project lifetime cost-effectiveness. The model will use a similar structure to previous CEA of protocolised care in US critical care units[31] and of interventions for severe sepsis in the UK.[32] The model will use the best, most relevant input parameters for this particular NHS context. Survival analysis of the RCT data will provide a basis for extrapolating any within trial differences in costs and QALYs.[33] The model will also use external data on the long-term survival for patients following septic shock.[34] The sensitivity analysis will test whether the results are robust to methodological assumptions, for example: the specification of the statistical model and data source (RCT versus external data) used to extrapolate the RCT results, and the source of unit cost data (average unit costs from Payment by Results versus Trust-specific estimates).

The CEA will therefore provide a thorough assessment of whether early, goal-directed, protocolised resuscitation is cost-effective for emerging septic shock.

15.6 Health related Quality of Life

HRQoL will be assessed using EQ-5D questionnaires at 90 days and one year post randomisation.

15.7 Sample size calculation

Estimates for baseline mortality in the usual resuscitation arm have been based on the CMPD. Patients were identified if they were admitted to a critical care unit from the ED having previously been not in hospital and if they satisfied at least two SIRS criteria and had evidence of infection. These definitions are relaxed from the entry criteria to the trial as patients are likely to have had physiological abnormalities stabilised prior to admission to critical care. During 2005 and 2006, 24,155 patients were admitted to 156 participating critical care units

from the ED (24 admissions per unit per year). Of these, 6,671 (28%) met the above criteria. Hospital mortality for these patients was 35%. Long-term follow-up studies of patients with severe sepsis indicate that, of patients discharged home from hospital, a further 16% will have died by 90 days.[35] However, these studies were predominantly based in the US, where the high provision of chronic care facilities means that more deaths occur outside hospital. We have therefore based our sample size calculations on an anticipated 90-day mortality in the usual resuscitation arm of 40%.

Rivers *et al* reported an absolute risk reduction of 16% in hospital mortality (13% at 60 days);[4] however, as this was a single-centre trial with concerns over internal and external validity, it is essential that ProMISe is powered to detect a smaller difference.

To achieve 80% power to detect a reduction in 90-day mortality from 40% to 32% associated with early, goal-directed, protocolised resuscitation versus usual resuscitation ($P<0.05$) requires a sample size of 589 patients per arm (1178 total). Allowing for 6% of patients refusing consent to follow-up (in the similar PAC-Man trial, only 2% of patients refused consent following randomisation) or being lost to follow-up prior to 90 days, we will aim to recruit 630 patients per arm (1260 total). This sample size will give in excess of 99% power to detect an absolute risk reduction of the magnitude observed in the Rivers *et al* trial. In the event that the mortality in the control arm is lower than anticipated, the trial would have greater power to detect the same absolute risk reduction. If the mortality were as low as 25%, the trial would have >80% power to detect a reduction to 18%.

If early, goal-directed, protocolised resuscitation (with pre-determined haemodynamic goals) was proven to be beneficial, such a mortality difference would be highly clinically significant (number needed to treat = 8) and would likely lead to widespread change in resuscitation practice in the UK.

Based on the observed rate of 24 admissions per unit per year (above), we anticipate that each participating hospital will be able to recruit 14 patients per year, allowing for ineligible patients, missed patients and refusals of consent. Small observational studies based in UK EDs have identified 11 patients in two EDs in five months (13 per site per year),[12] 75 patients in one ED in one year (75 per site per year),[36] and 50 patients in one ED in one month (600 per site per year).[37] Our anticipated average recruitment rate falls at the low end of these extremely wide-ranging observations. At this rate, recruitment will be completed with 48 hospitals recruiting for 26 months, allowing for sites commencing recruitment incrementally over the first 6 months of patient recruitment.

15.8 Interim analysis

A single interim analysis will be carried out at one year (500 patients) using a Peto-Haybittle stopping rule ($P<0.001$) to recommend termination on efficacy grounds. Further interim analyses will be performed if required by the DMEC.

16.0 Ethical and regulatory compliance

16.1 Regulatory compliance

The trial will be conducted in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, the Data Protection Act, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and (SI 2006/1928) and other applicable local regulations, including those transposed from the European Clinical Trials Directive 2001/20/EC.

16.2 Ethical compliance

The trial will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki.

The trial has been approved by the North West London 1 REC. The ICNARC CTU will maintain contact with REC and submit any protocol amendments to them. The ICNARC CTU will provide relevant documentation to participating sites.

The PI will provide their local R&D department with the current version of the protocol, patient information sheet and consent form, any other written information given to patients and any revisions to the protocol or any other trial documentation. It is the responsibility of the PI to obtain necessary local approval for the trial and any subsequent amendments where required. Evidence of local trust R&D approval must be provided to the ICNARC CTU prior to site activation. The trial will only be conducted at sites where all necessary approvals for the trial have been obtained.

16.3 Patient confidentiality & data protection

Patients' identification data, including full name, date of birth, address and NHS number will be required to successfully follow-up the patient and will be provided to the ICNARC CTU. The ICNARC CTU will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and the ICNARC CTU trials are registered in accordance with the Data Protection Act 1998.

16.4 Risks and anticipated benefits for trial participants and society, including how benefits justify any risks

ProMISe is not testing a new product or procedure, but will evaluate an early resuscitation protocol for delivering treatments that may not be used systematically in standard practice. Risks relating to the individual interventions incorporated into the protocol would be the same whether patients take part in the trial or receive these interventions outside of the trial.

In both arms (and in standard current practice), subjects are likely to receive a combination of IV fluids, vasopressors, and/or dobutamine. The risks of vasopressors include myocardial ischaemia, high blood pressure, peripheral ischaemia, and cardiac arrhythmias. The risks of dobutamine include myocardial ischaemia, low blood pressure, and cardiac arrhythmias. The only differences between treatment and control arms relate to the use of monitoring devices

and the protocolised use of combinations of IV fluids (including blood transfusions), vasopressors and dobutamine. The risks associated with central venous catheterisation include pneumothorax, bleeding, vessel injury or thrombosis, and infection. The risk of heart puncture is very rare (less than 1%).[38] Risks associated with blood transfusion include disease transmission or transfusion reaction, including anaphylaxis. Transfusion risks are rare, occurring in less than 0.1% of recipients, and mortality rates for these complications are less than 1 death per million units of blood transfused.[39]

Subjects have the potential for direct benefit from participation; the Rivers *et al.* protocol has shown direct benefit to trial subjects in a single-centre RCT (reduced mortality, length of stay, and fewer complications).[4]

16.5 Contamination

A theoretical concern in an open trial is that the usual resuscitation arm could gradually incorporate elements of the protocol, thereby affecting the capacity to detect the treatment effect. Contamination will be minimised by:

- the small number of patients recruited from each site;
- frequent ED staff rotation and multiple shifts;
- training, providing the protocol to, and delivering early, goal-directed, protocolised resuscitation by, a locally-determined ProMISe Team;
- delivering usual resuscitation from routine ED staff.

One possible strategy to reduce contamination would be to use a cluster-randomised design. However, heterogeneity, both in terms of standard practice and outcomes, is high and consequently the sample size for a cluster-randomised trial would need to be extremely large to be able to detect the same benefit. Analysis of patients in the CMPD admitted to critical care units from the ED with severe sepsis gives an intraclass correlation coefficient for the between site variation in mortality of 0.04. In the context of this trial, this would translate to a design effect of approximately 2, meaning that around 100 hospitals would need to participate in order to complete the trial in the proposed time frame. We therefore concluded that a cluster-randomised trial would not be feasible. This conclusion is backed up by the experience of a previous large, cluster-randomised trial of a complex critical care intervention delivered outside the critical care unit – the MERIT trial.[40] Despite recruiting over 100,000 patients from 23 hospitals, the between-cluster variation within this trial was higher than anticipated, rendering it underpowered and ultimately inconclusive. In addition to this, outcomes improved over time in the control hospitals suggesting that the cluster-randomised design may not have been effective in reducing contamination.

17.0 Sponsorship and indemnity

17.1 Sponsor details:

Sponsor Name: ICNARC

Address: ICNARC
Napier House
24 High Holborn
London WC1V 6AZ
Contact: Keryn Vella
Telephone: 020 7269 9277
Fax: 020 7831 6879

17.2 Indemnity:

ICNARC holds professional liability insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

18.0 Funding

The NIHR Health Technology Assessment (HTA) Programme (07/37/47) is supporting the central coordination of the trial through the ICNARC CTU, and the local site start up costs. This includes dedicated local research nurses. The funding will also cover the economic evaluation.

19.0 Publication policy

The final report to the NIHR HTA will present detailed results of ProMISe along with recommendations for practice and future research. In addition, ongoing progress of the trial will be disseminated to participants through newsletters and collaborators' meetings, to the wider clinical community through relevant professional newsletters, meetings, and national and international conferences, and to consumers via patient support groups and ICNARC, CEM, SAM and ICS websites. Articles will be prepared for relevant professional journals as well as for peer-reviewed scientific journals.

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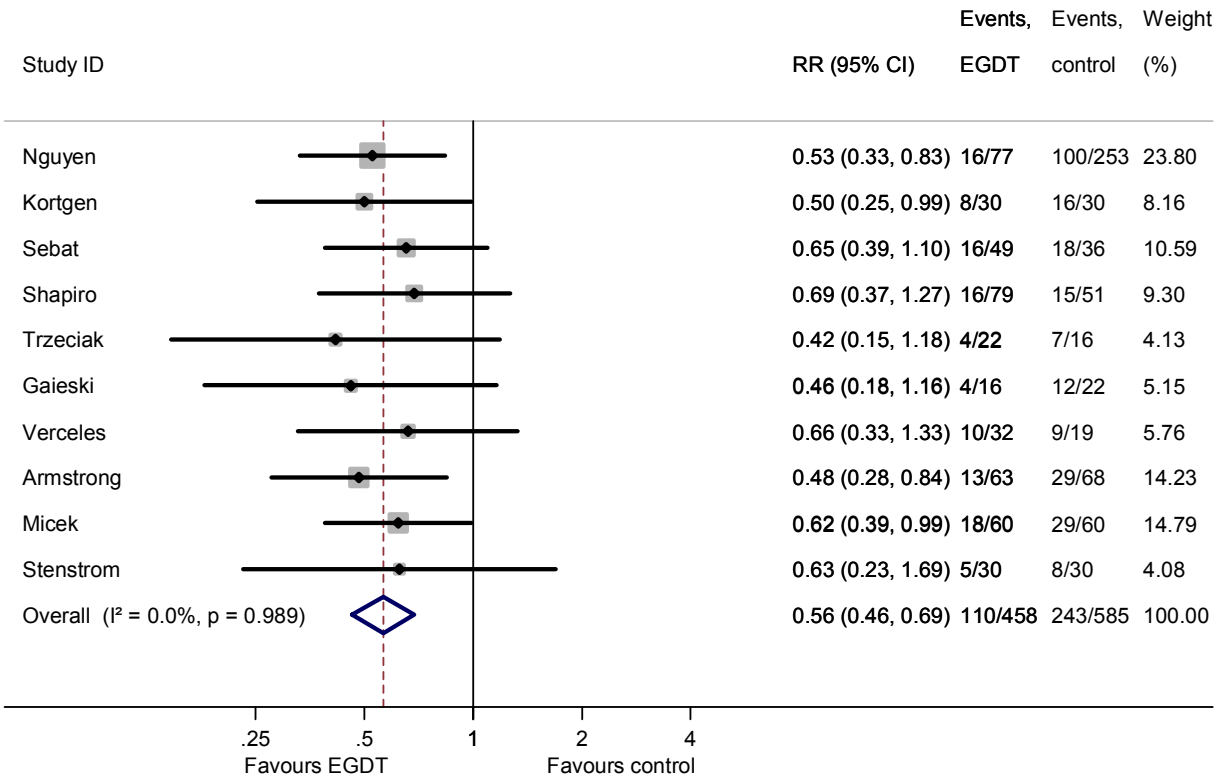
Appendix 1. Abbreviations

ACCP	American College of Chest Physicians
AE	Adverse Event
ARISE	Australasian Resuscitation In Sepsis Evaluation
ARR	Absolute Relative Risk
CEA	Cost-Effectiveness Analysis
CMP	Case Mix Programme
CMPD	Case Mix Programme Database
CPIS	Consultee Patient Information Sheet
CRF	Case Report Form
CTU	Clinical Trials Unit
CVC	Central Venous Catheter
CVP	Central Venous Pressure
DMEC	Data Monitoring & Ethics Committee
ED	Emergency Department
EGDT	Early Goal-Directed Therapy
EQ-5D	EuroQoL 5D
Hb	Haemoglobin
HRG	Healthcare Resource Group
HRQoL	Health Related Quality of Life
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICNARC	Intensive Care National Audit & Research Centre
ICNARC CTU	Intensive Care National Audit & Research Centre Clinical Trials Unit
IV	Intravenous
MAP	Mean Arterial Pressure
MET	Medical Emergency Team
MRC	Medical Research Council
MRIS	Medical Research Information Service
NEJM	New England Journal of Medicine
NIHR HTA	National Institute for Health Research Health Technology Assessment
PIS	Patient Information Sheet
PRBC	Packed Red Blood Cells
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RPIS	Retrospective Patient Information Sheet
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SCCM	Society of Critical Care Medicine
SIRS	Systemic Inflammatory Response Syndrome
SBP	Systolic Blood Pressure
$ScvO_2$	Central Venous Oxygen Saturation
SpO_2	Oxygen Saturation
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee

Appendix 2. Meta-analysis of non-randomised before and after studies of early, goal-directed, protocolised resuscitation for sepsis/septic shock



Appendix 3. Health Services Questionnaire

ProMISe

HEALTH SERVICES QUESTIONNAIRE

We would be grateful if you would complete this questionnaire. It will help us understand the care you needed after leaving the hospital.

The ProMISe trial aims to improve the care of patients with emerging septic shock.

A pen is provided and a FREEPOST envelope for return of the questionnaire. Please answer multiple choice questions by putting a ✓ in ONE BOX for each question.

Please complete today's date below:

_____ / _____ / _____

Day Month Year

Please also let us know whether you completed this questionnaire:

- ☐ Alone
- ☐ With help
- ☐ Or it was completed by someone who cares for you

NOW PLEASE TURN THE PAGE TO START THE QUESTIONNAIRE ▶

If you do not wish to complete this questionnaire, please return the unanswered questionnaire in the FREEPOST envelope provided.

Your current and future care will not be affected whether you decide to, or not to, fill out this questionnaire.

Health Services Questionnaire, Version 1.0, 18/02/11

The questions refer to ALL health services that you have used since leaving the hospital on [insert date], and before [insert date]

Part 1. Hospital Stay

A Since you left hospital on [insert date] have you stayed overnight in hospital for any reason?

☐ No - Go to Part 2

☐ Yes - Please give details about the number of stays below

B For EACH TIME you stayed in hospital please answer the following

	Number of nights		1-3 nights	4-10 nights	11 or more nights	Did you spend any part of your stay in critical care?
1st Stay	_____	or…	☐	☐	☐	☐
2nd Stay	_____	or…	☐	☐	☐	☐
3rd Stay	_____	or…	☐	☐	☐	☐
4th Stay	_____	or…	☐	☐	☐	☐

**If you have stayed in hospital overnight more than 4 times, please could you provide information on these further hospital stays in Part 6 of the questionnaire.*

Part 2. Hospital outpatient visits

Outpatient visits are when a patient comes to the hospital to see a specialist (e.g. consultant) but does not stay overnight.

A Since you left the hospital on [insert date] have you visited hospital outpatients about ANY ASPECT of your health?

☐ No - Go to Part 3

☐ Yes - Please give details about the number of outpatients visit(s) below

B

Number of visits		1-3 visits	4-10 visits	11 or more visits
_____	or…	☐	☐	☐

Part 3. Visits to health care providers

A Since you left the hospital on [insert date] have you visited any of the health care providers listed below?

☐ No - Go to Part 4

☐ Yes - Please give details about your visits below

B For EACH PROVIDER please answer the following

Did you visit this provider?		Number of visits		1-3 visits	4-10 visits	11 or more visits
GP	☐	_____	or…	☐	☐	☐
Nurse at your GP clinic	☐	_____	or…	☐	☐	☐
Nurse at hospital or elsewhere	☐	_____	or…	☐	☐	☐
Health visitor	☐	_____	or…	☐	☐	☐

Part 4. Visits to your home by health care providers

A Since you left the hospital on [insert date] have you had home visits from any the following health care providers about ANY ASPECT of your health?

☐ No - Go to Part 5

☐ Yes - Please give details about your visits below

B For EACH HOME VIST please answer the following

Were you visited at home by this provider?		Number of visits		1-3 visits	4-10 visits	11 or more visits
GP	☐	_____	or…	☐	☐	☐
Nurse from your GP clinic	☐	_____	or…	☐	☐	☐
Occupational Therapist	☐	_____	or…	☐	☐	☐
Health visitor or District nurse	☐	_____	or…	☐	☐	☐

Part 5. Visits to other service providers

A Since you left the hospital on [insert date] please indicate whether you have had contact (either visits to the provider or home visits) with any of the following service providers about any aspect of your health?

☐ No - Go to Part 6

☐ Yes - Please give details below

B For EACH PROVIDER please answer the following

Have you had contact with any of these providers?		Number of visits		1-3 visits	4-10 visits	11 or more visits
Occupational therapist	☐	_____	or…	☐	☐	☐
Hospital discharge coordinator	☐	_____	or…	☐	☐	☐
Counsellor	☐	_____	or…	☐	☐	☐
Physiotherapist	☐	_____	or…	☐	☐	☐
Continuing care nurse	☐	_____	or…	☐	☐	☐
Social worker	☐	_____	or…	☐	☐	☐

Part 6. Other services not listed so far

A Since you left the hospital on [insert date] have you had further hospital stays or used ANY OTHER health care services for any aspect of your health that you haven't included above?

☐ No - Go to Part 7

☐ Yes - Please give details below

B For EACH PROVIDER please answer the following

Type of service provider	Number of visits	Reason

Part 7. Comments

Your views are important to us. Please feel free to provide any other comments you have in the box below.

Thank you for help

If you would like to ask us any questions about completing the questionnaire please email or call:

Paul Mouncey
promise@icnarc.org
020 7269 9277

Richard Grieve
Richard.Grieve@lshtm.ac.uk
020 7927 2255

Appendix 4. Expected Adverse Events

Events related to central venous catheter placement:

- Pneumothorax – puncture of the lung with air between the lung and chest wall.
- Haemo-pneumothorax – puncture of the lung and artery or vein causing blood to collect in the chest.
- Bleeding – resulting from a blood vessel puncture
- Thrombosis
- Vascular catheter infection

Events related to arterial catheter placement:

Complications from arterial catheter are rare, but may include:

- Bleeding
- Infection
- Reduction of blood flow to tissue supplied by the artery (usually correctable by removal of the catheter).

Other trial treatments

There are specific risks associated with each of the individual standard treatments used for patients with severe infections.

Fluid infusions:

- Pulmonary emboli
- Pulmonary oedema
- Fluid overload where the patient temporarily has too much fluid for their blood vessels and heart to cope with easily.
    - This is reversible by slowing the speed at which the fluid is given and sometimes by giving other medications.

Blood transfusion:

- Can also contribute to fluid overload
- Blood transfusion reaction - reactions to the blood itself (uncommon).
- Transmission of viral disease, although all blood administered is screened for HIV, hepatitis B and hepatitis C.

Drugs: medications given to support the heart can cause abnormal heart rhythm or rarely, a decreased blood supply to the heart and extremities.

- Myocardial ischaemia
- Peripheral ischaemia
- Tachycardia
- Arrhythmia

Appendix 5. Protocol version history

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	04/05/2010	N/A	N/A	N/A
2.0	11/02/2011	1	4/Informed Consent 8/Assessments Appendix 3/Health Services questionnaire Appendix 4/Expected Adverse Events Other	Update of consent procedure for Consultees Finalisation of data points Addition Update of expected AEs Administrative
2.1	14/05/2011	2	4/Informed Conset 5/Selection of patients	Clarification of process Amendment to exclusion criteria
2.2	21/12/2011	3	N/A	Administrative
2.3	31/08/2012	4	Trial management Clinical management 6/Randomisation procedures 11/Adverse Events 17/Sponsorship and indemnity Other	Update of contact details for Sponsor and ICNARC CTU Admintstrative