

The Protocolised Management in Sepsis (ProMISe) trial statistical analysis plan

G Sarah Power, David A Harrison, Paul R Mouncey, Tiffany M Osborn, Sheila E Harvey and Kathryn M Rowan

The Protocolised Management in Sepsis (ProMISe) trial is an open, multicentre, randomised controlled trial (RCT) evaluating the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation (EGDPR) for early signs of septic shock in the United Kingdom National Health Service (NHS). The rationale for the ProMISe trial derives from an RCT in a single United States hospital by Rivers and colleagues,¹ which compared 6 hours' of EGDPR with usual resuscitation in patients presenting to the emergency department (ED) with early signs of septic shock. Protocolised resuscitation significantly reduced hospital mortality (from 46.5% to 30.5%). We describe our proposed statistical analysis plan for the evaluation of clinical effectiveness in the ProMISe trial. It is important to complete this plan before inspecting the data, and before completion of two related international studies, so that post-hoc, data-derived decisions are avoided.²

Trial design

Aim

Our aim is to evaluate the clinical effectiveness and cost-effectiveness of EGDPR compared with usual resuscitation for patients presenting with early signs of severe sepsis or septic shock.

Trial sites and patients

UK NHS hospitals are eligible to participate, and our target is to recruit a minimum of 48 sites. Patients who present at an ED with early signs of severe sepsis or septic shock and meet all inclusion criteria and no exclusion criteria are recruited to the trial.

Inclusion and exclusion criteria

The ProMISe trial aims to recruit patients as soon as possible after ED presentation. All inclusion criteria must be met within the ED and within 6 hours of ED presentation. Consent procedures and randomisation must occur within 2 hours of meeting the inclusion criteria. The inclusion criteria are:

- refractory hypotension or hypoperfusion:
 - refractory hypotension confirmed by the presence of a systolic blood pressure (SBP) < 90 mmHg or a mean arterial pressure (MAP) < 65 mmHg, despite a minimum intravenous (IV) fluid challenge of 1 L fixed bolus within a 60-minute period (including IV fluids administered by prehospital personnel)
 - hypoperfusion confirmed by a blood lactate concentration ≥ 4 mmol/L;

ABSTRACT

Background: The Protocolised Management in Sepsis (ProMISe) trial is an open, multicentre, randomised controlled trial (RCT) of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation compared with usual resuscitation for patients presenting to emergency departments (EDs) in the United Kingdom with early signs of severe sepsis or septic shock. The rationale for the ProMISe trial derives from a single-centre United States RCT that reported a reduction in hospital mortality from 46.5% to 30.5%.

Objective: To describe the proposed statistical analyses for the evaluation of clinical effectiveness for the ProMISe trial. It is important to complete this plan before inspecting the data, and before completion of two related international studies, so that post-hoc, data-derived decisions are avoided.

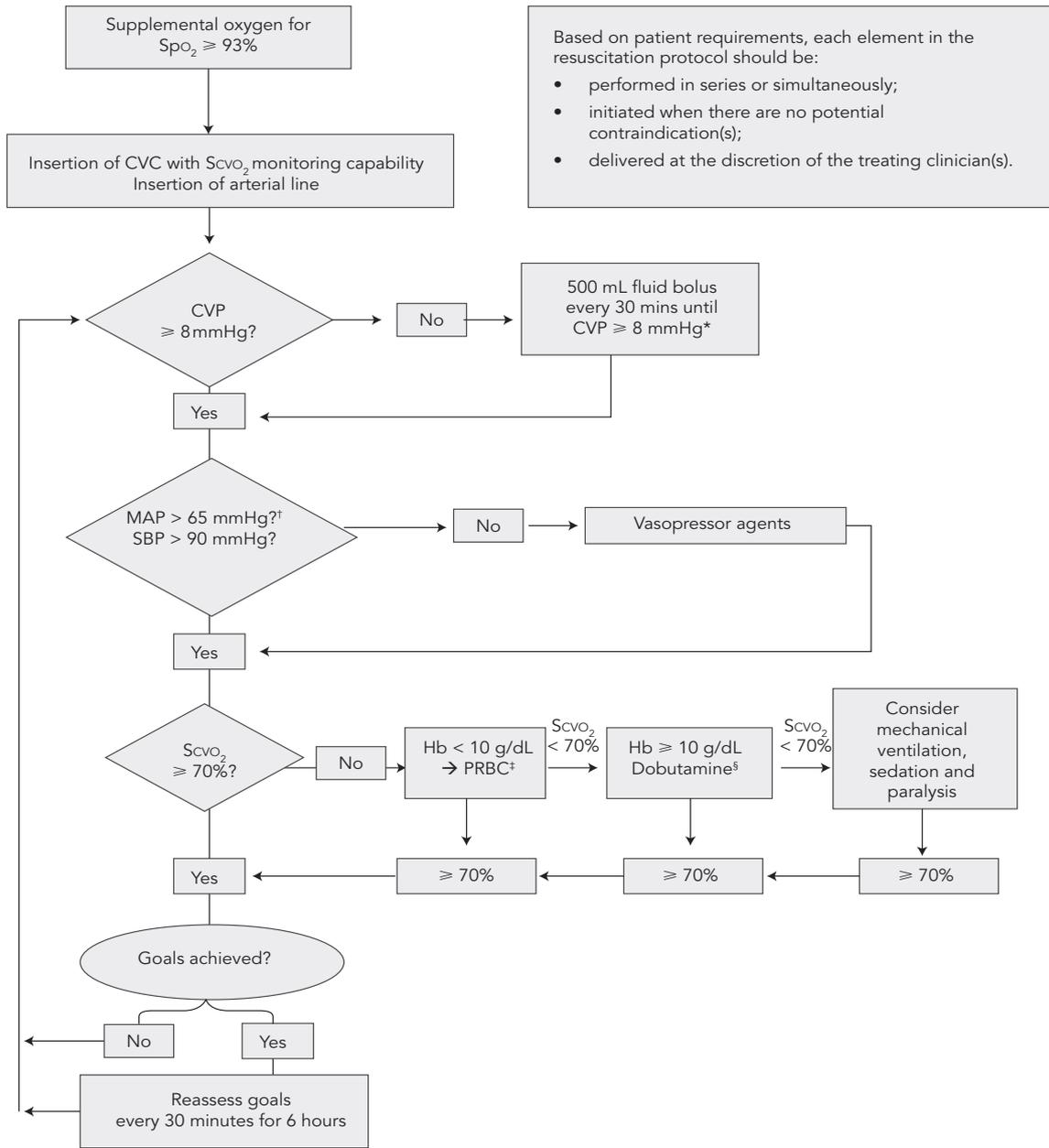
Methods: The primary and secondary outcomes were defined precisely, and the approach to safety monitoring and data collection summarised, with a description of the planned statistical analyses including prespecified subgroup and secondary analyses.

Results: The primary outcome is all-cause mortality at 90 days. The primary analysis will be reported as a relative risk and absolute risk reduction and tested with the Fisher exact test. Prespecified subgroup analyses will be based on age, baseline Medical Emergency Department Sepsis score, baseline Sequential Organ Failure Assessment score, and time from ED presentation to randomisation. Secondary analyses include adjustment for baseline covariates, estimation of learning curve effects and adjustment for non-compliance.

Conclusion: In keeping with best practice, we have developed a statistical analysis plan for the ProMISe trial and place it in the public domain before inspecting data from the trial.

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Figure 1. Early, goal-directed resuscitation protocol



SpO₂ = oxygen saturation measured by pulse oximetry. CVC = central venous catheter. ScvO₂ = central venous oxygen saturation. CVP = central venous pressure. MAP = mean arterial pressure. SBP = systolic blood pressure. Hb = haemoglobin. PRBC = packed red blood cells. * Crystalloid or colloid equivalent as standard practice. † If MAP > 90 mmHg, consider vasodilator. ‡ Hb after intravenous fluid administration. § 2.5 µg/kg/min over 30 minutes initially, then increased by 2.5 µg/kg/min every 30 minutes; maximum dose 20 µg/kg/min: reduce or discontinue if concerned about drug-induced tachycardia.

- known or presumed infection; and
- two or more systemic inflammatory response syndrome (SIRS) criteria.³

The first dose of IV antimicrobial therapy must be initiated before randomisation. Exclusion criteria are detailed in the ProMISe trial protocol.⁴

Randomisation and treatment allocation

Eligible patients are allocated 1:1 to one of two treatment groups, by randomised permuted blocks (with variable block lengths) stratified by recruiting site, via a dedicated 24 hour, 7 days per week telephone randomisation service.

Intervention

Patients randomised to EGDPR will be treated according to the early, goal-directed resuscitation protocol (Figure 1).

Outcomes

Primary outcome

The primary outcome for the clinical evaluation is all-cause mortality at 90 days.

Secondary outcomes

The secondary outcomes for the clinical evaluation are:

- Sequential Organ Failure Assessment (SOFA) score⁵ at 6 hours and 72 hours after randomisation (adjusted for baseline value)
- receipt of advanced cardiovascular, advanced respiratory and renal support (as defined by the UK Department of Health Critical Care Minimum Dataset⁶)
- days alive and days free from advanced cardiovascular, advanced respiratory and renal support
- lengths of stay:
 - length of stay (LOS) in the ED, defined as the duration in hours from randomisation to the first change in location of care or death in the ED
 - LOS in critical care, defined as the sum over all admissions to critical care of the duration in days from critical care admission to discharge or death in critical care
 - LOS in an “acute hospital”, defined as the duration in days from randomisation to acute hospital discharge or death in acute hospital (we define “acute hospital” as a hospital providing a range of services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals provide only specialist services and others provide general services)
- duration of survival
- mortality at 28 days after randomisation, at discharge from acute hospital and at 1 year after randomisation.

Safety monitoring

Patients are monitored for adverse events within 30 days after randomisation, by the principal investigator and authorised site staff. Severity of adverse events is graded using standard definitions.⁷ Any serious adverse event should be reported to the Intensive Care National Audit and Research Centre (ICNARC) Clinical Trials Unit (CTU) within 24 hours, regardless of whether it is related to participation in the trial.

Data collection and follow-up

Sites are responsible for collecting data from ED presentation to acute hospital discharge. All patients surviving to discharge from acute hospital are checked against death registrations on the NHS Health and Social Care Information

Centre Data Linkage and Extract Service (DLES) for subsequent reporting of mortality at 90 days and 1 year.

In addition, as part of the integrated economic evaluation, patients recorded on the DLES as being alive at 90 days and at 1 year are sent postal questionnaires by the ICNARC CTU to record their health-related quality of life, subsequent hospital admissions and use of personal health services. Non-responders are followed up with a further postal questionnaire and then by telephone.

Sample size

Estimates for baseline mortality for the usual resuscitation group were based on the ICNARC Case Mix Programme Database. Acute hospital mortality for patients who met criteria similar⁴ to the inclusion criteria was 35%. To allow for additional deaths after discharge from hospital and before Day 90, sample size calculations were based on an anticipated 90-day mortality of 40% in the usual resuscitation group.

To achieve 80% power to detect a reduction in 90-day mortality from 40% to 32% associated with EGDPR compared with usual resuscitation ($P < 0.05$, two-sided) requires a sample size of 589 patients per treatment group (1178 in total). Allowing for 6% of patients refusing consent to follow-up (in the PAC-Man trial, 2% of patients refused consent after randomisation⁸) or being lost to follow-up before 90 days, our aim is to recruit 630 patients per group (1260 in total). This sample size provides > 99% power to detect an absolute risk reduction of the magnitude observed in the trial of Rivers and colleagues (16%).¹

Interim analysis

Unblinded comparative data on recruitment, withdrawal, compliance with the trial protocol and serious adverse events are regularly reviewed by an independent data monitoring and ethics committee (DMEC), chaired by an experienced trialist.

Without specific analysis of the primary outcome, the DMEC reviewed data from the first 50 trial participants and continue to review data at least 6 monthly to assess potential safety issues and to review compliance with the study protocol. A single, planned formal interim analysis was performed once 90-day outcome data from the first 500 patients enrolled were available. A Haybittle–Peto stopping rule ($P < 0.001$) was used to guide recommendations for early termination due to harm.

Statistical analysis

Analysis principles

All analyses will be based on the intention-to-treat principle. Patients will be analysed according to the treatment group they were randomised to, irrespective of whether the

allocated treatment was received (ie, regardless of whether they have or have not complied with the early, goal-directed resuscitation protocol).

All tests will be two-sided with significance levels set at $P < 0.05$ and with no adjustment for multiplicity. All a-priori subgroup analyses will be carried out irrespective of whether there is strong evidence of a treatment effect associated with the primary outcome.

As missing data are anticipated to be minimal, a sensitivity approach will be taken when the primary outcome is missing. The primary analysis will be repeated once, assuming that all patients allocated to EGDPR with missing primary outcome survived, and all patients allocated to usual resuscitation with missing primary outcome did not survive. The analysis will then be repeated again with the opposite assumptions. This will give the absolute range of how much the results could change if the primary outcome were complete. In adjusted analyses, missing baseline data will be handled by multiple imputation.

Trial profile

The flow of patients through the trial will be displayed in a modified Consolidated Standards of Reporting Trials (CONSORT) diagram.⁹ The number of screened patients who met the trial inclusion criteria will be reported. The number of these patients who were included in the trial will be reported as well as the reasons for exclusion for those who were not included.

Baseline characteristics

Baseline demographic and clinical data will be presented by treatment group but not subjected to statistical testing. Discrete variables will be summarised as numbers and percentages, which will be calculated according to the number for whom data are available; where values are missing, the denominator will be stated in the table. Continuous variables will be summarised by standard measures of central tendency and dispersion, either mean and standard deviation and/or median and interquartile range (IQR) as specified below:

- Inclusion criteria:
 - hypotension, n (%)
 - SBP or MAP value at which criteria for hypotension were met, mean (SD)
 - hypoperfusion, n (%)
 - lactate value at which criteria for hypoperfusion were met, mean (SD)
- Age, mean (SD) and median (IQR)
- Sex, n (%)
- Severe comorbidity (as defined by Acute Physiology and Chronic Health Evaluation [APACHE] II past medical history [PMH] definitions¹⁰), n (%):

- severe liver condition present in PMH
- severe renal condition present in PMH
- severe respiratory condition present in PMH
- severe cardiovascular condition present in PMH
- immunocompromised in PMH
- Prerandomisation treatment, n received (%) and median volume (IQR) of:
 - IV fluids (total before admission to hospital and total from ED presentation to randomisation)
 - blood products (total from ED presentation to randomisation)
- Acute severity of illness:
 - SOFA score,⁵ mean (SD) and median (IQR)
 - individual SOFA score components, median (IQR)
 - Mortality in Emergency Department Sepsis (MEDS) score,¹¹ mean (SD) and median (IQR)
 - APACHE II score,¹⁰ mean (SD) and median (IQR)
- Time from ED presentation to randomisation, mean (SD) and median (IQR)
- Patient likely to be admitted directly to critical care from ED if not enrolled into the ProMISe trial, n (%)
- Infection, n (%):
 - site
 - organism
 - antimicrobial change since ED presentation.

Clinical management

Clinical management of patients will be presented by treatment group but not subjected to statistical testing. As with baseline characteristics, discrete variables will be summarised as numbers and percentages. Percentages will be calculated according to the number of patients for whom data are available; where values are missing, the denominator will be stated in the table. Continuous variables will be summarised by mean (SD) and/or median (IQR).

Clinical management data will be summarised as the total over the 6-hour intervention period (T_0 – T_6); the total from the end of the 6-hour intervention period to the end of the first 24 hours (T_6 – T_{24}); the total from the end of the first 24 hours to the end of the first 72 hours (T_{24} – T_{72}) and from randomisation to the end of the first 72 hours (T_0 – T_{72}). Fluids, vasoactive agents and dobutamine will also be reported hourly for the duration of the 6-hour intervention period. Line insertion details will be included in the T_0 – T_6 table:

- Line insertion, time from randomisation to insertion: n (%), mean (SD) and median (IQR)
 - arterial line
 - central venous catheter (CVC) line
- Interventions received: n (%)
 - supplemental oxygen
 - mechanical ventilation

- Fluids: number receiving, n (%); and volume received: median (IQR)
 - IV colloid
 - IV crystalloid
 - packed red blood cells (PRBC)
 - platelets
 - fresh frozen plasma
- Drugs: n (%) received
 - vasoactive agents
 - dobutamine
 - sedatives

Compliance with allocated treatment

Non-compliance with the allocated treatment will be reported as:

- Insertion of a CVC with superior vena caval oxygen saturation ($ScvO_2$) monitoring capability to a patient allocated to usual resuscitation
- Failure to insert a CVC with $ScvO_2$ monitoring capability to a patient allocated to EGDPR
- Failure to act on a goal in the early, goal-directed algorithm for a patient allocated to EGDPR, defined as:
 - no fluid resuscitation when central venous pressure (CVP) is < 8 mmHg
 - no administration of vasopressors when MAP is < 65 mmHg or SBP is < 90 mmHg and the CVP goal was met
 - no administration of PRBC when $ScvO_2$ is $< 70\%$ and haemoglobin concentration is < 10 g/dL and the prior two goals were met, or no dobutamine administered when $ScvO_2$ is $< 70\%$ and haemoglobin concentration is ≥ 10 g/dL and the CVP and MAP/SBP goals were met
- Early (< 6 hours) termination of EGDPR in a patient allocated to EGDPR (other than due to death).

Description of analysis

Primary outcome

The number and percentage of deaths by 90 days after randomisation will be reported for each treatment group. The primary-effect estimate will be the relative risk of 90-day mortality, reported with a 95% CI. The absolute risk reduction and 95% CI will also be reported. Deaths by 90 days after randomisation will be compared between the treatment groups, unadjusted, using the Fisher exact test.

A secondary analysis of the primary outcome, adjusted for baseline variables, will also be conducted, using multilevel logistic regression. Baseline variables adjusted for in the multilevel logistic regression model will be the components of the MEDS score (age, metastatic cancer, nursing home residence, altered mental status, septic shock, respiratory difficulty, low platelet count and low neutrophil

count) and a site-level random effect. Baseline variables were selected for inclusion in the adjusted analysis according to anticipated relationship with outcome. The results of the multilevel logistic regression model will be reported as an adjusted odds ratio with 95% CI. The unadjusted odds ratio will be presented for comparison.

Secondary outcomes

The mean SOFA score at 6 hours and 72 hours after randomisation, adjusted for baseline SOFA score, will be reported for each treatment group. Differences in the mean SOFA score at 6 hours and 72 hours after randomisation will be compared using analysis of covariance (ANCOVA). The mean score for each of the six SOFA components (respiratory, neurological, cardiovascular, coagulation, hepatic and renal) will be reported but not subjected to statistical testing.

The number and percentage of patients receiving advanced cardiovascular, advanced respiratory and renal support will be reported for each treatment group. Differences in receipt of advanced cardiovascular, advanced respiratory and renal support will be compared, unadjusted, using the Fisher exact test.

The mean and SD of number of days alive and free from advanced cardiovascular, advanced respiratory and renal support, up to 28 days, within each treatment group will be reported. Differences between the treatment groups will be tested using the t test, using bootstrapping to account for anticipated non-normality in the distributions.¹²

The median and IQR of the LOS in the ED, in critical care and in acute hospital will be reported for each treatment group. Differences in LOS between the treatment groups will be tested using the Wilcoxon rank-sum test, stratified by survival at end of ED stay, critical care discharge and acute hospital discharge, respectively.

Kaplan–Meier curves by treatment group will be plotted up to 90 days and 1 year after randomisation and compared using the log-rank test. An adjusted comparison will be performed using a Cox proportional hazards model adjusted for the same baseline variables as the primary outcome. The number and percentage of deaths at acute hospital discharge and by 28 days, 90 days and 1 year after randomisation will be reported for the treatment groups. Differences in mortality will be compared, unadjusted, using the Fisher exact test and adjusted using multilevel logistic regression; ie, adjusted for the same baseline variables as the primary outcome.

Serious adverse events

The number and percentage of serious adverse events occurring between randomisation and 30 days will be reported for each treatment group. Serious adverse events will be compared between treatment groups using the Fisher exact test.

Subgroup analysis

These analyses will test for an interaction between the subgroup categories and the treatment group in a multi-level logistic regression model, adjusted for the same baseline variables as the analysis of the primary outcome. The primary outcome (90-day mortality) will be analysed by degree of protocolised care for patients randomised to usual resuscitation (completeness of hourly measurements with reference to known sepsis resuscitation and management bundles¹³⁻¹⁵), age (quartiles), MEDS score (quartiles), SOFA score (quartiles) and time from ED presentation to randomisation (quartiles).

Learning curve analysis

The delivery of a complex intervention may improve with time as those delivering the intervention gain experience and familiarity. Typically, such improvements will be more rapid at first and then tail off over time to reach a steady state; termed a "learning curve". Modelling the learning curve enables estimation of the treatment effect for an experienced team. A site-level learning curve for patients randomly allocated to EGDPR will be modelled by repeating the multilevel logistic regression on the primary outcome and including a power curve (aX^{-b}) for the sequential observation number (X) for each EGDPR patient within each site.¹⁶

Compliance-adjusted analysis

While the intention-to-treat analysis gives the best estimate of the clinical effectiveness of EGDPR as delivered, it is also of interest to estimate what the efficacy of this intervention may be if all elements of the protocol were delivered as intended. In an RCT, the allocated treatment can be used as an "instrumental variable", ie, a variable associated with receipt of the intervention and only associated with the outcome through its association with the intervention.¹⁷ This relationship enables us to estimate what the treatment effect would be for patients who are compliant with all elements of the protocol. The primary analysis will be repeated, adjusting for compliance using a structural mean model with an instrumental variable of allocated treatment, assuming a linear relationship between the degree of compliance (proportion of the 6 hours that the patient is compliant with the early, goal-directed resuscitation protocol) and treatment effect.^{18,19}

Figures and tables

Planned figures include:

- a CONSORT-style diagram illustrating the flow of patients through the trial
- a line graph showing the mean cumulative IV fluids received by treatment group
- a Kaplan–Meier curve showing survival to 90 days after randomisation by treatment group.

Planned tables include:

- baseline characteristics by treatment group
- clinical management by treatment group
- non-compliance with allocated treatment by treatment group
- primary and secondary outcomes by treatment group
- serious adverse events until 30 days after randomisation by treatment group
- results of subgroup and secondary analyses.

Funding, registration and ethics approval

The ProMISe trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (07/37/47) and is registered on the NIHR Clinical Research Network (CRN) portfolio (9820) and the International Standard Randomised Controlled Trials Number register (ISRCTN36307479). The trial is endorsed by the NIHR CRN Injuries and Emergencies Specialty Group and the Critical Care Specialty Group, sponsored by the ICNARC and coordinated by the ICNARC CTU (UK Clinical Research Collaboration CTU registration 42). Approval for the trial was received from the North West London Research Ethics Committee (approval 10/H0722/42). The trial results will be published in full in *Health Technology Assessment*.

Competing interests

None declared. The views and opinions expressed are ours and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS or the Department of Health.

Author details

G Sarah Power, Statistician¹

David A Harrison, Senior Statistician¹

Paul R Mouncey, Trial Manager¹

Tiffany M Osborn, Trial Clinician,¹ and Associate Professor²

Sheila E Harvey, Manager and Senior Research Fellow¹

Kathryn M Rowan, Chief Investigator and Director¹

¹ Clinical Trials Unit, Intensive Care National Audit and Research Centre, London, United Kingdom.

² Department of Surgery and Division of Emergency Medicine, Washington University and Barnes-Jewish Hospital, St Louis, Mich, United States.

Correspondence: promise@icnarc.org

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Appendix. The Protocolised Management in Sepsis trial group

Management group

Kathy Rowan (Chief Investigator), Derek Bell, Julian Bion, Tim Coats, David Harrison, Sheila Harvey, Rahi Jahan, Paul Mouncey, Tiffany Osborne, Sarah Power, Mervyn Singer, Jermaine Tan, Duncan Young

Steering committee

Steve Goodacre (Chair), Julian Bion, Caroline Bowers, Phil Crow, Rupert Pearse, Kathy Rowan, David Yates

Data monitoring and ethics committee

Jon Nichol (Chair), Alasdair Gray, Tim Walsh

Investigators (all hospitals are in United Kingdom)

Addenbrooke's Hospital, Cambridge: V Ahmed, A Boyle, A Scott-Donkin. *Arrowe Park Hospital, Wirral*: H Black, D Jenkins, C Smalley. *Barnsley Hospital, Barnsley*: J Humphrey, J Griffiths, S A Pearson. *Bedford Hospital, Bedford*: D Subramanyam, D Niblett. *Birmingham Heartlands Hospital, Birmingham*: F Gao-Smith, T Melody, K Couper. *Bristol Royal Infirmary, Bristol*: J Bengner, J Bewley, L Flintoff. *Blackpool Victoria Hospital, Blackpool*: R Nichani, E Brennan, H Kenworthy. *Broomfield Hospital, Chelmsford*: D Arawwawala, C Mitchell-Inwang, F McNeela. *Chelsea and Westminster Hospital, London*: D Bell, C Emerson, T Weldring. *Derriford Hospital, Plymouth*: P MacNaughton, A Kehoe, H McMillan. *Dorset County Hospital, Dorchester*: T Doyle, S Moreton. *Frenchay Hospital, Bristol*: J Kendall, E Oldenbourg, A Gilbertson. *Hinchingbrooke Hospital, Huntingdon*: C Borland, S Boys. *Hull Royal Infirmary, Hull*: I Smith, N Smith, P Williams. *John Radcliffe Hospital, Oxford*: D Young, R Farras Araya. *Kettering General Hospital, Kettering*: P Watt, N Spencer, P Raymode. *King's College Hospital, London*: P Hopkins, G Parsons, S Helyar. *Leicester Royal Infirmary, Leicester*: J Thompson, T Coats, D Hales. *Leighton Hospital, Crewe*: S Gilby, P Chilton, R Miller. *Manchester Royal Infirmary, Manchester*: J Butler, B Foex, A Royle. *Medway Maritime Hospital, Gillingham*: G Sanders, P Hayden, C. Plowright. *Musgrove Park Hospital, Taunton*: R Innes, D Bayford, P Richards. *New Cross Hospital, Wolverhampton*: S Gopal, N Poonit, L Phiri. *Newham University Hospital, London*: J Napier, E Warrington. *North Devon District Hospital, Barnstaple*: L Kevern, J Hunt. *North Tyneside General Hospital, North Shields*: E Sykes, J Dickson, S Duffy. *Peterborough City Hospital, Peterborough*: C Carlie, T Croft. *Poole Hospital, Poole*: N Jenkins, H Reschreiter, J Camsooksai. *Queen Elizabeth Hospital Birmingham, Birmingham*: C Snelson, J Bion, F Keats. *Queen Elizabeth Hospital, Gateshead*: V Linnett, S Christian, J Ritzema. *Queen's Medical Centre, Nottingham*: A Jabbar, P Miller, R Ravenscroft. *Royal Berkshire Hospital, Reading*: L Keating, D Mossop, E Bowley. *Royal Bournemouth Hospital, Bournemouth*: D Martin, P Swallow, E Vickers. *Royal Lancaster Infirmary, Lancaster*: S McBride, M Entwistle, J Craig. *Royal Preston Hospital, Preston*: T Owen, J Baldwin, S McMullen. *Royal Surrey County Hospital, Guildford*: M Zuleika, P Carvalho. *Royal Sussex County Hospital, Brighton*: D Agranoff, F Ingoldby. *Royal Victoria Infirmary, Newcastle upon Tyne*: I Clement, C Higham. *Salford Royal Hospital, Salford*: B Martin, C Gavin, K Clayton. *South Tyneside District Hospital, South Shields*: C Frey, A Kumar, D Miller. *Southend University Hospital, Southend*: K Iftikhar, D Higgins, V Katsande. *Stafford Hospital, Stafford*: M Chikungwa, T Bentley, C Jackson. *The Ipswich Hospital, Ipswich*: R Howard-Griffin, S Bell, H Blaylock. *The James Cook University Hospital, Middlesbrough*: I Gonzalez, P Dissmann, K Colling. *The Queen Elizabeth Hospital, King's Lynn*: J Carter, P Moondi, K Wong. *The Royal Blackburn Hospital, Blackburn*: S Hartley, J Hinchcliffe, L Phoenix. *The Royal London Hospital, London*: T Harris, J Pott. *Torbay Hospital, Torquay*: M Mercer, P Mercer. *University College Hospital, London*: D Brealey, M Singer, J H Ryu. *University Hospital of North Staffordshire, Stoke-on-Trent*: M Poulson, S Plant, I Massey. *Wansbeck General Hospital, Ashington*: E Sykes, J Dickson, S Duffy. *Whipps Cross University Hospital, London*: T Harris, I Skene. *Whiston Hospital, Prescot*: P Nee, S Dowling, A McCairn. *Worthing Hospital, Worthing*: R Duckitt, R Venn, J Margalef. *York Hospital, York*: J Redman, D Yates, M Makiela.