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Abstract

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

Paul R Mouncey,[1] Tiffany M Osborn,[2] G Sarah Power,[1] David A Harrison,[1] M Zia Sadique,[3] Richard D Grieve,[3] Rahi Jahan,[1] Jermaine CK Tan,[1] Sheila E Harvey,[1] Derek Bell,[4,5] Julian F Bion,[6] Timothy J Coats,[7] Mervyn Singer,[8] J Duncan Young[9] and Kathryn M Rowan[1]*

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Background: Early goal-directed therapy (EGDT) is recommended in international guidance for the resuscitation of patients presenting with early septic shock. However, adoption has been limited and uncertainty remains over its clinical effectiveness and cost-effectiveness.

Objectives: The primary objective was to estimate the effect of EGDT compared with usual resuscitation on mortality at 90 days following randomisation and on incremental cost-effectiveness at 1 year. The secondary objectives were to compare EGDT with usual resuscitation for requirement for, and duration of, critical care unit organ support; length of stay in the emergency department (ED), critical care unit and acute hospital; health-related quality of life, resource use and costs at 90 days and at 1 year; all-cause mortality at 28 days, at acute hospital discharge and at 1 year; and estimated lifetime incremental cost-effectiveness.

Design: A pragmatic, open, multicentre, parallel-group randomised controlled trial with an integrated economic evaluation.

Setting: Fifty-six NHS hospitals in England.

Participants: A total of 1260 patients who presented at EDs with septic shock.

Interventions: EGDT ($n = 630$) or usual resuscitation ($n = 630$). Patients were randomly allocated 1 : 1.

Main outcome measures: All-cause mortality at 90 days after randomisation and incremental net benefit (at £20,000 per quality-adjusted life-year) at 1 year.

Results: Following withdrawals, data on 1243 (EGDT, $n = 623$; usual resuscitation, $n = 620$) patients were included in the analysis. By 90 days, 184 (29.5%) in the EGDT and 181 (29.2%) patients in the usual-resuscitation group had died [$p = 0.90$; absolute risk reduction −0.3%, 95% confidence interval (CI) −5.4 to 4.7; relative risk 1.01, 95% CI 0.85 to 1.20]. Treatment intensity was greater for the EGDT group, indicated by the increased use of intravenous fluids, vasoactive drugs and red blood cell transfusions. Increased treatment intensity was reflected by significantly higher Sequential Organ Failure Assessment scores and more advanced cardiovascular support days in critical care for the EGDT group. At 1 year, the incremental net benefit for EGDT versus usual resuscitation was negative at −£725 (95% CI −£3000 to £1550). The probability that EGDT was more cost-effective than usual resuscitation was below 30%. There were no significant differences in any other secondary outcomes, including health-related quality of life, or adverse events.

Limitations: Recruitment was lower at weekends and out of hours. The intervention could not be blinded.

Conclusions: There was no significant difference in all-cause mortality at 90 days for EGDT compared with usual resuscitation among adults identified with early septic shock presenting to EDs in England. On average, costs were higher in the EGDT group than in the usual-resuscitation group while quality-adjusted life-years were similar in both groups; the probability that it is cost-effective is < 30%.

Future work: The ProMISe (Protocolised Management In Sepsis) trial completes the planned trio of evaluations of EGDT across the USA, Australasia and England; all have indicated that EGDT is not superior to usual resuscitation. Recognising that each of the three individual, large trials has limited power for evaluating potentially important subgroups, the harmonised approach adopted provides the opportunity to conduct an individual patient data meta-analysis, enhancing both knowledge and generalisability.

Trial registration: Current Controlled Trials ISRCTN36307479.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 19, No. 97. See the NIHR Journals Library website for further project information.

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List of abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation version II
ARISE	Australasian Resuscitation In Sepsis Evaluation
CI	confidence interval
CLRN	Comprehensive Local Research Network
CRN	Clinical Research Network
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
ED	emergency department
EGDT	early goal-directed therapy
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FiO_2	fraction of inspired oxygen
GCS	Glasgow Coma Scale
ICNARC	Intensive Care National Audit & Research Centre
ICU	intensive care unit
INB	incremental net monetary benefit
IQR	interquartile range
MEDS	Mortality in Emergency Department Sepsis
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PaO_2	partial pressure of oxygen
PI	principal investigator
ProCESS	Protocolized Care for Early Septic Shock
ProMISe	Protocolised Management in Sepsis
QALY	quality-adjusted life-year
$ScvO_2$	central venous oxygen saturation
SD	standard deviation
SIRS	systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SpO_2	arterial oxygen saturation
TMG	Trial Management Group
TSC	Trial Steering Committee

Plain English summary

What was the problem/question?

Sepsis is a severe infection in the blood which can damage important organs in the body, such as the heart and lungs. Patients who develop sepsis are at a high risk of dying. A research study in a US hospital emergency department found that patients with sepsis treated using a 6-hour structured treatment plan (compared with usual treatment) were more likely to survive and to spend less time in hospital.

The ProMISe (Protocolised Management In Sepsis) study wanted to find out if the 6-hour structured treatment plan would work in the UK, compared with usual treatment.

What did we do?

A total of 1260 patients from 56 hospitals across the country took part in the study. Patients were evenly split into two groups to receive either the 6-hour structured treatment plan or usual treatment. They were followed up for 1 year to see the long-term effects of receiving treatment.

What did we find?

There was no significant difference in the number of patients who died after 3 months or after 1 year of receiving either treatment. The costs of treatment (in hospital and after leaving hospital) were higher for patients who received the 6-hour structured treatment plan.

What does this mean?

The 6-hour structured treatment plan did not improve survival for patients with sepsis and was more expensive.

Scientific summary

Background

The incidence of severe sepsis and septic shock in adults is estimated to range from 56 to 91 per 100,000 population per year. Affected patients have high mortality, morbidity and resource utilisation.

Since 2002, the Surviving Sepsis Campaign has promoted best practice, which includes early recognition, source control, appropriate and timely antibiotic administration, and resuscitation with intravenous fluids and vasoactive drugs. Resuscitation guidance is largely based on a 2001 single-centre, proof-of-concept trial, which indicated that protocolised delivery of 6 hours of early goal-directed therapy (EGDT) to patients presenting at the emergency department (ED) with early septic shock reduced hospital mortality and hospital length of stay. EGDT aims to optimise tissue oxygen transport using continuous monitoring of pre-specified physiological targets – central venous pressure, mean arterial pressure and central venous oxygen saturation ($ScvO_2$) – to guide the delivery of intravenous fluids, vasoactive drugs and packed red blood cell transfusions.

However, despite Surviving Sepsis Campaign recommendations, adoption of EGDT has been limited, with concerns about the external validity of results from a single-centre trial, the complexity of protocol delivery, the potential risks of the components and the resources required for implementation.

To address these concerns, multicentre trials of EGDT in the USA (Protocolized Care for Early Septic Shock: ProCESS), Australasia (Australasian Resuscitation In Sepsis Evaluation: ARISE) and England (Protocolised Management In Sepsis: ProMISe) were conducted, employing harmonised methods to permit an individual patient data meta-analysis.

The ProMISe trial tested the hypothesis that the 6-hour EGDT resuscitation protocol is superior, in terms of clinical effectiveness and cost-effectiveness, to usual resuscitation in patients presenting with early septic shock to NHS EDs in England.

Objectives

The primary objectives of the trial were:

- to estimate the effect of EGDT compared with usual resuscitation on all-cause mortality at 90 days
- to compare incremental cost-effectiveness at 1 year of EGDT with usual resuscitation.

The secondary objectives were to compare EGDT with usual resuscitation for:

- requirement for, and duration of, critical care unit organ support
- length of stay in the ED, critical care unit and acute hospital
- health-related quality of life at 90 days and at 1 year
- resource use and costs at 90 days and at 1 year
- all-cause mortality at 28 days, at acute hospital discharge and at 1 year
- estimated lifetime incremental cost-effectiveness.

Methods

Trial design and governance

ProMISe was a pragmatic, open, multicentre, parallel-group randomised controlled trial. The North West London Research Ethics Committee approved the trial. The UK National Institute for Health Research funded the trial and convened a Trial Steering Committee and an independent Data Monitoring and Ethics Committee. The Clinical Trials Unit at the Intensive Care National Audit & Research Centre (ICNARC) managed the trial. The trial was prospectively registered for an International Standard Randomised Controlled Trial Number (ISRCTN36307479).

Participants: sites and patients

The trial was conducted in English NHS hospitals not routinely using EGDT including continuous $ScvO_2$ monitoring. Patients aged 18 years or over were eligible if, within 6 hours of ED presentation, they had a known or presumed infection, two or more systemic inflammatory response syndrome criteria, and either refractory hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg, despite intravenous fluid resuscitation of at least 1 l within 60 minutes) or hyperlactataemia (blood lactate concentration ≥ 4 mmol/l) and did not meet any exclusion criteria.

Randomisation had to be completed within 2 hours of meeting inclusion criteria following informed consent from the patient or agreement from a personal/professional consultee or an independent clinician. Patients were allocated in a 1 : 1 ratio, via 24-hour telephone randomisation, to EGDT or usual resuscitation. Allocation was by randomised permuted blocks, with variable block lengths, stratified by site. Antimicrobials had to be commenced prior to randomisation.

Treatment groups

Following randomisation, the usual-resuscitation group continued to receive monitoring, investigations and treatment determined by the treating clinician(s) while the EGDT group commenced the resuscitation protocol. For the latter, during the first hour, a central venous catheter capable of continuous $ScvO_2$ monitoring was inserted. The resuscitation protocol was followed for 6 hours (intervention period) with personnel involved and treatment location decided by sites, although at least one trained member of staff was available throughout. All other treatment, during the intervention period and after, was at the discretion of the treating clinician(s). Blinding to treatment allocation was not possible. Edwards Lifesciences Ltd (Newbury, Berkshire) lent monitors and provided training and technical support, but had no other role in the trial.

Data sources

A secure, dedicated electronic case report form was set up to enable trial data to be entered by staff at participating sites. Inclusion criteria, baseline, intervention, physiology and location of care data to the point of hospital discharge were collected by the sites. Following linkage with the Health and Social Care Information Centre Data Linkage and Extract Service to confirm mortality status, a Health Services Questionnaire and a European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire were sent to patients at 90 days and 1 year. These provided information about the patient's use of health services and quality of life following discharge from the acute hospital. Linkage to the ICNARC Case Mix Programme database provided information on subsequent admission to adult general critical care following discharge from the acute hospital.

Analysis principles

All analyses were by intention to treat, following a pre-specified statistical analysis plan. A p-value of 0.05 was considered statistically significant. All tests were two-sided with no adjustment for multiple comparisons. As missing data for the clinical effectiveness primary outcome were anticipated to be minimal, a sensitivity approach was taken when the primary outcome was missing. Missing data for the cost-effectiveness analysis, as well as missing baseline data for adjusted analysis of clinical outcomes, were handled by multiple imputation using chained equations.

Outcome measures

The primary clinical effectiveness outcome was all-cause mortality at 90 days. The primary cost-effectiveness outcome was incremental net monetary benefits (INBs) at £20,000 per quality-adjusted life-year (QALY) at 1 year. Secondary outcomes were Sequential Organ Failure Assessment (SOFA) score at 6 and 72 hours; receipt of and days alive and free (up to 28 days) from advanced cardiovascular, advanced respiratory or renal support; ED, critical care and acute hospital length of stay; duration of survival; all-cause mortality at 28 days, at acute hospital discharge and at 1 year, and health-related quality of life (measured by the EQ-5D-5L questionnaire), resource use, and costs at 90 days and 1 year, and lifetime incremental cost-effectiveness. Adverse events were monitored to 30 days. The cost-effectiveness analysis estimated INBs by valuing incremental QALYs at the threshold value for a QALY gain (£20,000) that is recommended by the National Institute for Health and Care Excellence and then subtracting the incremental costs.

Secondary analyses of the primary outcomes included adjusted analysis [adjusted for Mortality in Emergency Department Sepsis (MEDS) score components], learning curve analysis (clinical effectiveness only) and adherence-adjusted analysis. Pre-specified subgroup analyses were conducted, testing interactions between the effect of EGDT and the following: degree of protocolised care for usual resuscitation; age; MEDS score; SOFA score; and time from ED presentation to randomisation. Sensitivity analyses were performed for missing data in the primary clinical outcome and to test the main assumptions of the cost-effectiveness analysis.

Results

Sites and patients

In total, 6192 patients were screened at 56 sites, with 1260 enrolled between 16 February 2011 and 24 July 2014. Four patients requested complete withdrawal and five were ineligible, resulting in 1251 patients for initial analysis (625 EGDT and 626 usual resuscitation). Eight patients withdrew before 90 days, resulting in 1243 patients for analysis of outcomes (623 EGDT and 620 usual resuscitation). Groups were well matched at baseline.

Adherence to protocol

Most patients randomised to EGDT had timely insertion of a central venous catheter capable of continuous $ScvO_2$ monitoring; two, inserted in error in the usual-resuscitation group, were not used for monitoring $ScvO_2$. Standard central venous catheters (not mandated) were inserted in 50.9% of the usual-resuscitation group and $ScvO_2$ measurement from aspirated blood samples occurred in six patients. Arterial catheters (not mandated) were inserted in most patients. EGDT was stopped prematurely in 21 patients. Overall, adherence to EGDT was good.

Delivery of care by treatment group

During the 6-hour intervention period, EGDT patients received more intravenous fluid. Hourly fluid volume decreased over the 6 hours but usual-resuscitation patients received a larger initial volume. In both groups, crystalloid was used more frequently. More EGDT patients received vasopressors and dobutamine. Although more EGDT patients received packed red blood cells, larger volumes were transfused in the usual-resuscitation group. During the 6-hour intervention period, administration of platelets and fresh-frozen plasma was similar, although volumes of both were higher in the EGDT group. At 6 hours, central venous pressure, mean arterial pressure, systolic blood pressure and haemoglobin, where measured (greater frequency in the EGDT group), were similar.

Between 6 and 72 hours, use of intravenous fluids was similar but usual-resuscitation patients received higher volumes. Intravenous colloid use was higher in EGDT patients but volumes were similar in the two groups, intravenous crystalloid use was similar but volumes were higher in usual-resuscitation patients and use of packed red blood cells was higher in EGDT patients but the volumes delivered were higher in usual-resuscitation patients. Although use of platelets and fresh-frozen plasma was similar, the volume of

platelets transfused was higher in EGDT patients and the volume of fresh-frozen plasma was higher in usual-resuscitation patients. Vasopressor and dobutamine use remained higher in EGDT patients. At 72 hours, physiological, biochemistry and SOFA values were similar.

Primary outcome: clinical effectiveness

At 90 days following randomisation, 184 (29.5%) patients randomised to EGDT had died, compared with 181 (29.2%) patients randomised to usual resuscitation, corresponding to an absolute risk reduction of −0.3 [95% confidence interval (CI) −5.4 to 4.7; $p = 0.90$] and a relative risk of 1.01 (0.85 to 1.20). This difference remained non-significant after adjustment for baseline characteristics (adjusted odds ratio 0.95, 95% CI 0.74 to 1.24; $p = 0.73$; unadjusted odds ratio 1.02, 95% CI 0.80 to 1.30).

Secondary outcomes: clinical effectiveness

For EGDT patients, the mean SOFA score at 6 hours, the proportion receiving advanced cardiovascular support and the median critical care length of stay were significantly greater. No other secondary outcomes were significantly different. Thirty (4.8%) EGDT patients and 26 (4.2%) usual-resuscitation patients experienced one or more serious adverse events ($p = 0.58$).

Subgroup and secondary analyses

There was no difference in effect of EGDT according to pre-specified subgroups (*p*-values for test of interaction 0.39 to 0.72). Sensitivity analyses for missing primary outcomes (EGDT, $n = 2$; usual resuscitation, $n = 6$) reported relative risks from 0.99 to 1.03. There was no evidence of a learning-curve effect ($p = 0.56$). Adherence-adjusted analysis reported a relative risk of 1.02 (95% CI 0.78 to 1.32; $p = 0.90$).

Cost-effectiveness analysis

At 1 year following randomisation, a slightly higher proportion of EGDT patients than usual-resuscitation patients were alive. The net effect of EGDT patients having higher survival but a lower average patients European Quality of Life-5 Dimensions utility score resulted in similar 1-year QALYs between the treatment groups. The mean total cost was higher in EGDT patients, with an incremental cost of £764 (95% CI −£1402 to £2930), and hence the INB for EGDT versus usual resuscitation was negative at −£725 (95% CI −£3000 to £1550). The estimated INBs were similar for adherence-adjusted analysis and across all pre-specified subgroups. The estimated INBs were also similar for the alternative scenarios considered in the sensitivity analyses. The probability that EGDT is cost-effective, at the recommended threshold of £20,000 per QALY, is below 30%. Cost-effectiveness results were similar at 90 days (INB −£1000, 95% CI −£2720 to £720) and when extrapolated to the lifetime (INB −£1446, 95% CI −£8102 to £5210).

Conclusions

Among adults identified with early signs of septic shock presenting to the ED of one of 56 NHS hospitals in England and receiving 6 hours of protocolised resuscitation, there was no significant difference in mortality at 90 days, compared with usual resuscitation. Although mortality was lower than anticipated, these results rule out a relative risk reduction with EGDT of > 15%. On average, EGDT increased costs and, given similar QALYs across groups, INB at 1 year was negative. The probability that EGDT is cost-effective (at a willingness to pay of £20,000 per QALY) is below 30%.

There was no significant interaction between treatment effect and mortality at 90 days across pre-specified subgroups. More patients receiving EGDT were admitted to critical care, resulting in significantly more days spent in critical care in this group. Treatment intensity was greater for EGDT patients, driven by adherence to the protocol, and indicated by increased use of central venous catheters, intravenous fluids, vasoactive drugs and packed red blood cells. Increased treatment intensity was reflected in significantly higher SOFA scores and more advanced cardiovascular support days in critical care for the EGDT group. There were no significant differences in any other secondary outcomes including health-related quality of life, which was substantially poorer in this severely ill patient group at both 90 days and 1 year than for the age-/sex-matched general population.

Implications for health care

The results suggest that usual resuscitation has evolved over the 15 years since the Rivers *et al.* trial (Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;**345**:1368–77); NHS hospitals now achieve levels of in-hospital survival similar to those achieved with EGDT in the Rivers *et al.* trial for patients with septic shock identified early and receiving intravenous antibiotics and adequate fluid resuscitation. The addition of continuous $ScvO_2$ monitoring and strict protocolisation of care was, on average, more costly and did not improve outcomes.

Recommendations for research

Recommendation 1: an individual patient data meta-analysis of the three completed trials should be conducted

These results complete the planned trio of evaluations of EGDT across the USA, Australasia and England. Each has their own strengths and weaknesses, but all have indicated that EGDT is not superior to usual resuscitation. Recognising that each of the three individual large trials has limited power for evaluating potentially important subgroups, the harmonised approach adopted provides the opportunity to conduct an individual patient data meta-analysis, enhancing both knowledge and generalisability.

Recommendation 2: further research to consider alternative definitions of adherence to the resuscitation protocol should be conducted

Both the clinical effectiveness and cost-effectiveness analyses reported estimates that were adherence-adjusted as part of pre-specified secondary analyses. However, further research to consider alternative definitions of adherence to the EGDT resuscitation protocol are warranted. In particular, future research could apply differential weights for adherence to the different elements of the EGDT resuscitation protocol, or to particular time points within the 6-hour intervention period. Hence subsequent research could report whether EGDT was clinically effective or cost-effective when these alternative definitions of adherence were met.

Trial registration

This trial is registered as ISRCTN36307479.

Funding

This project was funded by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Background and rationale

The incidence of infections severe enough to cause systemic sepsis and septic shock in adults is estimated to range from 56 to 91 per 100,000 population per year.[1] Affected patients have high mortality, morbidity and resource utilisation.[2–5] Efforts to improve care for these patients have been 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 during which prompt, rigorous, protocolised care may reduce unwanted consequences and improve clinical outcomes.

In 2001, Rivers *et al.*[6] reported the results of a single-centre, randomised controlled trial, which took place in the USA. This trial investigated the delivery of 6 hours of early goal-directed therapy (EGDT), with pre-determined haemodynamic goals, to patients presenting at an emergency department (ED) with emerging septic shock. EGDT, 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 EGDT is that many patients with emerging septic shock have global tissue hypoxia that is not adequately identified using traditional resuscitation end points (such as blood pressure) and that rapid correction of occult tissue hypoxia leads to improved survival. Accordingly, resuscitation incorporating EGDT incorporates the invasive measurement of central venous oxygen saturation ($ScvO_2$) to detect occult global tissue hypoxia. EGDT aims to optimise tissue oxygen transport by continuous monitoring of pre-specified physiological targets – central venous pressure, mean arterial pressure and $ScvO_2$ – to guide delivery of intravenous fluids, vasoactive drugs and packed red blood cell transfusions.

The plausible biological rationale for EGDT, combined with the results of the Rivers *et al.*[6] trial and some observational studies,[7–12] led to its recommendation for the initial management of patients with septic shock by the Surviving Sepsis Campaign guidelines for the resuscitation and management of severe sepsis[13–15] and incorporation into the associated 'bundles' of care.[16] However, adoption of, and compliance with, these resuscitation and management bundles has been limited.[2,17]

The lack of adoption of EGDT has primarily been due to concerns about the external validity of results from a single-centre trial, generalisability into other health-care settings, the complexity of delivery of EGDT, potential risks of the components of EGDT and the resources required for implementation.[18,19]

Reports of successful implementation of EGDT 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 intensive care unit (ICU); and locally determined delivery.[20,21]

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.

Despite its promising results, the Rivers *et al.*[6] trial can be considered only as 'proof of concept', and it is necessary to establish whether or not these results are generalisable to the UK NHS. The sample size was small ($n = 263$ patients) and single-centre studies often reflect local, and sometimes unique, processes of care. It may not be possible to replicate the results of single-centre studies in larger, multicentre studies, and important examples of this have recently been reported in the critical care literature.[22]

To address these concerns, three research teams collaborated to conduct multicentre trials of EGDT in the USA (Protocolized Care for Early Septic Shock: ProCESS),[23] Australasia (Australasian Resuscitation In Sepsis Evaluation: ARISE)[24] and England (Protocolised Management In Sepsis: ProMISe). The three trials employed harmonised methods[25] and, following full reporting, data will be pooled into one individual patient data meta-analysis.[26] Both ProCESS[23] and ARISE[24] have published their results (in March 2014 and October 2014, respectively) and reported no benefit of EGDT. However, both trials reported mortality in the usual-resuscitation group that was lower than anticipated (ProCESS, 60-day in-hospital mortality, 18.9% observed, 30–46% anticipated; ARISE, 90-day mortality, 18.8% observed, 38% anticipated). Consequently, neither trial could exclude, with 95% confidence, the potential for a 20% relative reduction in 90-day mortality for EGDT compared with usual resuscitation [ProCESS, relative risk 0.94, 95% confidence interval (CI) 0.77 to 1.15; ARISE, relative risk 0.98, 95% CI 0.80 to 1.21].

Aim

The overall aim of the ProMISe trial was to test the hypothesis that EGDT is superior, in terms of both its clinical effectiveness and its cost-effectiveness, to usual resuscitation in patients presenting with early septic shock to NHS EDs in England.

Objectives

Primary

The primary objectives of the ProMISe trial were:

- to estimate the effect of EGDT compared with usual resuscitation on all-cause mortality at 90 days
- to compare incremental cost-effectiveness at 1 year of EGDT with usual resuscitation.

Secondary

The secondary objectives of the ProMISe trial were to compare EGDT with usual resuscitation for:

- requirement for, and duration of, critical care unit organ support
- length of stay in the ED, critical care unit and acute hospital
- health-related quality of life at 90 days and at 1 year
- resource use and costs at 90 days and at 1 year
- all-cause mortality at 28 days, at acute hospital discharge and at 1 year
- estimated lifetime incremental cost-effectiveness.

Chapter 2 Methods

Trial design

ProMISe was a pragmatic, open, multicentre, parallel-group randomised controlled trial with an integrated economic evaluation.

Research governance

ProMISe was sponsored by the Intensive Care National Audit & Research Centre (ICNARC) and co-ordinated by the ICNARC Clinical Trials Unit (CTU). An ethics application was made to the North West London Research Ethics Committee 1 on 4 May 2010 and a favourable opinion was received on 2 August 2010 (reference number 10/H0722/42).

Global NHS permissions were obtained from London North West Comprehensive Local Research Network (CLRN) on 8 September 2010 and local NHS permissions were obtained from each participating NHS hospital trust. A clinical trial site agreement, based on the model agreement for non-commercial research in the NHS, was signed by each participating NHS hospital trust and the sponsor (ICNARC).

The National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio details high-quality clinical research studies that are eligible for support from the NIHR CRN in England. The trial was adopted onto the NIHR CRN Portfolio on 11 July 2011.

To ensure transparency, the trial was registered for an International Standard Randomised Controlled Trial Number (ISRCTN). Registration was confirmed on 19 November 2009 (ISRCTN36307479).

Following guidelines from the NIHR, a Trial Steering Committee (TSC), with a majority of independent members, was convened to oversee the trial on behalf of the funder (NIHR) and the sponsor (ICNARC). The TSC met at least annually during the trial and comprised an independent chair (an experienced triallist); independent lay members (representing patient perspectives); independent clinicians (specialising in critical care medicine and emergency care medicine); the chief investigator (KR); and a co-investigator (JB) representing the Trial Management Group (TMG).

Additionally, an independent Data Monitoring and Ethics Committee (DMEC) was convened to monitor trial data and ensure the safety of trial participants. The DMEC met at least annually during the trial and comprised two expert clinicians specialising in critical care medicine and emergency care medicine, and was chaired by an experienced statistician.

Management of the trial

The trial manager (PM) was responsible for the day-to-day management of the trial with support from the research assistant (RJ), data manager (JT) and trial statistician (SP). The TMG was responsible for overseeing the day-to-day management of the trial and comprised the chief investigator (KR), SH, TO and the co-investigators (DB, JB, TC, DH, MS and DY). The TMG met regularly throughout the trial to ensure adherence to the trial protocol and to monitor the conduct and progress of the trial.

Network support

To maintain the profile of the trial, regular updates on trial progress were provided at quarterly meetings of the NIHR CRN Critical Care Specialty Group and at local CLRN meetings. In addition, updates were provided at national meetings, such as the Annual Meeting of the Case Mix Programme and the UK Critical Care Research Forum.

Design and development of the protocol

As part of the international collaboration to evaluate the effectiveness of EGDT for managing patients with septic shock, the ProMISe TMG worked closely with the ProCESS and ARISE TMGs in developing the trial protocol to ensure common standards, design elements and the data variables collected across the three trials. This will enable a prospective individual patient data meta-analysis to be conducted on completion and publication of all three trials.[25]

Individuals representing emergency medicine, acute medicine and critical care medicine from NHS hospitals across the UK were invited to attend a meeting to discuss the trial protocol and the proposed intervention, EGDT. The meeting took place on 16 March 2010 and was attended by 91 clinicians from 54 NHS hospitals. The chairperson of the ARISE TMG also attended the meeting to share experiences in the set-up and ongoing delivery of the ARISE trial in Australasia.

Following the meeting, minor changes were made to Rivers' EGDT protocol[6] as follows:

- arterial catheter – insertion of an arterial catheter was changed from being mandated to recommended
- physiological goals – rather than a range for physiological goals, clinicians agreed that they preferred a minimum physiological goal, with no upper limit, for both central venous pressure and blood pressure
- blood pressure – a minimum physiological goal was agreed for systolic blood pressure as well as for mean arterial pressure to allow for variation in practice across NHS hospital trusts.

The trial protocol was approved by the TSC and DMEC.

Amendments to the trial protocol

Following receipt of a favourable opinion of the trial protocol from the research ethics committee on 2 August 2010, five substantial amendments were submitted and received favourable opinion. In summary, these were as follows.

Amendment 1 (March 2011): the consultee consent form was amended to the consultee agreement form to clarify that, in accordance with the Mental Capacity Act 2005,[27] personal/professional consultees were being asked for their agreement, rather than their consent, for the patient to participate in the trial. A telephone agreement form was added to document cases where personal/professional consultee agreement was obtained via telephone and an emergency consent form was added to document cases where emergency consent was obtained from an independent clinician.

Amendment 2 (September 2011): in consultation with the research ethics committee, guidance was added for situations where a patient did not regain the mental capacity to provide informed consent (retrospectively) to continue participating in the trial; where possible, agreement was to be sought from a personal consultee. The exclusion criterion – immunosuppressive agents for uncured cancer or immunosuppression for organ transplantation or from systemic disease – was removed following review by the trial clinicians, who felt that this was an important group of patients who potentially might benefit from an intervention for septic shock. In addition, minor semantic changes were made to the trial protocol and the patient follow-up letter.

Amendment 3 (January 2012): the letter to the patient's general practitioner informing them of the patient's participation in the trial was amended for use in cases where the patient was known to have died. The patient follow-up letters were amended to be specific to the follow-up time point, namely 90 days and 1 year post randomisation. Following feedback from patients, relatives and clinicians, a short version of the patient information sheet was produced which provided salient information about the trial.

Amendment 4 (November 2012): the exclusion criterion 'known to be participating in an interventional study' was removed following review by the TMG; it was agreed that patients could be co-enrolled into two interventional studies if, after careful consideration, there were no concerns about patient safety, risk of biological interaction or the scientific integrity of the trial. Local principal investigators (PIs) were advised to contact the trial on a case-by-case basis to discuss the co-enrolment of patients. In addition, minor semantic changes were made to the trial protocol and the consent/consultee agreement forms.

Amendment 5 (November 2013): a newsletter for patients participating in the trial was produced and sent with the follow-up questionnaires at 90 days and at 1 year post randomisation. Permission was also sought from the research ethics committee to e-mail follow-up questionnaires to patients, if requested.

NHS support costs

Trials in emergency and critical care are challenging and expensive to conduct. Unlike in other areas of health care, such as oncology, recruitment cannot take place solely within usual office hours. Resources are needed to enable screening and recruitment 24 hours per day, 7 days per week. Patients with severe sepsis and emerging septic shock are more likely to present at the ED in the afternoon through to late at night. Another challenge of emergency and critical care research is the informed consent process, which often has to be completed within a very short time frame, as treatments are often time limited. For ProMISe, consent and randomisation occurred within 2 hours of the patient meeting eligibility. Critically ill patients usually lack the mental capacity to be able to provide informed consent prior to randomisation, in which case it is necessary to involve a personal or professional consultee in accordance with the Mental Capacity Act 2005.[27] Senior, experienced staff are needed to be able to assess the patient's mental capacity and to be able to effectively communicate information about the trial to the patient and/or their relatives in a stressful situation.

To this end, resources equivalent to 0.9 whole-time equivalent band 8 research nurse NHS support costs were successfully agreed with the London North West CLRN on 3 December 2010. Resources were based on an estimated 22 eligible admissions per site per year, of whom 14 would be recruited and 7 would be randomised to receive EGDT. Using these recommendations, participating sites, assisted by the TMG, negotiated resources required locally for the trial with their respective research and development departments and CLRNs.

Trial equipment

The central venous catheters with $ScvO_2$ monitoring capability (PreSep™ central venous oximetry catheter), for use in patients allocated to the EGDT (intervention) group, were purchased from Edwards Lifesciences Ltd (Newbury, Berkshire) and distributed to participating sites by the ICNARC CTU. Edwards Lifesciences loaned the Vigileo™ monitor required for continuous monitoring of $ScvO_2$ to each participating site for the duration of the trial. Both the PreSep™ central venous oximetry catheter and the Vigileo™ monitor are manufactured by Edwards Lifesciences and are commercially available and licensed for use in the UK. Each participating site received training in the use of the PreSep™ central venous oximetry catheter and the Vigileo™ monitor, provided free of charge by Edwards Lifesciences. In addition, Edwards Lifesciences provided 24-hour, 7-days-per-week telephone support for any technical queries. Edwards Lifesciences had no further role in the trial.

Patient and public involvement

Engagement with patients was vital to the successful conduct of the trial. Two former critical care patients were independent members of the TSC and provided input into the conduct of the trial, including reviewing literature to be given to patients and their families (e.g. patient information sheets and patient newsletters).

Participants: sites

The trial aimed to recruit a representative sample of 48 NHS hospitals in the UK. The criteria for inclusion were:

- EGDT, including continuous monitoring of $ScvO_2$, was not already part of usual resuscitation for patients presenting with severe sepsis/septic shock
- agreement from senior clinical staff in emergency care, acute care and critical care to recruit eligible patients and to adhere to the trial protocol – sites were asked to identify a 'champion' from each specialty to promote the trial locally
- identification of a local PI and a dedicated research nurse to take responsibility for the local conduct of the trial
- provision of timely data on recruited patients entered onto a secure, dedicated, electronic case report form.

Invitations for expressions of interest were sent to lead clinicians in acute medicine, emergency medicine and critical care medicine at NHS hospitals throughout the UK. Invitations were also circulated via the College of Emergency Medicine, the Society of Acute Medicine and the Intensive Care Society. The trial was promoted through presentations at national meetings of all three organisations.

Site initiation

Prior to opening sites to recruitment, regional site initiation meetings were held across England. The purpose of these meetings was to present the background and rationale for the ProMISe trial and to discuss delivery of the protocol, including screening and recruiting patients; delivery of the intervention, EGDT; data collection and validation; and safety monitoring. The operational challenges of conducting the trial at sites were discussed in detail, including strategies for ensuring effective communication between the ED, the acute care units/ward and the critical care unit. The PI from each participating site was required to attend the meeting. A representative from Edwards Lifesciences also attended the meeting to provide training in the use of the PreSep™ central venous oximetry catheter and the Vigileo™ monitor to be used as part of delivery of the intervention, EGDT.

Investigator site file

An investigator site file was provided to all participating sites. This contained all essential documents for the conduct of the trial and included the approved trial protocol; all relevant approvals (e.g. local NHS permissions); a signed copy of the clinical trial site agreement; the delegation of trial duties log; copies of the approved patient information sheets, patient consent form and personal/professional consultee agreement forms; and all standard operating procedures, for example for screening participants, for obtaining informed consent or consultee agreement, for randomising patients, for delivery of the intervention and for collecting and entering data onto the secure, dedicated, electronic case report form. The site PI was responsible for maintaining the investigator site file.

Site management

Communication

The trial manager (PM), with support from the data manager (JT) and research assistant (RJ), maintained close contact with the PI and trial team at participating sites by e-mail and telephone throughout the trial.

Teleconferences were held, initially every month and then every 2 months, with trial teams at participating sites. The purpose of these was to provide updates on trial progress and to provide a forum for site teams to ask questions, discuss local barriers and challenges to the conduct of the trial and to share successes and best practice. Notes, including 'hints and tips', from the teleconferences were distributed to all participating sites. The ICNARC CTU team facilitated communication between sites via an e-mail forum for research nurses.

Teleconferences were also held with individual site teams, as required, to address site-specific issues in the conduct of the trial and/or to support training new staff.

Site monitoring visits

At least one routine monitoring visit was conducted at all participating sites during the trial. During the site visit, the investigator site file was checked for completeness, that is that all essential documents were present; the patient consent forms, personal/professional consultee agreement forms and emergency consent forms were checked to ensure that the relevant completed form was present for every patient recruited into the trial; and a random sample of patient case report forms were checked against the source data for accuracy and completeness. After the visit, the PI and the site team were provided with a report summarising the trial documents that had been reviewed and actions required by the site team. The site PI was responsible for addressing the actions and reporting back to the ICNARC CTU.

Maintenance and motivation

During the trial, an e-mail was sent each week to site teams with an update on patient recruitment and a newsletter was sent every quarter. These provided an opportunity to clarify any issues related to the conduct of the trial and to share ideas for maximising recruitment, as well as maintaining motivation and involvement through regular updates on progress.

To maintain the profile of the trial at participating sites, posters were displayed in staff areas and at relevant locations within the ED, for example beside the blood gas machine; pocket cards summarising the eligibility criteria were distributed; and certificates were given to clinical staff in recognition of their contribution to the trial. Other promotional materials distributed to staff included pens and lanyards.

Support

A 24-hour, 7-days-per-week telephone support service was available to site teams for advice on screening and recruitment of patients and on delivery of the intervention. In addition, Edwards Lifesciences provided a 24-hour, 7-days-per-week telephone support service for queries relating to the $ScvO_2$ monitoring equipment.

Collaborators' meeting

A collaborators' meeting was held on 30 May 2013 to provide an update on trial progress and to provide a forum for site teams and investigators to discuss operational challenges to the trial and identify possible solutions, and to share successes and best practice.

Participants: patients

The trial procedures for recruitment and follow-up of patients are summarised in *Figure 1*.

Eligibility

Eligibility was confirmed within 6 hours of the patient presenting at the ED. Patients were eligible for inclusion in the trial if they met all of the following criteria:

- known or presumed infection
- refractory hypotension – defined as a systolic blood pressure of < 90 mmHg or a mean arterial pressure of < 65 mmHg, despite an intravenous fluid challenge of a minimum of 1 l (fixed bolus) within 60 minutes (including intravenous fluids administered pre hospital), or hyperlactataemia – defined as a venous or arterial blood lactate concentration of ≥ 4 mmol/l

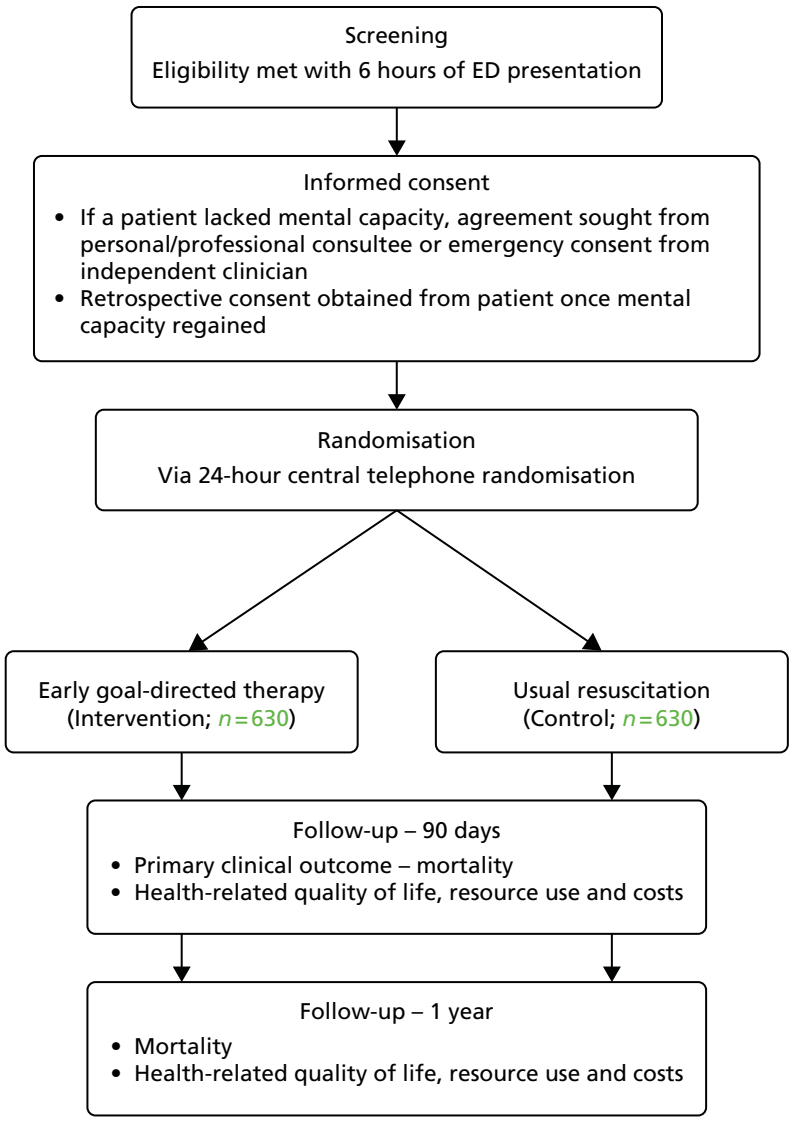

FIGURE 1 Summary of trial procedures for the recruitment and follow-up of patients. HSCIC, Health and Social Care Information Centre.

- two or more of the following systemic inflammatory response syndrome (SIRS) criteria:[28]
  - core temperature of $\leq 36\,^{\circ}C$ or of $\geq 38\,^{\circ}C$
  - heart rate of ≥ 90 beats/minute
  - respiratory rate of ≥ 20 breaths/minute [or hyperventilation indicated by either a partial pressure of carbon dioxide ($PaCO_2$) of < 4.3 kPa or mechanical ventilation for an acute process]
  - white blood cell count of $\leq 4 \times 10^9$/l or of $\geq 12 \times 10^9$/l [or the presence of $> 10\%$ immature neutrophils (bands)].

Patients were excluded from the trial if they met any of the following criteria:

- were aged < 18 years
- had a known pregnancy
- had a primary diagnosis of:
  - acute cerebral vascular event
  - acute coronary syndrome
  - acute pulmonary oedema
  - status asthmaticus
  - major cardiac arrhythmia (as part of primary diagnosis)
  - seizure
  - drug overdose
  - injury from burns or trauma
- had haemodynamic instability due to active gastrointestinal haemorrhage
- had a requirement for immediate surgery
- had a known history of acquired immunodeficiency syndrome
- had a do-not-attempt-resuscitation order
- had advanced directives restricting implementation of the EGDT resuscitation protocol
- had a contraindication to central venous catheterisation
- had a contraindication to blood transfusion
- the attending clinician deemed aggressive resuscitation unsuitable
- had been transferred from another in-hospital setting
- were not able to commence the EGDT resuscitation protocol within 1 hour of randomisation or complete 6 hours of EGDT from commencement.

The first dose of intravenous antimicrobial therapy had to be initiated prior to the patient being randomised.

During the trial, on the advice of the research ethics committee, patients who were known to have a pre-existing condition, such as dementia, which would have precluded them from providing informed consent at any point during the trial were also excluded.

Screening and recruitment

Following attendance at a site initiation meeting, screening and recruitment was commenced at participating sites once the clinical trial site agreement had been signed and all necessary approvals were in place.

To promote awareness of the trial and facilitate recruitment, posters providing information about ProMISe were displayed in the ED and in family/visitor waiting rooms.

Potentially eligible patients were identified and approached by authorised members of staff about taking part in the trial. Information about the trial was provided to the patient; this included the purpose of the trial, the consequences of taking part or not, data security and funding of the trial. This information was also provided in a patient information sheet (see *Appendix 1*), along with the name and contact details of the local PI, which was given to the patient to read before making the decision whether or not to take part in the trial. A short version of the patient information sheet, summarising the salient information about the trial, was also provided (see *Appendix 2*).

If the patient lacked mental capacity (because of their acute illness) to understand the information about the trial, then, in accordance with the UK Mental Capacity Act 2005,[27] a personal consultee, who could be a relative or close friend, was identified with whom the patient's participation in the trial could be discussed. If there was no personal consultee available, the patient was provided with a professional consultee – an independent mental capacity advocate appointed by the NHS hospital trust – with whom the patient's participation in the trial could be discussed. If there was neither a personal nor a professional consultee immediately available in person or via the telephone, an independent clinician (senior doctor or nurse) was consulted in person or via telephone for emergency consent. The personal/professional consultee or independent clinician was provided with the same information as patients (see *Appendix 1*) along with an explanation that they were being asked for their agreement for the patient taking part in the trial. Patients, personal/professional consultees and independent clinicians were provided with an opportunity to ask questions before being invited to sign the consent form, personal/professional consultee agreement form or emergency consent form, as appropriate.

Informed consent

Staff members who had received training on the background, rationale and purpose of ProMISe and on the principles of the International Conference on Harmonisation Good Clinical Practice guidelines were authorised to take informed consent from patients, informed agreement from a personal or professional consultee or emergency consent from an independent clinician.

Once the staff member taking informed consent, consultee agreement or emergency consent was satisfied that the patient, personal/professional consultee or independent clinician had read and understood the patient information sheet and all their questions about the trial had been answered, the patient, personal/professional consultee or independent clinician was invited to sign the consent form, personal/professional consultee agreement form or emergency consent form, as appropriate.

For patients who had lacked mental capacity prior to randomisation, informed consent to continue participating in the trial was sought as soon as possible after the patient had regained mental capacity. If a patient did not regain mental capacity, then, if possible, agreement from a personal consultee was obtained for the patient to continue participating in the trial.

Randomisation and allocation procedure

Following informed consent from the patient, agreement from a personal/professional consultee or emergency consent from an independent clinician, eligible patients were randomised within 2 hours of meeting eligibility via a central 24-hour, 7-days-per-week, telephone randomisation service hosted by Sealed Envelope Ltd. Patients were randomly allocated 1 : 1 to either the EGDT group or the usual-resuscitation group, by computer-generated randomised permuted blocks (with variable block lengths of 4, 6 and 8) stratified by recruiting site. A manual randomisation list was prepared a priori by the trial statistician in case the central telephone randomisation service was not available for any reason. Staff at participating sites were advised to call the 24-hours-per-day, 7-days-per-week telephone support service if they experienced any problems with the central telephone randomisation service. Manual randomisation was carried out, as required, by the on-call member of the TMG.

Screening log

To enable full and transparent reporting for the trial, brief details of all patients who met eligibility criteria or who met all inclusion criteria plus one or more of the exclusion criteria were recorded in the screening log. The reasons for eligible patients not being recruited were recorded, which included the patient declining the invitation to take part, the patient being excluded by the treating clinician, logistical reasons, etc. No patient identifiers were recorded in the screening log.

Treatment groups

Early, goal-directed therapy (intervention)

For patients randomised to the EGDT group, during the first hour (defined as the next whole hour, e.g. if randomised at 09.24, then by 11.00), a PreSep™ central venous oximetry catheter was inserted into either a subclavian or an internal jugular vein using standard techniques for central venous access and calibrated against a sample aspirated from the catheter and analysed by co-oximetry. Central venous catheters were managed according to the guidelines of the Central Venous Catheter Care Bundle.[29] If not already initiated, supplemental oxygen was administered, with intubation and mechanical ventilation as needed, to maintain an arterial oxygen saturation (SpO_2) of $\geq 93\%$. An arterial catheter was recommended, but not mandated.

The EGDT resuscitation protocol (*Figure 2*) was followed for 6 hours (intervention period) with personnel involved and treatment location decided by each site. At least one trained member of staff was available throughout the 6-hour intervention period. All other treatment, during the intervention period and after, was at the discretion of the treating clinician(s).

Each element of the resuscitation protocol was administered in series or simultaneously, depending on the clinical assessment of the patient's requirements. For example, the clinical team could choose to administer intravenous fluids in conjunction with vasopressors if a patient was in extremis.

Central venous pressure

Intravenous fluid boluses in half-litre or equivalent increments were given every 30 minutes until a minimum central venous pressure of 8 mmHg was achieved, unless the treating clinician discerned a risk to patient safety. The type of intravenous fluid and the rate of administration were at the discretion of the treating clinician(s).

Blood pressure

If the mean arterial pressure was < 65 mmHg or the systolic blood pressure was < 90 mmHg and the central venous pressure was at least 8 mmHg, vasopressors were administered and titrated to a achieve a minimum mean arterial pressure of 65 mmHg or a systolic blood pressure of 90 mmHg. The choice of vasopressor was at the discretion of the treating clinician(s) based on best evidence, the patient's clinical needs and local policy. If the mean arterial pressure was > 90 mmHg, clinicians could consider administering a vasodilator agent to reduce afterload, if clinically indicated.

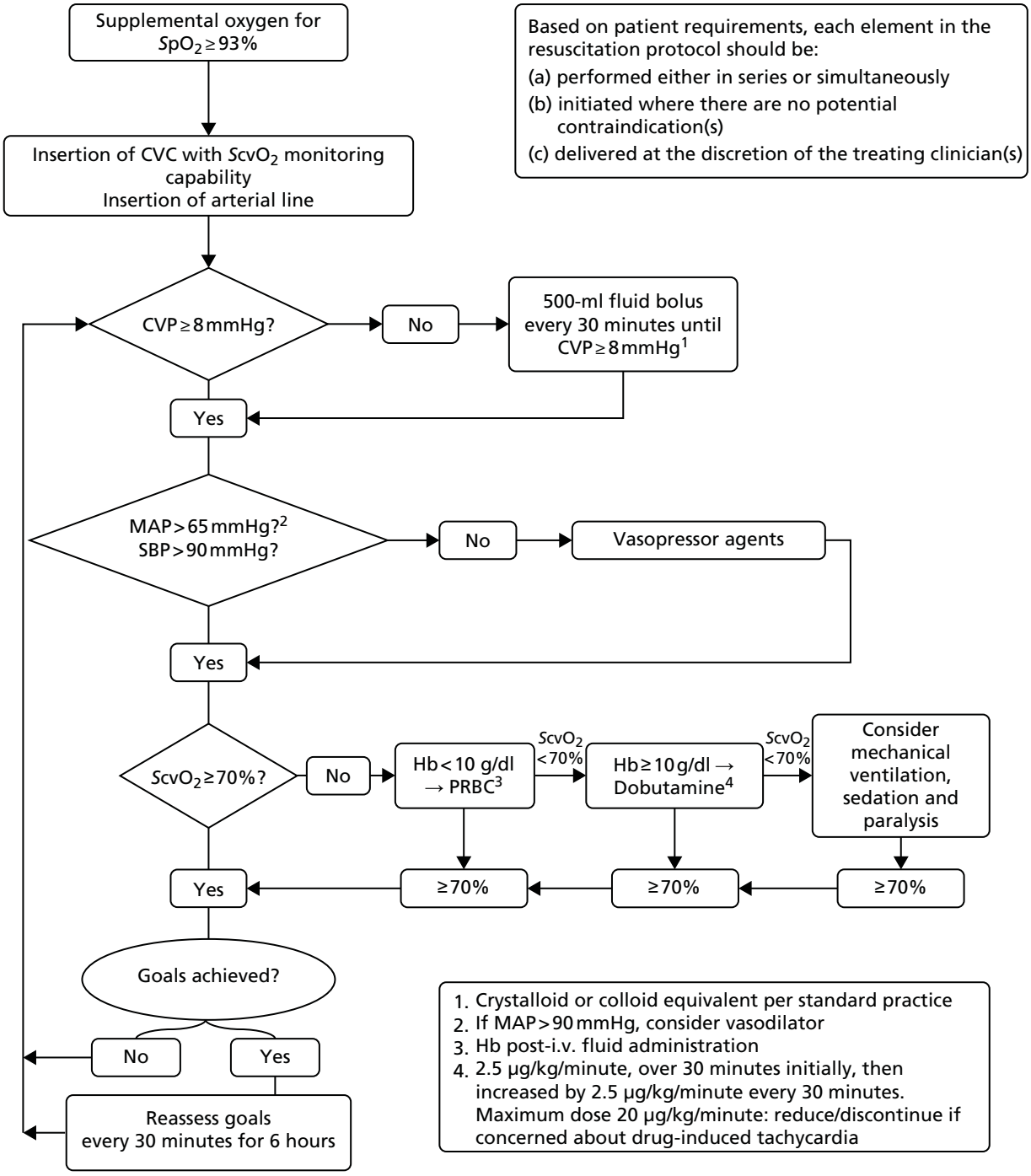

FIGURE 2 Early goal-directed therapy resuscitation protocol. CVC, central venous catheter; CVP, central venous pressure; Hb, haemoglobin; i.v., intravenous; MAP, mean arterial pressure; PRBC, packed red blood cells; SBP, systolic blood pressure.

Central venous oxygen saturation

Once the central venous pressure was at least 8 mmHg and the mean arterial pressure was at least 65 mmHg or the systolic blood pressure at least 90 mmHg, treatment was initiated, if necessary, to achieve a minimum $ScvO_2$ of 70%. If the $ScvO_2$ was < 70% and the post-fluid resuscitation haemoglobin was < 10 g/dl, packed red blood cells were transfused. If the $ScvO_2$ was < 70% and the haemoglobin was at least 10 g/dl, an infusion of dobutamine was commenced, at an initial rate of 2.5 µg/kg/minute for 30 minutes, and then increased by 2.5 µg/kg/minute every 30 minutes, to a maximum dose of 20 µg/kg/minute, until a $ScvO_2$ of ≥ 70% was achieved. The dose of dobutamine was reduced or the infusion discontinued if there was concern about drug-induced tachycardia or arrhythmia. If the $ScvO_2$ remained < 70%, the clinician could consider mechanical ventilation (with sedation and paralysis) to decrease oxygen consumption.

Monitoring

Once all physiological goals for central venous pressure, blood pressure and $ScvO_2$ were met, the patient was monitored continuously for the remainder of the intervention period (a total of 6 hours). If the central venous pressure, blood pressure or $ScvO_2$ fell below its physiological goal during the 6-hour intervention period, the EGDT resuscitation protocol recommenced. At the end of 6 hours, continuous $ScvO_2$ monitoring was no longer mandated and the patient returned to standard care.

Usual resuscitation (control)

For patients randomised to usual resuscitation, all investigations, monitoring and treatment were determined by the treating clinician(s). Although $ScvO_2$ could be measured intermittently, continuous monitoring of $ScvO_2$ was not permitted in control group patients.

Outcome measures

The primary clinical effectiveness outcome was all-cause mortality at 90 days following randomisation and the primary cost-effectiveness outcome was incremental net monetary benefit (INB) gained at 1 year, at a willingness to pay of £20,000 per quality-adjusted life-year (QALY). Secondary outcomes were as follows:

- Sequential Organ Failure Assessment (SOFA) score[30] at 6 and 72 hours
- receipt of and days alive and free (up to 28 days) from advanced cardiovascular, advanced respiratory or renal support[31]
- ED, critical care and acute hospital length of stay
- duration of survival
- all-cause mortality at 28 days, at acute hospital discharge and at 1 year
- health-related quality of life, resource use and costs at 90 days and at 1 year
- lifetime incremental cost-effectiveness.

Safety monitoring

Patients were monitored for adverse events that occurred between randomisation and 30 days following randomisation. Specified adverse events were defined as follows:

- pneumothorax – defined as any new pneumothorax requiring insertion of a chest drain (intercostal catheter)
- haemo-pneumothorax – defined as any new haemo-pneumothorax requiring insertion of a chest drain
- bleeding – defined as any new, overt blood loss requiring transfusion of one or more units of blood
- thrombosis – defined as any new clinical and radiographic evidence of a deep-vein thrombus
- pulmonary emboli – defined as any new evidence from computed tomography pulmonary angiogram with appropriate clinical history
- vascular catheter infection – defined as any new vascular catheter-related infection in which a vascular catheter, such as a central venous catheter, was identified as the primary source of infection and associated with signs and symptoms of infection requiring antimicrobials
- pulmonary oedema – defined as any new radiographic evidence consistent with pulmonary oedema
- blood transfusion reaction – defined as any allergic reaction to blood transfusion, haemolysis related to incompatible blood type or alteration of the immune system related to blood transfusion
- myocardial ischaemia – defined as any new acute electrocardiogram changes with appropriate clinical findings and changes in cardiac troponins or non-ST segment elevation myocardial infarction with appropriate increases in cardiac troponins but without electrocardiogram changes
- peripheral ischaemia – defined as any new sustained depression or loss of arterial pulse (as determined by palpation or Doppler ultrasonography) resulting in symptoms consistent with ischaemia or obvious gangrene.

Unspecified adverse events were defined as an unfavourable symptom or disease temporally associated with the use of the trial treatment, whether or not it was related to the trial treatment, that was not deemed to be a direct result of the patient's medical condition and/or standard critical care treatment.

All adverse events were recorded in the electronic case report form and reported, as part of routine reporting throughout the trial, to the DMEC and the research ethics committee. Adverse events that were assessed to be serious (i.e. prolonging hospitalisation or resulting in persistent or significant disability/incapacity), life-threatening or fatal – collectively termed serious adverse events – were reported to the ICNARC CTU and reviewed by a clinical member of the TMG. Serious adverse events that were unspecified and considered to be possibly, probably or definitely related to the trial treatment were reported to the research ethics committee within 15 calendar days of the event being reported.

Data collection

A secure, dedicated electronic case report form, hosted by ICNARC, was set up to enable trial data to be entered by staff at participating sites. The electronic case report form was accessible only to authorised users, and access was approved centrally by the trial manager or the data manager (after cross-checking the site delegation of trial duties log). Each individual was provided with a unique username and password, and had access to data only for the patients recruited at their site.

The data set for ProMISe included the minimum data required to confirm patient eligibility, to describe the patient population, to monitor and describe delivery of the intervention, to assess primary and secondary outcomes and to enable linkage to the ICNARC Case Mix Programme, the national clinical audit of adult critical care[32] (see *Appendix 3*).

Randomisation

Data were collected to enable the patient to be randomised, and included confirmation that the patient met all of the inclusion criteria and none of the exclusion criteria and that the first dose of intravenous antimicrobial(s) had been initiated (see *Appendix 3*).

Baseline

The following data were collected at baseline to enable follow-up and to describe the patient population:

- full name and address of the patient and their general practitioner
- date of birth
- sex
- raw physiology data to enable calculation of the of the following severity of illness scores:
    - SOFA score[30] (see *Appendix 4*)
    - Acute Physiology And Chronic Health Evaluation version II (APACHE II) score and predicted risk of hospital death[33] (see *Appendix 4*)
    - Mortality in Emergency Department Sepsis (MEDS) score[34] (see *Appendix 4*)
- severe comorbidities defined according to APACHE II[33] which were present and documented in the past medical history within the 6 months prior to presentation at the ED (see *Appendix 4*).

Intervention period

Data were collected hourly throughout the 6-hour intervention period to monitor adherence to the treatment allocation (EGDT resuscitation or usual resuscitation) and to describe and cost delivery of the EGDT resuscitation protocol compared with usual resuscitation. During the 6-hour intervention period, data were collected prospectively for the EGDT group and retrospectively for the usual-resuscitation group in order to avoid data collection influencing treatment delivery. The data collected comprised:

- interventions delivered during the previous hour, for example supplemental oxygen, mechanical ventilation, intravenous fluids, blood products and vasoactive drugs
- physiology, for example central venous pressure, blood pressure, $ScvO_2$ and haemoglobin.

At 6 hours

At 6 hours post randomisation, the following data were collected:

- interventions delivered during the previous hour, for example supplemental oxygen, mechanical ventilation, intravenous fluids, blood products and vasoactive drugs
- physiology, for example central venous pressure, blood pressure, $ScvO_2$ and haemoglobin
- raw physiology data to enable calculation of the SOFA score[30] (see *Appendix 4*).

Ancillary care

Data were collected to describe and cost interventions delivered after the end of the 6-hour intervention period up to discharge from the acute hospital.

At 24 hours

At 24 hours post randomisation, the following data were collected:

- interventions delivered between 6 and 24 hours, for example supplemental oxygen, mechanical ventilation, intravenous fluids, blood products and vasoactive drugs
- raw physiology data to enable calculation of the SOFA score[30] (see *Appendix 4*).

At 72 hours

At 72 hours post randomisation, the following data were collected:

- interventions delivered between 24 and 72 hours, for example supplemental oxygen, mechanical ventilation, intravenous fluids, blood products and vasoactive drugs
- raw physiology data (48–72 hours) to enable calculation of the SOFA score[30] (see *Appendix 4*)
- site of infection and causative organism.

At acute hospital discharge

At the time of discharge from the acute hospital, the following data were collected:

- the locations of care during the patient's stay in the acute hospital, for example ED, critical care unit or ward
- date of discharge from, or death in, the acute hospital
- discharge location, for example home, nursing home or other hospital
- organ support, as defined by the UK Department of Health Critical Care Minimum Data Set[31] (see *Appendix 5*) during the critical care unit stay, if applicable
- co-interventions for the source of sepsis, for example surgery, steroids or activated protein C.

Longer-term follow-up

Following randomisation, a letter was sent to the patient's general practitioner informing them of the patient's participation in the trial and issuing a request for assistance with follow-up, if required. All patients who survived to leave hospital were followed up at 90 days for the primary clinical effectiveness outcome (all-cause mortality) and secondary outcomes (health-related quality of life and resource use), and at 1 year for secondary outcomes (all-cause mortality, duration of survival, health-related quality of life and resource use) and to calculate the primary cost-effectiveness outcome (INB).

Data linkage with death registration

Follow-up of patients was carefully monitored to prevent any potential distress to those who care for the patient receiving a letter addressed to a deceased relative, partner or friend. The follow-up process started at 75 days for the 90-day follow-up and at 350 days for the 1-year follow-up to allow for the administrative processes. Each week a list of all patients who had been discharged alive from hospital and who were either 75 days or 350 days post randomisation was sent to the Health and Social Care Information Centre Data Linkage and Extract Service to confirm their mortality status. Patients indicated as having died were logged and the follow-up process ended.

Follow-up procedure

Patients identified by the Health and Social Care Information Centre Data Linkage and Extract Service as not having died started the follow-up process, as summarised in *Figure 3*. A questionnaire pack was sent from the ICNARC CTU, by post, to the patient. Following evidence-based practice for maximising responses to postal surveys,[35] the questionnaire pack included a cover letter (see *Appendix 6*); the patient information sheet (see *Appendix 1*) or patient newsletter (which replaced the patient information sheet in November 2013); two questionnaires – the Health Questionnaire (see *Appendix 7*) and the Health Services Questionnaire (see *Appendix 7*); a stamped, addressed return envelope; and a pen. The Health Questionnaire (see *Appendix 7*) included the required questions from the European Quality of Life-5

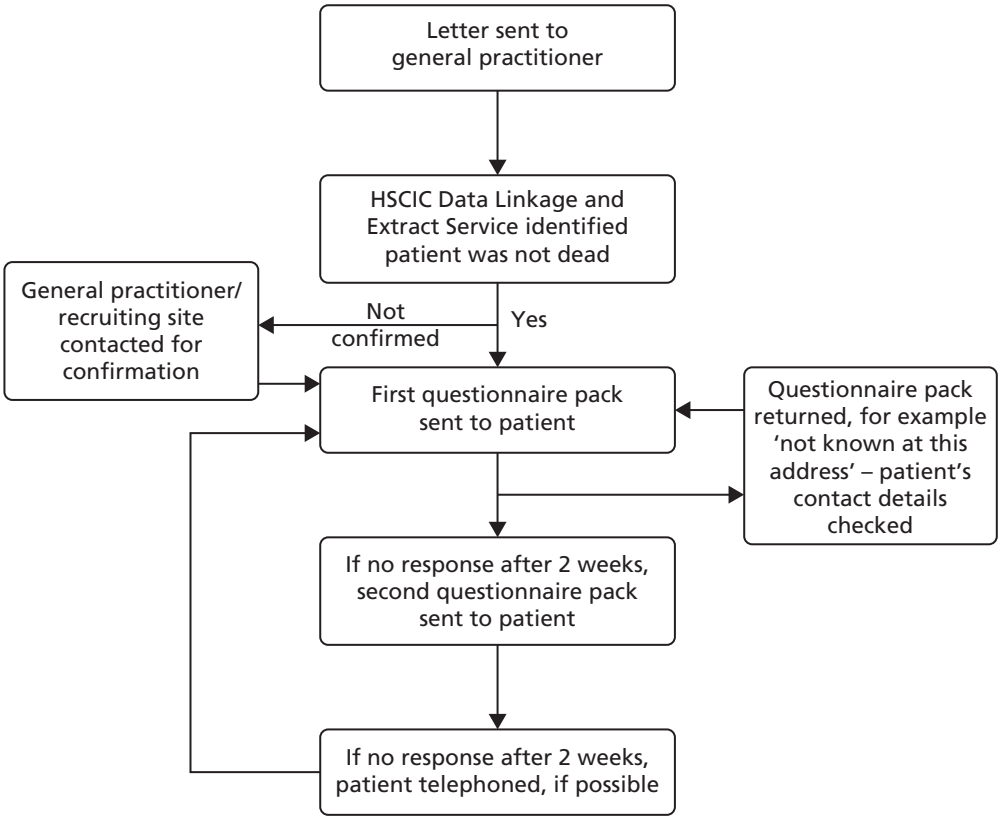

FIGURE 3 Patient follow-up process at 90 days and at 1 year. HSCIC, Health and Social Care Information Centre.

Dimensions-5-Level (EQ-5D-5L) questionnaire to evaluate health-related quality of life and the Health Services Questionnaire (see *Appendix 7*) included questions about the patient's use of health services following discharge from the acute hospital and was used to cost subsequent use of health services. The cover of the questionnaires included a 'do not wish to participate' tick box.

If no response was received after 2 weeks, a reminder letter was sent with another questionnaire pack. If no response was received after a further 2 weeks, the patient was telephoned, if his or her contact details were available. Telephone calls were made at various times from Monday to Friday between 08.30 and 20.30 to maximise the chances of contacting the patient. Patients who were successfully contacted by telephone were asked if they had received the questionnaire pack and were invited to complete the questionnaires over the telephone, if this was convenient. In addition, patients were reminded about completing the questionnaire when they attended hospital follow-up appointments.

Follow-up ended on receipt of a completed (or blank) questionnaire; on receipt of a questionnaire with a ticked 'do not wish to participate' box; on notification to the ICNARC CTU by telephone or e-mail that the patient wished to withdraw from the trial; or if there was no response to the telephone follow-up. For questionnaire packs returned indicating that the recipient was not known at the address, the contact details for the patient were checked with the recruiting hospital and/or general practitioner.

For patients who were identified as being either a hospital inpatient or resident in a care home or rehabilitation centre, the relevant institution was contacted to establish the status of the patient and the most appropriate way to proceed with follow-up. If the patient had the mental capacity to consent but required assistance in reading and/or completing the questionnaire, health-care professionals usually assisted the patient. For patients who lacked the mental capacity to consent, institutions advised on the most appropriate person to contact to complete the questionnaires.

If patients were identified as having no fixed abode but were registered with a general practitioner or had regular contact with a homeless shelter, the questionnaire pack was sent to be given (when appropriate) to them at their next appointment or visit.

Data linkage with the Case Mix Programme

The linkage of patient identifiable trial data to the ICNARC Case Mix Programme database provided information on subsequent admission to adult, general, critical care following discharge from the acute hospital.[32]

Data for the CMP are collected by trained data collectors to precise rules and definitions. The data then undergo extensive local and central validation for completeness, illogicalities and inconsistencies prior to pooling.

Data management

Data management was an ongoing process. Data entered by sites onto the electronic case report form were monitored and checked throughout the recruitment period to ensure that they were as complete and accurate as possible.

Two levels of data validation were incorporated into the electronic case report form. The first was to prevent obviously erroneous data from being entered, for example entering a date of birth that occurred after the date of randomisation. The second level involved checks for data completeness and any unusual data entered, for example a physiological variable, such as blood pressure, that was outside the pre-defined range. Site staff could generate data validation reports, listing all outstanding data queries, at any time via the electronic case report form. The site PI was responsible for ensuring that all data queries were resolved. Ongoing data entry and validation at sites were closely monitored by the data manager (JT) and any concerns were raised with the site PI.

The contact details for patients and their general practitioners (name and postal address) were checked weekly for completeness to avoid unnecessary delays in sending out questionnaire packs at 90 days and at 1 year.

Adherence to the trial protocol was closely monitored, including adherence to all elements of the EGDT resuscitation protocol. Any queries relating to adherence were generated in a separate report which was sent to the site PI.

Data received from completed European Quality of Life-5 Dimensions (EQ-5D) and Health Services Questionnaires were entered centrally into a secure database at the ICNARC CTU following a standard operating procedure. All identifiable information, such as names (e.g. of patients, family members or hospital staff members), was removed. All queries relating to data entry were reviewed by two members of the TMG (SH/PM) and any disagreement was reviewed and discussed with a third member (KR).

To ensure that data were entered accurately, all questionnaire data entered into the database were cross-checked by a second member of the CTU team. Any errors found were logged and corrected on the database.

Sample size

Estimates for baseline mortality in the usual-resuscitation group were based on the ICNARC Case Mix Programme database.[32] Between 1 January 2005 and 31 December 2006, there were 24,155 patients admitted to 156 participating adult general ICUs direct from the ED. Of these, 6671 (28%) met at least two SIRS criteria during the first 24 hours following ICU admission and had evidence of infection. Acute hospital mortality for these patients was 35%. To allow for additional deaths after discharge from hospital and before 90 days, sample size calculations were based on an anticipated mortality at 90 days of 40% in the usual-resuscitation group. To achieve 80% power to detect a 20% relative reduction in mortality at 90 days (corresponding to an 8% absolute reduction) from 40% to 32% associated with EGDT compared with usual resuscitation ($p < 0.05$, two-sided) required a sample size of 589 patients per treatment group (Stata/SE version 10.1, StataCorp LP, College Station, TX, USA). Allowing for 6% of patients refusing consent to follow-up (in the PAC-Man trial, 2% of patients refused consent after randomisation[36]) or being lost to follow-up before 90 days, our aim was to recruit 630 patients per group (1260 patients in total). This sample size provided > 99% power to detect an absolute risk reduction of the magnitude observed in the Rivers *et al.* trial (i.e. 16%).[6]

Interim analysis

Unblinded comparative data on recruitment, withdrawal, adherence with the trial protocol and serious adverse events were regularly reviewed by the DMEC. Without specific analysis of the primary outcome, the DMEC reviewed data from the first 50 trial participants and continued to review data at least 6-monthly to assess potential safety issues and to review adherence with the trial 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 owing to harm.

Analysis principles

All analyses were based on the intention-to-treat principle. Patients were analysed according to the treatment group they were randomised to, irrespective of whether or not the allocated treatment was received (i.e. regardless of whether or not they adhered to the EGDT algorithm). All tests were two-sided with significance levels set at $p < 0.05$ and with no adjustment for multiplicity. All a priori subgroup analyses

were carried out irrespective of whether or not there was strong evidence of a treatment effect associated with the primary outcome. As missing data for the clinical effectiveness primary outcome were anticipated to be minimal, a sensitivity approach was taken when the primary outcome was missing (see *Secondary analyses of the primary outcome*). Missing data for the cost-effectiveness analysis, as well as missing baseline data for adjusted analysis of clinical outcomes, were handled by multiple imputation.

Multiple imputation

Missing data in baseline covariates, resource use and health-related quality of life variables at 90 days and 1 year were handled with multivariate imputation by chained equations.[37] Under this approach each variable was imputed conditional on fully observed baseline variables such as age, sex, past medical history, site of sepsis, SOFA score, MEDS score, admitted from nursing home, length of stay in critical care and general medical wards up to 90 days and 1 year, and all other imputed variables. Patients who were eligible for 90-day follow-up (i.e. alive at 90 days) but did not return or fully complete the EQ-5D questionnaire administered at 90 days, had their EQ-5D utility scores imputed from those survivors who did fully complete the questionnaire. Similarly, for those eligible patients who did not return the Health Services Questionnaire, information on the use of outpatient services up to 90 days following randomisation, was imputed from those patients who did complete this questionnaire. In the same way, patients who were eligible for 1-year follow-up but did not return or fully complete the EQ-5D questionnaire or the Health Services Questionnaire administered at 1 year also had their information imputed from those survivors who did fully complete the questionnaire. When addressing the missing data, multiple imputation assumes that the data are missing at random conditional on the observed data.

The same multiple imputation approach was used to address the administrative censoring, which applied to the total costs, vital status and quality of life at 1 year for patients randomised after 12 November 2013. In this case it was assumed that the data were censored completely at random, which was plausible as the censoring was administrative, that is it is unlikely that there would be systematic differences between those whose end points (cost, vital status and quality of life) were observed and those who were censored. One-year cost and quality-of-life end points were conditional on survival status; as such, the imputation was conducted in 2 stages. In the first stage, imputation models were specified for mortality at 1 year according to baseline covariates and auxiliary variables, including duration of the initial inpatient stay, and costs at 90 days. In the second stage, for each of the imputed data sets from stage 1, imputation models were specified for costs and quality of life at 1 year for those patients who were missing these but were known to be alive at 1 year, or were predicted to be alive by the first-stage imputation model. These imputation models included those variables in the first-stage imputation model but also information on costs and quality of life at 1 year for those individuals for whom this end point was observed. Each of the resultant estimates was combined with Rubin's rules, which recognise uncertainty both within and between imputations. All multiple imputation models were implemented in the statistical package R (The R Foundation for Statistical Computing, Vienna, Austria).

Statistical analysis: clinical effectiveness

Statistical analyses were conducted according to a pre-specified, published statistical analysis plan.[38] The final analyses were conducted using Stata/SE version 13.0.

Baseline characteristics

Baseline demographic and clinical data were summarised by treatment group but not subjected to statistical testing. Discrete variables were summarised as numbers and percentages, which were calculated according to the number of patients for whom data were available; where values were missing, the denominator was reported. Continuous variables were summarised by standard measures of central

tendency and dispersion: mean and standard deviation (SD) and/or median and interquartile range (IQR), as specified below.

- Inclusion criteria
  - refractory hypotension, *n* (%)
    - systolic blood pressure or mean arterial pressure value at which criterion for refractory hypotension was met, mean (SD)
  - hyperlactataemia, *n* (%)
    - blood lactate value at which criterion for hyperlactataemia was met, mean (SD).
- Age, mean (SD) and median (IQR).
- Sex, *n* (%).
- Severe comorbidities (as defined by APACHE II[33]), *n* (%).
  - severe liver disease
  - severe renal disease
  - severe respiratory disease
  - severe cardiovascular disease
  - immunocompromised.
- Pre-randomisation treatment, *n* (%) received and median (IQR) volume of
  - intravenous 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.
  - APACHE II score,[33] mean (SD) and median (IQR)
  - MEDS score,[34] mean (SD) and median (IQR)
  - individual MEDS score components, *n* (%)
  - SOFA score,[30] mean (SD) and median (IQR)
  - individual SOFA score components, *n* (%).
- Time from ED presentation to inclusion criteria met, mean (SD) and median (IQR).
- Time from ED presentation to randomisation, mean (SD) and median (IQR).
- Patient likely to be admitted directly to ICU from ED if not enrolled in ProMISe, *n* (%).
- Infection, *n* (%).
  - site
  - organism
  - antimicrobial change between ED presentation and 72 hours.

Adherence

Non-adherence with the allocated treatment was reported as:

- insertion of a central venous catheter with $ScvO_2$ monitoring capability to a patient allocated to usual resuscitation
- failure to insert a central venous catheter with $ScvO_2$ monitoring capability to a patient allocated to EGDT

- failure to act on a goal in the EGDT algorithm for a patient allocated to EGDT, defined as
  - no fluid resuscitation when central venous pressure < 8 mmHg
  - no administration of vasopressors when mean arterial pressure < 65 mmHg or systolic blood pressure < 90 mmHg and the central venous pressure goal was met
  - no administration of packed red blood cells when $ScvO_2$ < 70% and haemoglobin < 10 g/dl and the central venous pressure and blood pressure goals were met
  - no administration of dobutamine when $ScvO_2$ < 70% and haemoglobin ≥ 10 g/dl and the central venous pressure and blood pressure goals were met
- early (< 6 hours) termination of EGDT in a patient allocated to EGDT (other than due to death or discharge from hospital).

For comparison, adherence in ProMISe was also assessed according to the criteria used in the published reports of ProCESS[23] and ARISE.[24]

Delivery of care

Delivery of care was summarised by treatment group but not subjected to statistical testing. As with baseline characteristics, discrete variables were summarised as numbers and percentages. Percentages were calculated according to the number of patients for whom data were available; where values were missing, the denominator was reported. Continuous variables were summarised by mean (SD) and/or median (IQR).

Intervention data were summarised as the total over the 6-hour intervention period (hour 0 to hour 6); the total from the end of the 6-hour intervention period to the end of the first 72 hours (hour 6 to hour 72); and from randomisation to the end of the first 72 hours (hour 0 to hour 72). Where measurements were recorded, baseline values were also reported. Catheter insertion and location of care details were included in the hour 0 to hour 6 table. The following were reported:

- catheter insertion, *n* (%), and time from randomisation to insertion, mean (SD) and median (IQR)
  - central venous catheter with $ScvO_2$ monitoring capability
  - any central venous catheter
  - arterial catheter
- interventions, *n* (%) received
  - supplemental oxygen
  - mechanical ventilation
- fluids, *n* (%) received and mean (SD) and median (IQR) volume of
  - any intravenous fluid
  - intravenous colloid
  - intravenous crystalloid
  - packed red blood cell transfusion
  - platelets
  - fresh-frozen plasma

- drugs, *n* (%) received
  - vasopressors
  - dobutamine
  - sedatives
  - neuromuscular blocking agent
- co-interventions for the source of sepsis, *n* (%) received
  - surgery
  - activated protein C
  - steroids
- location of care
  - critical care admission, *n* (%), and mean (SD) and median (IQR) time from randomisation to admission
  - location of protocol delivery, *n* (%)
  - review by consultant, *n* (%)
  - specialty of most senior doctor to review the patient, *n* (%).

The mean volume of intravenous fluids and the number and percentage receiving vasopressors, packed red blood cell transfusions, dobutamine, sedatives, mechanical ventilation and neuromuscular blocking agents were additionally reported hourly for the duration of the 6-hour intervention period.

Physiology data were summarised as the total over the 6-hour intervention period (hour 0 to hour 6); the total from the end of the 6-hour intervention period to the end of the first 24 hours (hour 6 to hour 24); and from the end of the first 48 hours to the end of the first 72 hours (hour 48 to hour 72). Where measurements were recorded, baseline values were also reported. The following values were reported:

- lowest mean arterial pressure, mean (SD)
- lowest systolic blood pressure, mean (SD)
- haemoglobin value at the end of the time period, mean (SD)
- blood lactate value at the end of the time period, mean (SD)
- lowest partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), mean (SD)
- highest creatinine, mean (SD)
- highest bilirubin, mean (SD)
- lowest platelets, mean (SD)
- lowest Glasgow Coma Scale (GCS) score, mean (SD)
- individual SOFA score components, *n* (%).

Mean (SD) of central venous pressure, mean arterial pressure, systolic blood pressure and $ScvO_2$ were additionally reported hourly for the duration of the 6-hour intervention period.

Primary outcome: clinical effectiveness

The number and percentage of deaths at 90 days following randomisation due to any cause were reported for each treatment group. The primary effect estimate was the relative risk of all-cause mortality at 90 days, reported with a 95% CI. The absolute risk reduction and 95% CI were also reported. Deaths at 90 days after randomisation were compared between the treatment groups, unadjusted, using Fisher's exact test. A secondary analysis of the primary outcome, adjusted for baseline variables, was conducted using multilevel logistic regression. Baseline variables adjusted for in the multilevel logistic regression model were the components of the MEDS score (age, metastatic cancer, nursing home residence, altered mental status, septic shock, respiratory difficulty, low platelet count, high bandforms 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 were reported as an adjusted odds ratio with 95% CI. The unadjusted odds ratio was presented for comparison.

Secondary outcomes: clinical effectiveness

The mean SOFA score at 6 hours and 72 hours after randomisation was reported for each treatment group. Differences in the mean SOFA score at 6 hours and 72 hours after randomisation were compared, adjusted for baseline SOFA score, using analysis of covariance.

The number and percentage of patients receiving advanced cardiovascular, advanced respiratory and renal support were reported for each treatment group. Differences in receipt of advanced cardiovascular, advanced respiratory and renal support were compared, unadjusted, using Fisher's exact test. The mean (SD) of the number of days alive and free from advanced cardiovascular, advanced respiratory and renal support, up to 28 days, in each treatment group were reported. Patients who died within the first 28 days were assigned 0 days alive and free of each organ support. Differences between the treatment groups were tested using the *t*-test, using the non-parametric bootstrap to account for anticipated non-normality in the distributions.[39] A total of 1000 bootstrap replications were taken, stratified by treatment group, with bias-corrected and accelerated CIs reported.

The median (IQR) of the length of stay in the ED, in critical care and in acute hospital was reported for each treatment group. Differences in length of stay between the treatment groups were 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 were plotted up to 90 days and 1 year after randomisation and compared using the log-rank test. An adjusted comparison was performed using a Cox proportional hazards model adjusted for the same baseline variables as the primary outcome, including shared frailty within sites (gamma-distributed latent random effects). The appropriateness of the proportional hazards assumption was assessed graphically by plotting –log[–log(survival)] against log(time) within treatment groups. The number and percentage of deaths at acute hospital discharge and by 28 days, 90 days and 1 year after randomisation were reported for the treatment groups. Differences in all-cause mortality at each time point were compared, unadjusted, using Fisher's exact test and adjusted using multilevel logistic regression, adjusted for the same baseline variables as the primary outcome.

Safety monitoring

The number and percentage of patients experiencing each serious adverse event (occurring between randomisation and 30 days) were reported for each treatment group. The total number of patients experiencing one or more serious adverse events was compared between treatment groups using Fisher's exact test and summarised as a relative risk with 95% CI.

Subgroup analyses of the primary outcome

Subgroup analyses were conducted using the likelihood ratio test to assess interactions between treatment group and pre-specified subgroups in multilevel logistic regression models for all-cause mortality at 90 days, adjusted for the same baseline variables as the analysis of the primary outcome. The subgroups compared were degree of protocolised care for the usual-resuscitation group; age; MEDS score; SOFA score; and time from ED presentation to randomisation. Degree of protocolised care for the usual-resuscitation group was assessed based on established guidelines[14,16,40] as the proportion of patients allocated to the usual-resuscitation group that had lactate measured at baseline and, if ≥ 4 mmol/l at baseline, remeasured within 6 hours. Sites were categorised as having a higher degree of protocolised care if the proportion of patients in the usual-resuscitation group who met this condition was > 50%. Sites with fewer than three patients allocated to the usual-resuscitation group were excluded from this subgroup analysis. The remaining subgroups were analysed in quartiles.

Secondary analyses of the primary outcome

Sensitivity analyses for missing data in the primary outcome

The primary analysis was repeated once, assuming that all patients allocated to EGDT with missing data in the primary outcome survived and all patients allocated to usual resuscitation with missing data in the primary outcome did not survive. The analysis was then repeated again with the opposite assumptions. This gave the absolute range of how much the results could change if the primary outcome was complete.

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; this relationship is termed a 'learning curve'. Modelling the learning curve enables estimation of the treatment effect for an experienced team (the asymptotic value to which the curve trends over time). A site-level learning curve for patients allocated to EGDT was 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 EGDT patient within each site.[41] The power curve model was estimated by direct maximisation of the log-likelihood function using a modified Newton–Raphson algorithm.[42] A single estimate for each of the parameters a and b was fitted across all sites.

Adherence-adjusted analysis

While the intention-to-treat analysis gives the best estimate of the clinical effectiveness of EGDT 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 a randomised controlled trial, the allocated treatment can be used as an 'instrumental variable', that is, a variable associated with receipt of the intervention and only associated with the outcome through its association with the intervention.[43] This relationship enables us to estimate what the treatment effect would be for patients who were fully adherent to the protocol. The primary analysis was repeated, adjusting for adherence using a structural mean model with an instrumental variable of allocated treatment, assuming a linear relationship between the degree of adherence (proportion of the 6 hours that the patient was adherent to the EGDT protocol) and treatment effect.[37,44]

Cost-effectiveness analysis

A full cost-effectiveness analysis was undertaken to assess which treatment strategy, EGDT or usual resuscitation, was more cost-effective. This analysis assessed whether or not any intervention costs associated with EGDT were offset by any subsequent reduction in morbidity costs, for example from reduced use of critical care, and whether there were improvements in either mortality or health-related quality of life. The cost-effectiveness analysis was reported for three time periods: randomisation to 90 days, randomisation to 1 year and lifetime. For each time period the cost-effectiveness analysis took a health and personal health services perspective,[45] using information on health-related quality of life collected at 90-day and 1-year follow-up, combined with information on vital status, to report QALYs. Each QALY was valued using the National Institute for Health and Care Excellence (NICE)-recommended threshold of willingness to pay for a QALY gain (£20,000), in conjunction with the costs of each treatment strategy to report the INBs of EGDT versus usual resuscitation.

The primary objective of the cost-effectiveness analysis was to compare incremental cost-effectiveness at 1 year between the treatment groups. There were also a number of secondary objectives:

- to compare health-related quality of life at 90 days and 1 year between the treatment groups
- to compare resource use and costs at 90 days and 1 year between the treatment groups
- to estimate the lifetime incremental cost-effectiveness between the treatment groups.

The main assumptions of the cost-effectiveness analysis were subjected to extensive sensitivity analyses.

Resource use

The resource use categories considered were chosen a priori, where differences between the treatment groups were judged as being possible and likely to drive incremental costs, and were reported for each treatment group. Data for interventions, staff time and acute hospital stay for the index hospital admission were collected as part of the ProMISe data set. Readmissions to acute hospital including a critical care stay were identified from the Case Mix Programme database.[32] Readmission to acute hospital not involving critical care as well as hospital outpatient and community services use were collected as part of the Health Services Questionnaires completed at 90 days and 1 year.

Interventions

The type of catheter inserted (central venous catheter capable of $ScvO_2$ monitoring, standard central venous catheter and/or arterial catheter) as well as the use of other catheter insertion-related consumables including pressure transducers to measure intravascular pressures, and the consumables (saline infusion, cleaning packs, sterile gloves) associated with each type of catheter insertion were considered (*Table 1*). The use of packed red blood cells, platelets, fresh-frozen plasma and dobutamine was also considered. The costs associated with other clinical interventions such as intravenous crystalloid, intravenous colloid, albumin, other blood products and other vasoactive drugs were not anticipated to differ across treatment groups. As such, these were not considered as separate items; however, their costs were included within the unit cost per critical care bed-day according to the Healthcare Resource Group definition. The duration for which EGDT was delivered (up to 6 hours) in the ED and in total was reported.

Staff time

The EGDT protocol required additional staff time for central venous catheter insertion (doctors' time); monitor set-up (nurses' time); monitoring patients in ED (nurses' time); and staff training (nurses' and doctors' time). The level of additional staff time for EGDT was estimated according to expert opinion (see *Table 1*), with alternative levels considered in the sensitivity analyses. It was assumed that in the ED at least one trained nurse was available for the duration of delivery of EGDT. The base-case analysis assumed that, when delivered in the ED, each patient in the EGDT group required an additional 10 minutes of nurses' monitoring time per hour of EGDT. To provide EGDT in the ED as part of routine practice required additional formal or informal training beyond the existing hospital education program. It was assumed that at each site each clinical member of ED staff required 20 minutes' additional training to deliver EGDT. The total training time for introducing the EGDT protocol into the ED was then calculated for each site in the trial. The average mix of ED staff was assumed to be seven (attending) consultants, 23 junior doctors and 75 nurses[46] over the life cycle of EGDT, which was assumed to be 5 years. Where EGDT was delivered in ICU, it was assumed that no additional staff training time or monitoring time for patients was required.

TABLE 1 Equipment, consumables and staff time for catheter insertion and monitor set-up

Catheter	Equipment	Doctor time (catheter insertion)	Nurse time (monitor set-up)	Consumables
PreSep™ central venous oximetry catheter	Monitor	30 minutes	20 minutes[a] + 30 minutes[b]	Transducer,[a] saline, consumables pack for insertion
Standard CVC	–	30 minutes	20 minutes[a]	Transducer,[a] saline, consumables pack for insertion
Arterial catheter	–	20 minutes	20 minutes[a]	Transducer,[a] saline, skin cleaning device and dressing

CVC, central venous catheter.
a It is assumed that one transducer pack and the same amount of nurse time is required whether single or multiple catheters are inserted.
b Additional nurse time for setting up the monitor.

Acute hospital length of stay

Length of stay in ED, critical care and general medical wards within the index acute hospital admission (i.e. the hospital in which a patient was randomised to the trial) were reported. For critical care stays, Healthcare Resource Groups were assigned according to the maximum number of organs supported during the stay.[31] An acute hospital readmission was defined as a further hospital admission, for any reason, following discharge from the index admission. Length of stay in critical care and general medical wards within acute hospital readmissions were taken from the Case Mix Programme database and the Health Services Questionnaires.

Hospital outpatient visits and community service use

The number of hospital outpatient visits and community service use for any reason were reported. Items of community service use included visits to the general practitioner (family doctor), nurse, health visitor, occupational therapist, physiotherapist and psychologist. The levels of resource use were taken from responses to the Health Services Questionnaire.

Unit costs

The unit costs required for valuing the resource use data listed in *Table 2* were taken from three sources: manufacturers' list and procurement prices, national unit cost databases and published sources. The unit costs of the additional monitor and central venous catheter required for delivering EGDT were obtained from the manufacturer and the procurement department of a participating hospital. The fixed unit costs of the monitor were assigned to an individual patient, according to the assumed 5-year life cycle of the monitor, and assuming that the volume of eligible patients was the annual average recorded in the trial screening logs. In calculating the unit cost per patient, it was also assumed that to provide EGDT in routine practice each site would require two monitors, which would have an average lifespan of 5 years. The monitor costs per patient were calculated by dividing the total costs of the monitors by the expected number of eligible patients over 5 years. Unit costs for blood products and other drugs were taken from NHS Blood and Transplant[47] and the *British National Formulary*.[48]

TABLE 2 Unit costs in GBP

Items	Unit costs (£)	Source
Equipment and consumables		
Monitor[a]	70	Manufacturer's price
PreSep™ central venous oximetry catheter	130	Manufacturer's price
Standard CVC	24	Local NHS finance department
Arterial catheter	13	Local NHS finance department
Other equipment/consumables		
Transducer	13	NHS supply chain
Insertion pack for CVC[b]	22	Local NHS finance department
Cleaning device for arterial catheter[b]	5	Local NHS finance department
Blood products		
PRBC (280 ml)	122	NHSBT[47]
Platelets (200 ml)	208	NHSBT[47]
Frozen fresh plasma (250 ml)	28	NHSBT[47]

TABLE 2 Unit costs in GBP (*continued*)

Items	Unit costs (£)	Source
Drugs		
Dobutamine (250 mg)[c]	9	BNF[48]
Staff time		
Doctor: consultant (per hour)	139	Curtis[49]
Doctor: registrar level (per hour)	59	Curtis[49]
Nurse: grade 6 (per hour)	49	Curtis[49]
Staff training costs (per patient)[d]	11	ProMISe data and assumption
Hospital costs (bed-day)		
ED (per hour)	27	Dixon *et al.* 2009[50]
Critical care bed-day: 0 organs supported	619	Department of Health[51]
Critical care bed-day: 1 organ supported	852	Department of Health[51]
Critical care bed-day: 2 organs supported	1236	Department of Health[51]
Critical care bed-day: 3 organs supported	1422	Department of Health[51]
Critical care bed-day: 4 organs supported	1573	Department of Health[51]
Critical care bed-day: 5 organs supported	1697	Department of Health[51]
Critical care bed-day: 6+ organs supported	1867	Department of Health[51]
General ward bed-day	265	Department of Health[51]
Outpatient and community health services		
Hospital outpatient (per visit)	135	Curtis[49]
GP practice visit (per visit)	45	Curtis[49]
GP home visit (per visit)	114	Curtis[49]
GP practice nurse[e]	10	Curtis[49]
Hospital staff nurse[e]	12	Curtis[49]
Health visitor[e]	13	Curtis[49]
Occupational therapist[e]	9	Curtis[49]
Psychologist[e]	15	Curtis[49]
Speech and language therapist[e]	9	Curtis[49]
Physiotherapist[e]	9	Curtis[49]
Dietitian[e]	9	Curtis[49]

BNF, *British National Formulary*; CVC, central venous catheter; GP, general practitioner; NHSBT, NHS Blood and Transport; PRBC, packed red blood cells.

a Two monitors per site over average life span of 5 years were costed. The monitor costs per patient were calculated by dividing the total costs of the monitors (£4000 each) by the expected number of eligible patients (23 patients per year) over 5 years.

b Cost of saline included.

c Cost of syringe, giving set and saline included.

d The training costs per patient per hour of protocol were calculated from total training costs per site divided by total eligible patients (23 patients per site per year) over 5 years.

e 15 minutes of consultation time.

The unit costs associated with the additional staff training required to deliver EGDT were taken from national sources. The total additional training cost per site was calculated by valuing the time of the average mix of ED staff who required training to deliver EGDT. The average additional staff training cost per patient was calculated by dividing the total training costs per site, by the volume of eligible patients per site over 5 years, the assumed life cycle of EGDT. The costs per critical care bed-day, by Healthcare Resource Group, and per general medical bed-day were taken from the 'Payment by Results' database.[51] Unit costs for hospital outpatient visits and community service use were obtained from a recommended published source for Health and Social Care costs.[49] All unit costs were reported in 2012–13 prices.

Health-related quality of life

The responses to the EQ-5D questionnaire were used to report each patient's described health, which was then valued according to health state preferences from the general population to calculate EQ-5D utility scores, anchored on a scale from 0 (death) to 1 (perfect health).[52] The number and percentage of patients in each level of each dimension were reported by treatment group.

Sensitivity analysis

The main assumptions of the cost-effectiveness analysis were subjected to extensive sensitivity analyses. The main assumptions made in the base-case scenario, and how each was relaxed in sensitivity analyses, are detailed below and summarised in *Table 3*.

Equipment costs for the intervention

In the base case, unit costs for the monitor and central venous catheter for $ScvO_2$ monitoring were taken from the manufacturer's discounted costs, which were judged to be those which would be paid by NHS providers if EGDT was introduced into routine clinical practice. These unit costs imply discounts of over 50% from list prices. In the sensitivity analysis, full list prices were applied for the requisite monitor and catheters.

Staff monitoring time during delivery of the early goal-directed therapy resuscitation protocol

The intervention requires intensive monitoring of patients for the duration of EGDT (up to 6 hours). In the base case, it was assumed that this monitoring would require an additional 10 minutes of nurses' time per hour of the resuscitation protocol. In the sensitivity analysis, the additional nurses' time was varied from 5 to 15 minutes per hour over the duration of EGDT.

Staff training time for delivery of the early goal-directed therapy resuscitation protocol

The base-case analysis assumed that when EGDT was provided in the ED, each member of staff would require 20 minutes of training. In the sensitivity analysis, training time was varied between 15 and 30 minutes.

TABLE 3 Alternative assumptions for sensitivity analysis

Assumption	Base case	Sensitivity analysis
Equipment costs for the intervention	Unit costs as per business deal option	Manufacturer's list price
Staff monitoring time	10 minutes per hour of protocol	5–15 minutes per hour of protocol
Staff training time	20 minutes' training time for all ED staff	15–30 minutes' training time for all ED staff
Location of protocol delivery	Protocol delivered in both ED and ICU	Protocol delivered exclusively either in ED or in ICU
Readmissions from Health Services Questionnaires	Included in the analysis	Excluded from the analysis
Baseline covariates	Unadjusted analysis	Adjusted for components of MEDS score
Distributional assumptions	Costs and QALYs normally distributed	Costs and QALYs gamma distributed

Location of delivery of the early goal-directed therapy resuscitation protocol

The base-case analysis incorporated the relative time that each patient in the EGDT group received the protocol in the ED versus an ICU. In practice, EGDT may be exclusively delivered in either setting. The sensitivity analysis allowed the costs of monitoring and training to reflect either extreme, namely EGDT delivered entirely in the ED or EGDT delivered entirely in ICU. All other aspects of staff time required to deliver the EGDT protocol were assumed to be the same across location (ED or ICU). As with the preceding scenarios, only the costs were allowed to change in the sensitivity analysis; it was assumed that the relative effectiveness of EGDT versus usual care was the same as in the original base-case analysis.

Readmissions from Health Services Questionnaire

The base-case analysis included hospital readmissions including a critical care stay recorded in the Case Mix Programme database but also hospital readmissions recorded from responses to the Health Services Questionnaire. To consider the possible impact of double-counting the same readmissions across both sources, in the sensitivity analysis only the readmissions from the Case Mix Programme database were included.

Baseline covariates

The base-case analysis reported incremental costs and QALYs without any covariate adjustment, assuming randomisation had ensured no imbalances in key prognostic factors such as components of the MEDS score.[34] In the sensitivity analysis, any chance imbalances in components of the MEDS score were adjusted for using seemingly unrelated regression.

Distributional assumptions for costs and quality-adjusted life-years

The base-case analysis assumed that costs and QALYs were normally distributed when reporting the 95% CIs around incremental costs and QALYs. In sensitivity analyses the robustness of the cost-effectiveness results to alternative distributional assumptions about both outcomes were assessed. Following methodological guidance, the sensitivity analysis considered a gamma distribution for costs as they had a right-skewed distribution. For QALYs, the sensitivity analysis also considered a gamma distribution because a large proportion of decedents had zero QALYs, and the remainder of the distribution was again right-skewed. In this sensitivity analysis, costs and QALYs were modelled as univariate regression models assuming a gamma distribution for each end point (i.e. ignoring possible correlation between the end points).

Cost-effectiveness at 90 days following randomisation

Mean EQ-5D utility scores, QALYs, total costs and INBs up to 90 days were reported for each treatment group. Unadjusted mean differences between the treatment groups in quality of life, QALYs, incremental costs and INBs at 90 days were reported with 95% CIs. These were reported both overall and by each of the pre-specified subgroups, and tested using the *t*-test.

For survivors at 90 days, QALYs were calculated by valuing each patient's survival time by their health-related quality of life according to the 'area under the curve' approach,[53] assuming an EQ-5D utility score of zero at randomisation, and a linear interpolation between randomisation and 90 days. Zero QALYs were assumed for decedents between randomisation and 90 days. Total costs up to 90 days were calculated by combining the resource use with unit costs. The differences in average costs and QALYs between the treatment groups were used to calculate the INBs of EGDT versus usual resuscitation. The incremental QALY was valued according to the NICE recommended threshold of willingness to pay for a QALY gain (£20,000); the incremental cost was then subtracted from this.

The uncertainty around the differences in average costs and QALYs between the treatment groups was illustrated on the cost-effectiveness plane. The incremental costs and QALYs were estimated with a seemingly unrelated regression model. To express the uncertainty in the estimation of the incremental costs and QALYs, the estimates of the means, variances and the covariance from the regression model were used to generate 500 estimates of incremental costs and QALYs from the joint distribution of these end points, assuming asymptotic normality. These incremental costs and QALYs were then plotted on the cost-effectiveness plane. A cost-effectiveness acceptability curve was also plotted by calculating the

probability that, compared with usual resuscitation, EGDT is cost-effective given the data, at alternative levels of willingness to pay for a QALY gain.

As sensitivity analyses, the mean INB at 90 days with corresponding 95% CIs was also reported for each of the alternative assumptions (see *Table 3*).

Cost-effectiveness at 1 year following randomisation (primary outcome)

Mean EQ-5D utility scores, QALYs, total costs and INBs up to 1 year were reported for each treatment group. Unadjusted mean differences between the treatment groups in quality of life, QALYs, incremental costs and INBs at 1 year were reported with 95% CIs. These were reported both overall and by each of the pre-specified subgroups, and tested using the *t*-test. The incremental costs and QALYs at 1 year were plotted on the cost-effectiveness plane and the cost-effectiveness acceptability curve was plotted.
As sensitivity analyses, the mean INB at 1 year with corresponding 95% CI was also reported for each of the alternative assumptions (see *Table 3*).

All analyses followed the same approach as that at 90 days, although for survivors at 1 year QALYs were calculated assuming an EQ-5D utility score of zero at randomisation, and using the quality-of-life scores at 90 days and 1 year, applying linear interpolation between each pair of time points. Quality-of-life scores at 90 days were applied for decedents between 90 days and 1 year.

Lifetime incremental cost-effectiveness

The cost and outcome data reported at 1 year were used to estimate the effect of EGDT versus usual resuscitation on longer-term costs and outcomes. The chosen time horizon of 20 years was judged a reasonable time frame over which to fully assess the relative impact of EGDT versus usual resuscitation, and exceeded those taken in previous studies.[54] The maximum available survival data from the trial was used to plot Kaplan–Meier survival curves out to the date of censoring (12 November 2014). Alternative parametric functions were considered for extrapolating mortality by fitting commonly recommended alternatives to the survival data, excluding that for the first 30 days, as the event rate during this early period was atypical and did not provide an appropriate basis for subsequent extrapolation. Although the relative fit of the alternative curves to the observed data was reported, the one applied gave the most plausible extrapolation according to the previous literature.[55,56] After 15 years following randomisation, it was assumed that all-cause death rates were those of the age-/sex-matched general population.
The parametric extrapolation for years 2–15 was combined with applying all-cause death rates for years 16–20 to report life expectancy for each patient observed to survive at 1 year.

The lifetime analysis allowed for the mean differences in estimated survival at 1 year, but these differences were judged small and unlikely to be maintained, and were not statistically significant, and therefore, after 1 year, the same mortality rates were applied to both treatment groups. For calculating lifetime QALYs, it was judged plausible to assume that the mean differences in quality of life reported at 1 year, although not statistically significant, were maintained. For each treatment group, the level of the quality-of-life decrement observed at 1 year versus the age-/sex-matched general population[57] was maintained for years 2–15, which was the same duration as the period of assumed excess mortality, after which quality-of-life values for the age-/sex-matched general population were applied. To project lifetime costs attributable to the initial episode of severe sepsis, it was assumed that the average inpatient (general medical not critical care), outpatient and community service costs reported up to 1 year following randomisation applied annually for years 2–15 (period of excess mortality). For years 16–20, it was assumed that there were no further costs attributable to the initial episode. Long-term INB over 20 years was calculated by valuing each QALY at £20,000 per QALY. All future costs and life-years were discounted at the recommended rate of 3.5%.[45]

Mean lifetime QALYs, total costs and INBs were reported for each treatment group. Unadjusted mean differences between the treatment groups in lifetime QALYs, incremental costs and INBs were reported with 95% CIs. These were reported both overall and by each of the pre-specified subgroups, and tested using the *t*-test. The lifetime cost-effectiveness acceptability curves were also plotted.

The sensitivity analyses for lifetime INB considered the scenario from *Table 3* that was judged most relevant, that of providing EGDT exclusively in the ED versus in ICU. The following additional scenarios pertinent to the lifetime analysis were also reported:

- allowing for excess mortality versus the general population to be maintained for a shorter (10 years) and a longer (20 years) period of time than the base case (15 years)
- allowing for a larger (30%) and smaller (10%) decrement in quality of life over years 2–15 versus the general population than the base case (20%)
- allowing for the excess costs attributable to the initial episode to be maintained for a shorter (10 years) and a longer (20 years) period of time than the base case (15 years).

Chapter 3 Results: sites and patients

Participants: sites

Expressions of interests were received from 83 NHS hospitals in the UK. A total of 57 hospitals in England obtained local NHS permissions and opened to recruitment between 15 February 2011 and 25 March 2013. Forty-four sites were opened within the first 9 months of the trial's opening on 15 February 2011 (*Figure 4*).

The rate at which sites were opened for the ProMISe trial was higher than for ProCESS and ARISE. Within 12 months of the trial opening, 47 sites had been opened for ProMISe, compared with 20 each for ProCESS and ARISE (*Figure 5*).

FIGURE 4 Sites open to recruitment during the trial recruitment period.

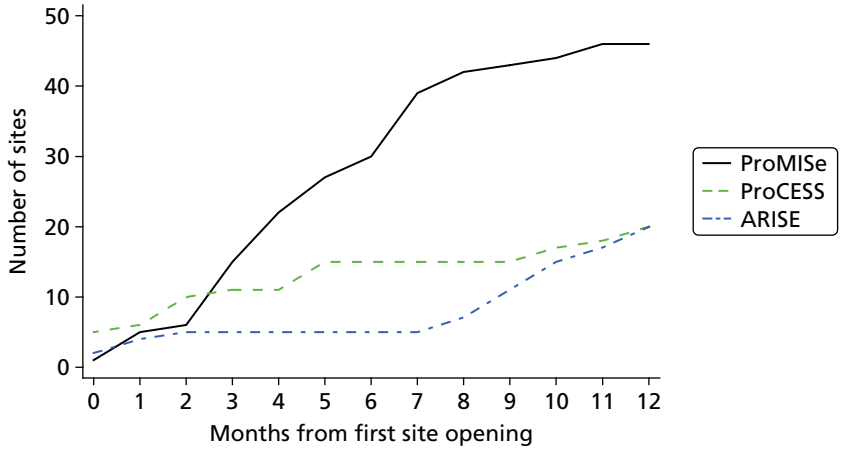

FIGURE 5 Recruitment of sites for ProMISe compared with ProCESS and ARISE.

The median time from local NHS permission to the trial opening at sites (i.e. start of screening) was 83 (IQR 51–151) days (*Figure 6*). Reasons for delays in opening were issues related to the confirmation of NHS support costs from the CLRN and delays in the local set-up of the trial, for example training staff.

Overall, sites participated in the ProMISe trial for a median of 30 (IQR 19–35) months. Of the 57 sites that opened, seven were closed early because of poor recruitment (one site recruited no patients), two were closed because of insufficient resources locally for screening and recruitment and two were closed for other local logistical reasons. As part of the staggered close-down of the trial, nine sites were closed in October 2013 and a further eight were closed in April 2014, with 29 sites remaining open until the end of recruitment in July 2014 (*Figure 7*).

There were eight sites that had at least one period when screening and recruitment was suspended either because of insufficient resources ($n = 6$) or to enable new staff to be trained in delivery of the trial protocol ($n = 2$) (see *Figure 7*).

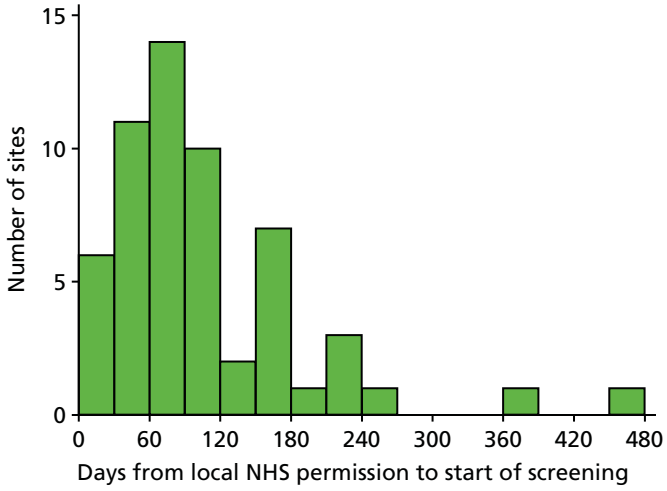

FIGURE 6 Time (in days) from local NHS permission to start of screening.

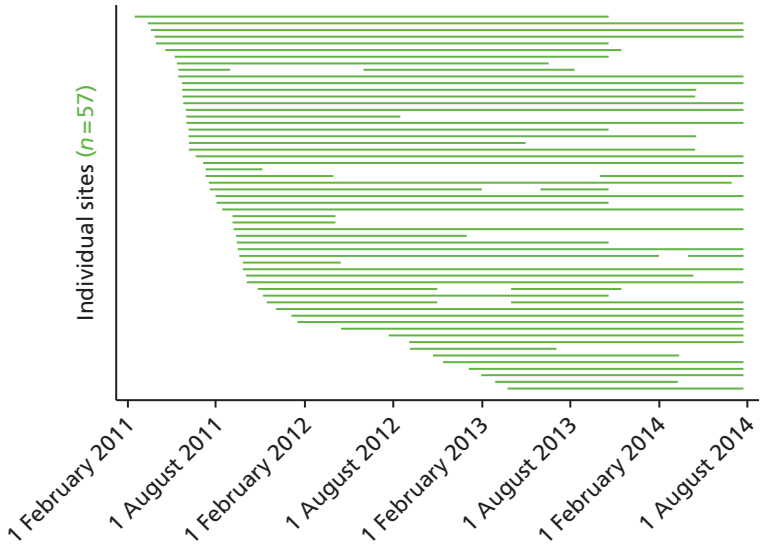

FIGURE 7 Duration of participation of sites.

Characteristics of participating sites

A slightly higher proportion of the hospitals that participated in ProMISe were university teaching hospitals [defined as the main hospital(s) linked with each medical school] than all acute hospitals in England with an ED (*Table 4*).

The characteristics of the 57 participating sites are presented in *Table 5*. There was considerable variation in the number of hospital beds, ranging from 234 to 1313, and in the annual number of ED presentations, ranging from 40,000 to 185,000. The number of patients recruited ranged from 1 to 83 patients per site in the 56 sites that recruited one or more patients.

TABLE 4 Representativeness of participating sites

Type of hospital	Hospitals in ProMISe, *n* (%)	All hospitals in England with an ED, *n* (%)
Teaching	16 (28.1)	36 (19.9)
Non-teaching	41 (71.9)	145 (80.1)

TABLE 5 Characteristics of participating sites

Site	Type of hospital	Recruitment period	Hospital beds	Annual ED presentations	Total patients randomised
Addenbrooke's Hospital	Teaching	November 2011–October 2012 and April 2013–July 2014	950	100,000	30
Arrowe Park Hospital	Non-teaching	June 2011–July 2014	750	93,000	31
Barnsley Hospital	Non-teaching	September 2011–January 2014 and April 2014–July 2014	450	80,000	28
Bedford Hospital	Non-teaching	November 2011–October 2013	380	70,000	11
Birmingham Heartlands Hospital	Non-teaching	May 2011–October 2013	730	112,171	14
Blackpool Victoria Hospital	Non-teaching	November 2012–July 2014	769	92,000	9
Bristol Royal Infirmary	Teaching	September 2011–December 2012	450	65,000	6
Broomfield Hospital	Non-teaching	May 2011–April 2014	521	81,513	15
Chelsea and Westminster Hospital	Non-teaching	May 2011–July 2014	430	114,695	16
Derriford Hospital	Teaching	April 2011–November 2013	900–1000	87,000	12
Dorset County Hospital	Non-teaching	October 2011–April 2014	292	40,000	17
Frenchay Hospital	Non-teaching	April 2012–July 2014	526	88,000	25
Good Hope Hospital	Non-teaching	September 2011–April 2012	480	78,713	0
Hinchingbrooke Hospital	Non-teaching	May 2011–April 2014	247	44,962	19
Hull Royal Infirmary	Teaching	May 2011–July 2014	709	122,000	30
John Radcliffe Hospital	Teaching	July 2011–January 2013 and June 2013–October 2013	832	137,766	8
Kettering General Hospital	Non-teaching	February 2011–October 2013	580	88,000	15

continued

TABLE 5 Characteristics of participating sites (*continued*)

Site	Type of hospital	Recruitment period	Hospital beds	Annual ED presentations	Total patients randomised
King's College Hospital	Teaching	July 2012–July 2014	1000	140,000	33
Leicester Royal Infirmary	Teaching	December 2011–July 2014	1000	150,000	41
Leighton Hospital	Non-teaching	June 2011–October 2013	460	82,000	12
Manchester Royal Infirmary	Teaching	July 2011–July 2014	650	100,000	41
Medway Maritime Hospital	Non-teaching	June 2011–April 2014	550	90,000	27
Musgrove Park Hospital	Non-teaching	August 2011–July 2014	700	56,000	29
New Cross Hospital	Non-teaching	September 2011–October 2013	700	111,000	8
Newham University Hospital	Non-teaching	September 2012–July 2013	234	125,000	10
North Devon District Hospital	Non-teaching	September 2012–July 2014	281	40,000	20
North Tyneside General Hospital	Non-teaching	September 2011–April 2012	450	60,000	1
Peterborough City Hospital	Non-teaching	March 2013–July 2014	611	90,475	24
Poole Hospital	Non-teaching	May 2011–June 2013	623	67,000	42
Queen Elizabeth Hospital, Birmingham	Teaching	July 2011–March 2012 and October 2013–July 2014	1313	102,000	21
Queen Elizabeth Hospital, Gateshead	Non-teaching	September 2011–July 2014	600	87,000	30
Queen's Medical Centre	Teaching	January 2013–July 2014	1300	185,000	25
Royal Berkshire Hospital	Non-teaching	August 2011–July 2014	660	100,000	55
Royal Bournemouth Hospital	Non-teaching	July 2011–June 2014	607	71,316	23
Royal Lancaster Infirmary	Non-teaching	May 2011–July 2014	428	56,000	21
Royal Preston Hospital	Non-teaching	June 2011–July 2014	708	74,852	22
Royal Surrey County Hospital	Non-teaching	March 2011–October 2013	550	71,175	15
Royal Sussex County Hospital	Teaching	September 2011–July 2014	850	110,000	29
Royal Victoria Infirmary	Teaching	May 2011–August 2011 and June 2012–August 2013	1000	130,756	2
Salford Royal Hospital	Non-teaching	January 2012–July 2014	661	88,000	53
South Tyneside District Hospital	Non-teaching	June 2011–August 2012	400	74,000	4
Southend University Hospital	Non-teaching	July 2011–November 2011	700	89,965	1
Stafford Hospital	Non-teaching	June 2011–May 2013	299	46,761	15

TABLE 5 Characteristics of participating sites (*continued*)

Site	Type of hospital	Recruitment period	Hospital beds	Annual ED presentations	Total patients randomised
The Great Western Hospital	Non-teaching	October 2011–October 2012 and April 2013–November 2013	400	70,000	15
The Ipswich Hospital	Non-teaching	June 2011–April 2014	500	80,000	18
The James Cook University Hospital	Non-teaching	January 2012–July 2014	1000	104,000	28
The Queen Elizabeth Hospital, King's Lynn	Non-teaching	May 2011–July 2014	489	55,000	71
The Royal Blackburn Hospital	Non-teaching	October 2012–March 2014	693	177,901	8
The Royal London Hospital	Teaching	September 2011–July 2014	680	150,000	49
Torbay Hospital	Non-teaching	February 2013–March 2014	400	117,896	3
University College Hospital	Teaching	March 2011–July 2014	665	129,000	33
University Hospital of North Staffordshire	Teaching	March 2011–July 2014	1180	128,000	21
Wansbeck General Hospital	Non-teaching	September 2011–April 2012	350	60,000	1
Whipps Cross University Hospital	Non-teaching	January 2013–July 2014	450	110,000	8
Whiston Hospital	Non-teaching	March 2011–July 2014	646	100,895	83
Worthing Hospital	Non-teaching	August 2011–October 2013	500	58,000	17
York Hospital	Teaching	October 2011–July 2014	700	85,000	15

Participants: patients

In total, 6192 patients were screened between 15 February 2011 and 24 July 2014. Of these, 2415 (39.0%) met one or more exclusion criteria. There were 2517 (40.6%) patients who, although eligible for inclusion in the trial, were not recruited. The most frequently reported reason for not recruiting eligible patients was logistical issues, mainly no research staff being available, for example if the patient presented at the ED outside usual office hours. Other reported reasons included refusal by the treating clinician to recruit the patient; the patient declined to take part; or the patient was identified as eligible for the trial outside the 2-hour window for obtaining consent and randomising (*Figure 8*).

The 1260 (20.3%) patients were recruited between 16 February 2011 and 24 July 2014, with 630 randomised to the EGDT group and 630 randomised to the usual-resuscitation group (*Figure 9*). There was variation across the 56 sites in the rate of recruitment (*Figure 10*), the overall median recruitment rate being 0.15 (IQR 0.10–0.22) patients per site per week, with a highest recruitment rate of 0.48 patients per week. Patients were recruited over a relatively shorter time period than in ProCESS and ARISE (*Figure 11*). Manual randomisation was required for three patients.

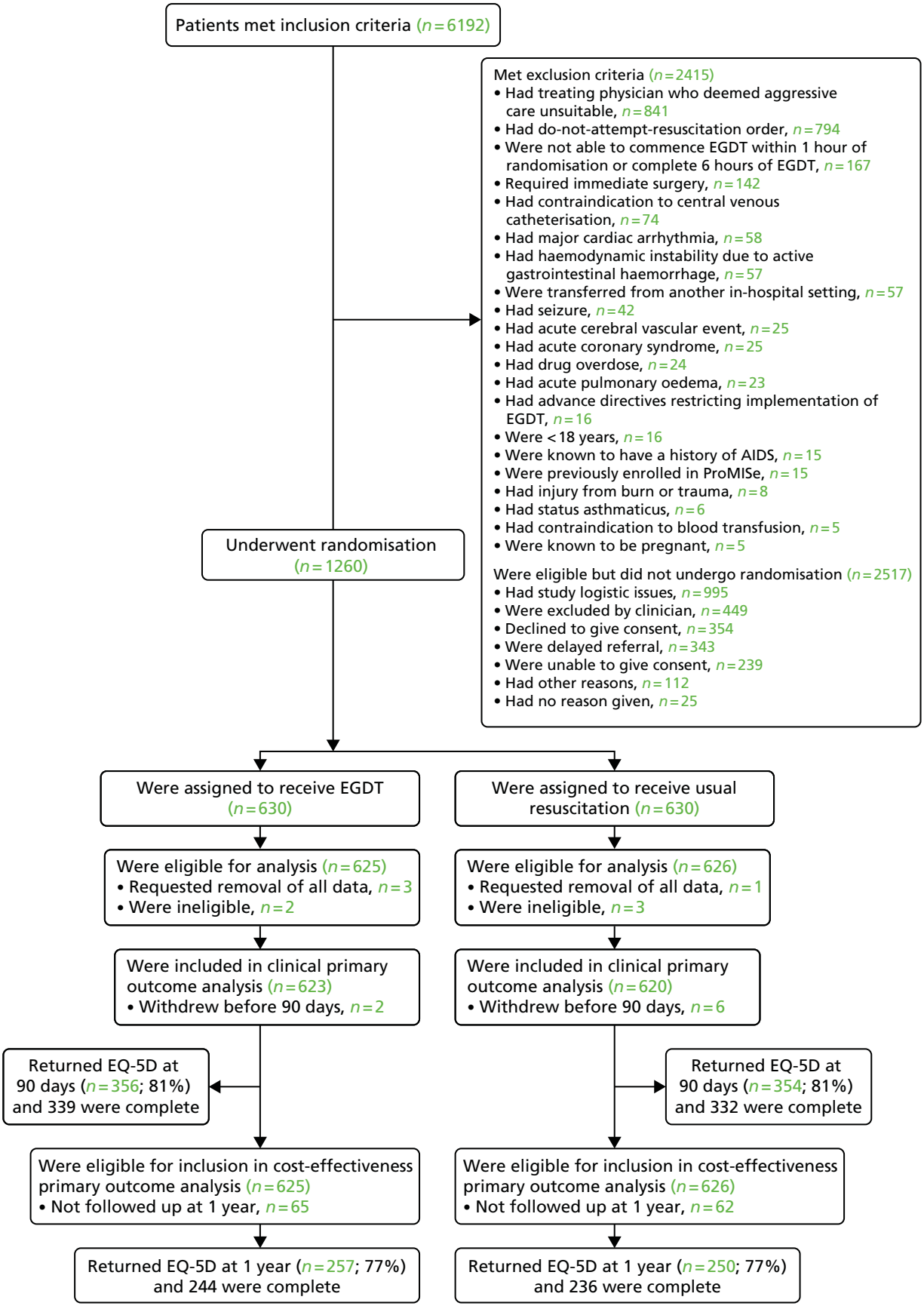

FIGURE 8 Screening, randomisation and follow-up. AIDS, acquired immune deficiency syndrome.

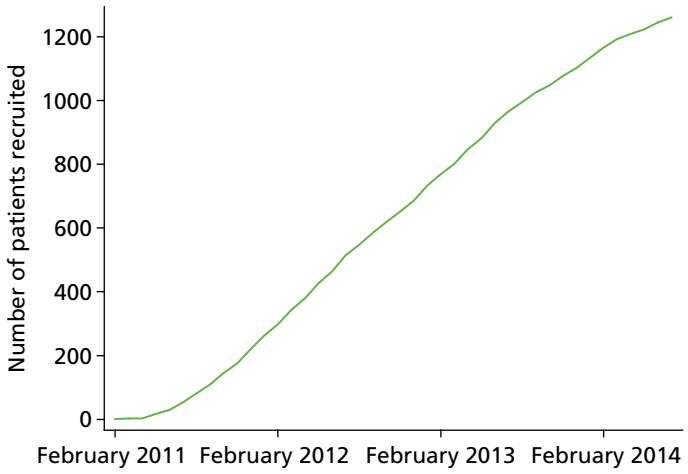

FIGURE 9 Patient recruitment.

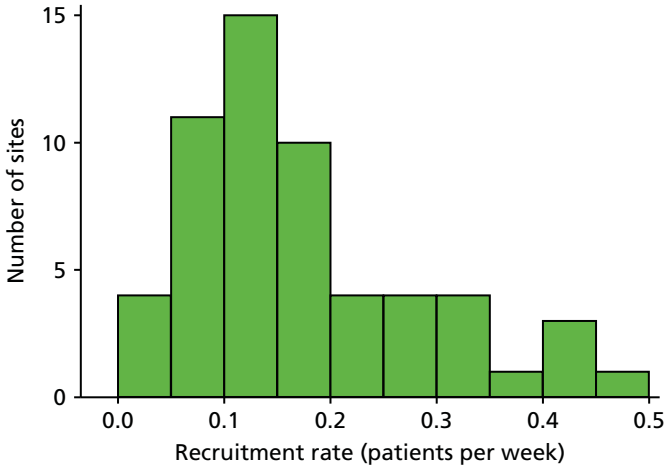

FIGURE 10 Patient recruitment rate.

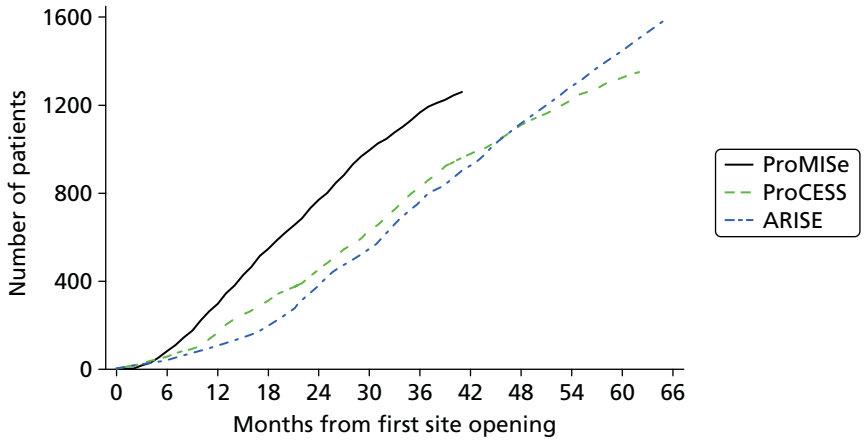

FIGURE 11 Recruitment of patients for ProMISe compared with ProCESS and ARISE.

Patients were generally recruited into ProMISe during weekdays (Monday to Friday) and during usual office hours (*Figure 12*); most of the recruiting sites reported having insufficient resources to enable screening and recruitment at weekends and outside usual office hours.

Almost half of patients provided informed consent prior to randomisation ($n = 624$, 49.5%). For the remaining patients, agreement was obtained from a personal (34.8%) or professional (2.9%) consultee or from an independent clinician using emergency consent (12.8%) (*Table 6*). Four patients withdrew from the trial, requesting the removal of all of their data from the analysis, and five patients were ineligible and

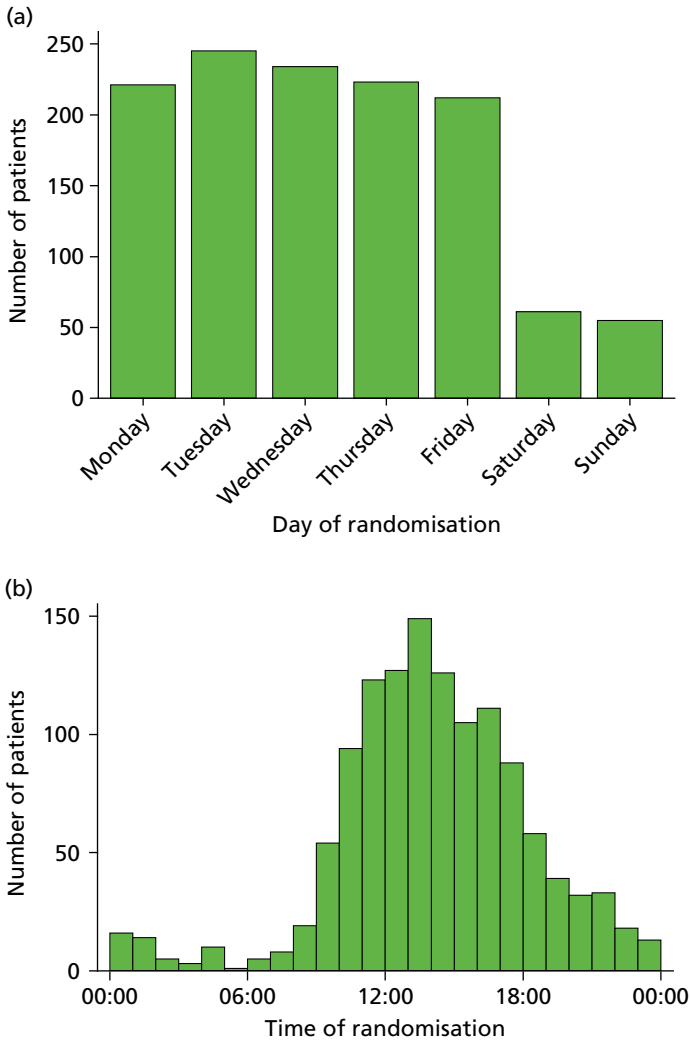

FIGURE 12 Randomisation by (a) day of the week and (b) time of day.

TABLE 6 Informed consent, withdrawals and exclusions

Type of consent/agreement	Patients, *n* (%)	Requested removal of all data, *n*	Ineligible: excluded from analysis, *n*	Withdrew before 90 days, *n*
Informed consent from patient prior to randomisation	624 (49.5)	0	5	1
Agreement from a personal consultee	439 (34.8)	1	0	4
Agreement from a professional consultee	36 (2.9)	1	0	0
Agreement via emergency consent	161 (12.8)	2	0	3
Total	1260 (100)	4	5	8

recruited in error, resulting in data on 1251 for initial analysis ($n = 625$ EGDT; $n = 626$ usual resuscitation). Eight patients subsequently withdrew before 90 days, resulting in 1243 patients for analysis of outcomes ($n = 623$, 99.7% EGDT; $n = 620$, 99.0% usual resuscitation). Owing to the truncation of follow-up, 127 patients were not followed up at 1 year ($n = 65$ EGDT; $n = 62$ usual resuscitation) (see *Figure 8* and *Table 6*). Follow-up was completed on 30 October 2014.

Characteristics of patients at baseline

The groups were well matched at baseline (*Table 7*). The criterion for refractory hypotension was met in 338 (54.1%) EGDT and 348 (55.6%) usual-resuscitation patients and for hyperlactataemia in 409 (65.4%) EGDT and 399 (63.7%) usual-resuscitation patients. Intravenous fluid volume prior to randomisation was similar [median 1950 ml (IQR 1000–2500 ml) EGDT, 2000 ml (IQR 1000–2500 ml) usual resuscitation]. The median time from ED presentation to meeting inclusion criteria [1.3 (IQR 0.5–2.3) hours for EGDT and 1.3 (IQR 0.6–2.4) hours for usual resuscitation] and from ED presentation to randomisation [2.5 (IQR 1.8–3.5) hours EGDT and usual resuscitation] was the same in both groups. Only two-thirds of patients in either group were deemed as likely to be admitted to an ICU from ED (if not enrolled in the trial); those deemed unlikely to be admitted were less severely ill.

The mean age of patients was similar in both groups (EGDT, 66.4 years; usual resuscitation, 64.3 years) and more than half were male (57.0% EGDT, 58.6% usual resuscitation). The site of infection (most commonly lungs) was well balanced. All patients received antimicrobials prior to randomisation.

Multiple imputation

Table 8 reports all the variables considered for multiple imputation and, for each variable, the number of missing values and the imputation model chosen.

TABLE 7 Baseline characteristics of patients by treatment group

Characteristics	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)
Refractory hypotension, *n* (%)	338 (54.1)	348 (55.6)
SBP (mmHg), mean (SD)	77.7 (11.0)	78.4 (10.2)
MAP (mmHg), mean (SD)	58.8 (15.8)	59.0 (10.7)
Hyperlactataemia, *n* (%)	409 (65.4)	399 (63.7)
Blood lactate concentration (mmol/l), mean (SD)	7.0 (3.5)	6.8 (3.2)
Intravenous fluids pre hospital to randomisation,[a] *n/N* (%)	612/625 (97.9)	606/625 (97.0)
Intravenous fluids pre hospital to randomisation (ml), median (IQR)	1950 (1000–2500)	2000 (1000–2500)
Intravenous fluids pre hospital,[b] *n/N* (%)	119/616 (19.3)	128/617 (20.7)
Intravenous fluids pre hospital (ml), median (IQR)	500 (250, 500)	500 (255, 500)
Intravenous fluids ED presentation to randomisation,[b] *n/N* (%)	607/625 (97.1)	599/625 (95.8)
Intravenous fluids ED presentation to randomisation (ml), median (IQR)	1600 (1000–2500)	1790 (1000–2500)
Blood products ED presentation to randomisation, *n/N* (%)	4/614 (0.7)	10/616 (1.6)
Blood products ED presentation to randomisation (ml), median (IQR)	922 (559–1000)	919 (500–1000)
Supplemental O_2,[c] *n/N* (%)	397/539 (73.7)	407/542 (75.1)
Time from ED presentation to inclusion criteria met (hours), mean (SD)	1.6 (1.3)	1.7 (1.4)

continued

TABLE 7 Baseline characteristics of patients by treatment group (*continued*)

Characteristics	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)
Time from ED presentation to inclusion criteria met (hours), median (IQR)	1.3 (0.5–2.3)	1.3 (0.6–2.4)
Time from ED presentation to randomisation (hours), mean (SD)	2.7 (1.3)	2.8 (1.4)
Time from ED presentation to randomisation (hours), median (IQR)	2.5 (1.8–3.5)	2.5 (1.8–3.5)
Would have been admitted direct to ICU from ED if not enrolled into ProMISe, *n* (%)	419 (67.0)	427 (68.2)
Yes (APACHE II score[d]), mean (SD)	20.5 (6.9)	19.0 (7.1)
No (APACHE II score[d]), mean (SD)	15.0 (6.1)	15.8 (6.5)
Age (years), mean (SD)	66.4 (14.6)	64.3 (15.5)
Age (years), median (IQR)	68 (58–78)	67 (54–76)
Male sex, *n* (%)	356 (57.0)	367 (58.6)
APACHE II score,[d] mean (SD)	18.7 (7.1)	18.0 (7.1)
APACHE II score,[d] median (IQR)	18 (13–23)	17 (13–22)
MEDS score,[e] mean (SD)	8.0 (3.4)	7.9 (3.3)
MEDS score,[e] median (IQR)	8 (6–10)	8 (6–10)
MEDS terminal illness, *n* (%)	11/622 (1.8)	14/626 (2.2)
MEDS respiratory difficulties, *n* (%)	510/620 (82.3)	499/618 (80.7)
MEDS septic shock, *n* (%)	277/624 (44.4)	305/622 (49.0)
MEDS platelets $< 150 \times 10^9$/l, *n* (%)	144/585 (24.6)	144/585 (24.6)
MEDS bandforms > 5%, *n* (%)	52/54 (96.3)	64/70 (91.4)
MEDS lower respiratory infection, *n* (%)	220 (35.2)	196 (31.3)
MEDS nursing home resident, *n* (%)	18/622 (2.9)	14/626 (2.2)
MEDS altered mental status, *n* (%)	206/608 (33.9)	208/602 (34.6)
MEDS age > 65 years, *n* (%)	363 (58.1)	329 (52.6)
SOFA score,[f] mean (SD)	4.2 (2.4)	4.3 (2.4)
SOFA score,[f] median (IQR)	4 (2–5)	4 (3–6)
SOFA respiratory dysfunction, *n* (%)	323 (51.7)	357 (57.0)
SOFA neurological dysfunction, *n* (%)	196 (31.4)	200 (31.9)
SOFA cardiovascular dysfunction, *n* (%)	410 (65.6)	433 (69.2)
SOFA coagulation dysfunction, *n* (%)	144 (23.0)	144 (23.0)
SOFA hepatic dysfunction, *n* (%)	211 (33.8)	199 (31.8)
SOFA renal dysfunction,[f] *n* (%)	426 (68.2)	406 (64.9)
Any severe condition in the past medical history,[g] *n/N* (%)	181/622 (29.1)	161/626 (25.7)
Severe liver disease	11/622 (1.8)	11/626 (1.8)
Severe renal disease	4/622 (0.6)	3/626 (0.5)
Severe respiratory disease	93/622 (15.0)	81/626 (12.9)

TABLE 7 Baseline characteristics of patients by treatment group (*continued*)

Characteristics	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)
Severe cardiovascular disease	22/622 (3.5)	17/626 (2.7)
Immunocompromised	84/622 (13.5)	70/626 (11.2)
Site of infection, *n* (%)		
Lungs	228 (36.5)	207 (33.1)
Abdomen	40 (6.4)	51 (8.1)
Blood	97 (15.5)	86 (13.7)
Central nervous system	12 (1.9)	9 (1.4)
Soft tissue	39 (6.2)	39 (6.2)
Urinary tract	108 (17.3)	117 (18.7)
Other	21 (3.4)	37 (5.9)
Not sepsis[h]	4 (0.6)	3 (0.5)
Unknown	76 (12.2)	77 (12.3)
Organism causing infection, *n* (%)		
Gram positive	138 (22.1)	141 (22.5)
Gram negative	175 (28.0)	171 (27.3)
Fungus/yeast	14 (2.2)	19 (3.0)
Parasite	0 (0.0)	2 (0.3)
Virus	12 (1.9)	9 (1.4)
Mixed growth	7 (1.1)	12 (1.9)
Not sepsis[h]	4 (0.6)	3 (0.5)
Unknown (not reported or no growth)	275 (44.0)	269 (43.0)
Antimicrobial change between ED admission and 72 hours, *n/N* (%)	359/615 (58.4)	342/617 (55.4)

MAP, mean arterial pressure; SBP, systolic blood pressure.
a Includes intravenous crystalloid and colloid > 20 ml and all blood products.
b Includes intravenous crystalloid and colloid administration > 20 ml.
c Supplemental O_2 is based on recording of $FiO_2 > 0.21$.
d The APACHE II score was calculated using the last recorded physiology data prior to randomisation and is not based on data over a 24-hour time period.
e The MEDS score was calculated using the last recorded physiology data prior to randomisation.
f The SOFA score was calculated using the last recorded physiology data prior to randomisation. The SOFA renal score was based on plasma creatinine concentration only (i.e. did not include urine output).
g Severe conditions in the past medical history defined according to APACHE II.
h Confirmed following randomisation.

TABLE 8 Variables considered for multiple imputation and form of imputation model

Variable	Missing values,[a] *n* (%)	Imputation model
Baseline variables		
Treatment group	0 (0)	None required
Age	0 (0)	None required
Sex	0 (0)	None required
Past medical history	3 (0.2)	None required[b]
Site of infection	0 (0)	None required
SOFA score	0 (0)	None required
MEDS score	0 (0)	None required
Admitted from nursing home	3 (0.2)	None required[b]
Shortness of breath with light activity	3 (0.2)	None required[b]
Altered mental status	41(3.3)	Logistic regression
Septic shock	5 (0.4)	Logistic regression
Respiratory difficulty	13 (1.0)	Logistic regression
Low platelet count	81 (6.5)	Logistic regression
Volume of intravenous fluid ED presentation to randomisation	3 (0.2)	Predictive mean matching
Baseline blood lactate concentration	32 (2.6)	Predictive mean matching
Baseline respiratory rate	5 (0.4)	Predictive mean matching
Baseline heart rate	1 (0.1)	Predictive mean matching
Baseline haemoglobin	31 (2.5)	Predictive mean matching
Baseline white blood cell count	49 (3.9)	Predictive mean matching
Resource use variables		
Length of stay in critical care	0 (0)	None required
Length of stay on general medical ward	0 (0)	None required
Outpatient visits at 90 days	242 (27.3)	Predictive mean matching
Acute hospital readmissions, 90 days to 1 year		
Length of stay in critical care	135 (10.8)	Predictive mean matching
Length of stay on general medical ward	135 (10.8)	Predictive mean matching
Outpatient visits at 1 year	306 (38.5)	Predictive mean matching
Mortality and quality-of-life variables		
EQ-5D at 90 days	215 (24.3)	Predictive mean matching
Mortality at 1 year	135 (10.8)	Logistic regression
EQ-5D at 1 year	314 (39.5)	Predictive mean matching

a For baseline variables, length of stay and mortality, the overall sample size was all randomised patients ($n = 1251$). For other resource use and quality-of-life variables, the relevant sample sizes were those patients eligible for the 90-day follow-up ($n = 886$) or 1-year follow-up ($n = 794$).
b When past medical history was missing, patients were assumed to have no past medical history.

Chapter 4 Results: clinical effectiveness

Adherence to the protocol

Most patients randomised to EGDT ($n = 545$, 87.3%) had timely insertion of a PreSep™ central venous oximetry catheter (*Table 9*). Two (0.3%) patients in the usual-resuscitation group had one inserted in error but these were not used for monitoring $ScvO_2$. The reasons for failure of insertion in the EGDT group were that patients were determined either to no longer meet inclusion criteria or to now meet exclusion criteria ($n = 22$); process of care (lack of equipment, staff, beds, communication, error; $n = 20$); technical or patient difficulties ($n = 18$); clinician decision ($n = 9$); refusal by the patient (without withdrawal from the trial; $n = 5$); and death before insertion ($n = 2$). No reason was provided for four patients. The mean first $ScvO_2$ value recorded after catheterisation (at hour 1) was 70% (SD 12%). Standard central venous catheters (not mandated) were inserted in 318 (50.9%) of the usual-resuscitation group and measurement of $ScvO_2$ from aspirated blood samples occurred in six patients. Arterial catheters (not mandated) were inserted in the majority of patients ($n = 462$, 74.2% EGDT; $n = 389$, 62.2% usual resuscitation). EGDT was stopped prematurely in 21 patients (median time to cessation, 3 hours) owing to withdrawal of active treatment ($n = 9$); patient no longer considered to be septic ($n = 5$); error ($n = 3$); transfer to operating theatre ($n = 1$); and refusal by the patient ($n = 1$). No reason was provided for two patients. Of the patients who died within 6 hours ($n = 17$ EGDT; $n = 18$ usual resuscitation), five in the EGDT group and six in the usual-resuscitation group had active treatment withdrawn prior to death.

TABLE 9 Interventions delivered during the intervention period

Interventions	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)
Supplemental O_2, *n/N* (%)	558/623 (89.6)	557/625 (89.1)
PreSep™ central venous oximetry catheter insertion, *n/N* (%)	545/624 (87.3)	2/625 (0.3)
Timing of insertion, *n* (%)		
Before hour 1	459 (84.5)	–
Hour 1 to hour 2	67 (12.3)	–
Hour 2 to hour 3	15 (2.8)	–
Hour 3 to hour 4	2 (0.4)	–
Hour 4 to hour 5	0 (0.0)	–
Hour 5 to hour 6	0 (0.0)	–
Any CVC insertion, *n/N* (%)	575/624 (92.1)	318/625 (50.9)
Time from randomisation to insertion (hours), mean (SD)	1.2 (0.9)	1.8 (1.7)
Time from randomisation to insertion (hours), median (IQR)	1.1 (0.8–1.5)	1.4 (0.6–2.9)
Arterial catheter insertion, *n/N* (%)	462/623 (74.2)	389/625 (62.2)
Time from randomisation to insertion (hours), mean (SD)	1.3 (1.6)	1.2 (1.7)
Time from randomisation to insertion (hours), median (IQR)	1.1 (0.4–1.9)	1.0 (0.2–1.9)
Any intravenous fluid,[a] *n/N* (%)	609/623 (97.8)	604/625 (96.6)
Volume (ml), mean (SD)	2226.0 (1443.3)	2022.3 (1271.4)

continued

TABLE 9 Interventions delivered during the intervention period (*continued*)

Interventions	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)
Volume (ml), median (IQR)	2000 (1150–3000)	1784 (1075–2775)
Intravenous colloid,[a] *n/N* (%)	197/623 (31.6)	180/625 (28.8)
Volume (ml), mean (SD)	1061.5 (800.5)	913.4 (626.8)
Volume (ml), median (IQR)	1000 (500–1500)	750 (500–1000)
Intravenous crystalloid,[a] *n/N* (%)	584/623 (93.7)	597/625 (95.5)
Volume (ml), mean (SD)	1963.2 (1356.9)	1766.7 (1178.4)
Volume (ml), median (IQR)	1750 (999–2750)	1500 (900–2380)
Vasopressors, *n/N* (%)	332/623 (53.3)	291/625 (46.6)
Packed red blood cell transfusion, *n/N* (%)	55/623 (8.8)	24/625 (3.8)
Volume (ml), mean (SD)	426.3 (209.4)	539.5 (294.2)
Volume (ml), median (IQR)	309 (285–577)	535 (305–607)
Dobutamine, *n/N* (%)	113/623 (18.1)	24/625 (3.8)
Mechanical ventilation, *n/N* (%)	126/623 (20.2)	119/625 (19.0)
Sedatives, *n/N* (%)	138/623 (22.2)	130/625 (20.8)
Neuromuscular blocking agent, *n/N* (%)	53/623 (8.5)	40/625 (6.4)
Critical care admission, *n/N* (%)	551/625 (88.2)	467/626 (74.6)
Time from randomisation to admission (hours), mean (SD)	2.0 (2.3)	2.5 (5.7)
Time from randomisation to admission (hours), median (IQR)	1.2 (0.4–2.8)	1.2 (0.3–2.8)
Location of protocol delivery, *n* (%)		
ED	64 (10.2)	–
ICU	275 (44.0)	–
Ward	10 (1.6)	–
ED and ICU	235 (37.6)	–
ED and ward	37 (5.9)	–
ICU and ward	2 (0.3)	–
ED, ICU and ward	1 (0.2)	–
Review by consultant, *n/N* (%)	520/624 (83.3)	494/625 (79.0)
Specialty of most senior doctor to review the patient, *n* (%)		
Emergency medicine	181 (29.0)	211 (33.8)
Critical care medicine	388 (62.2)	304 (48.6)
Acute medicine	39 (6.3)	92 (14.7)
Other	16 (2.6)	18 (2.9)

CVC, central venous catheter.
a Includes intravenous colloid and crystalloid > 20 ml.

Figure 13 shows the adherence with each element of the EGDT protocol across the 6-hour intervention period. The bars plotted on each hour report the percentage of patients (of those meeting the previous targets) who did not meet or met each physiological target at that hour, or for whom the relevant physiological value was not recorded (within 15 minutes either side of the hour). The bars plotted between each hour report the percentage of patients (of those who did not meet the physiological target at the previous hour) that received the associated action either during the intervention period or after the intervention period, or who no longer required the action as the target was subsequently met. Adherence with the protocol was generally good, particularly for delivery of fluid and vasopressors, but there were delays in obtaining packed red blood cells and dobutamine, such that the $ScvO_2$ value had often resolved spontaneously before these were delivered.

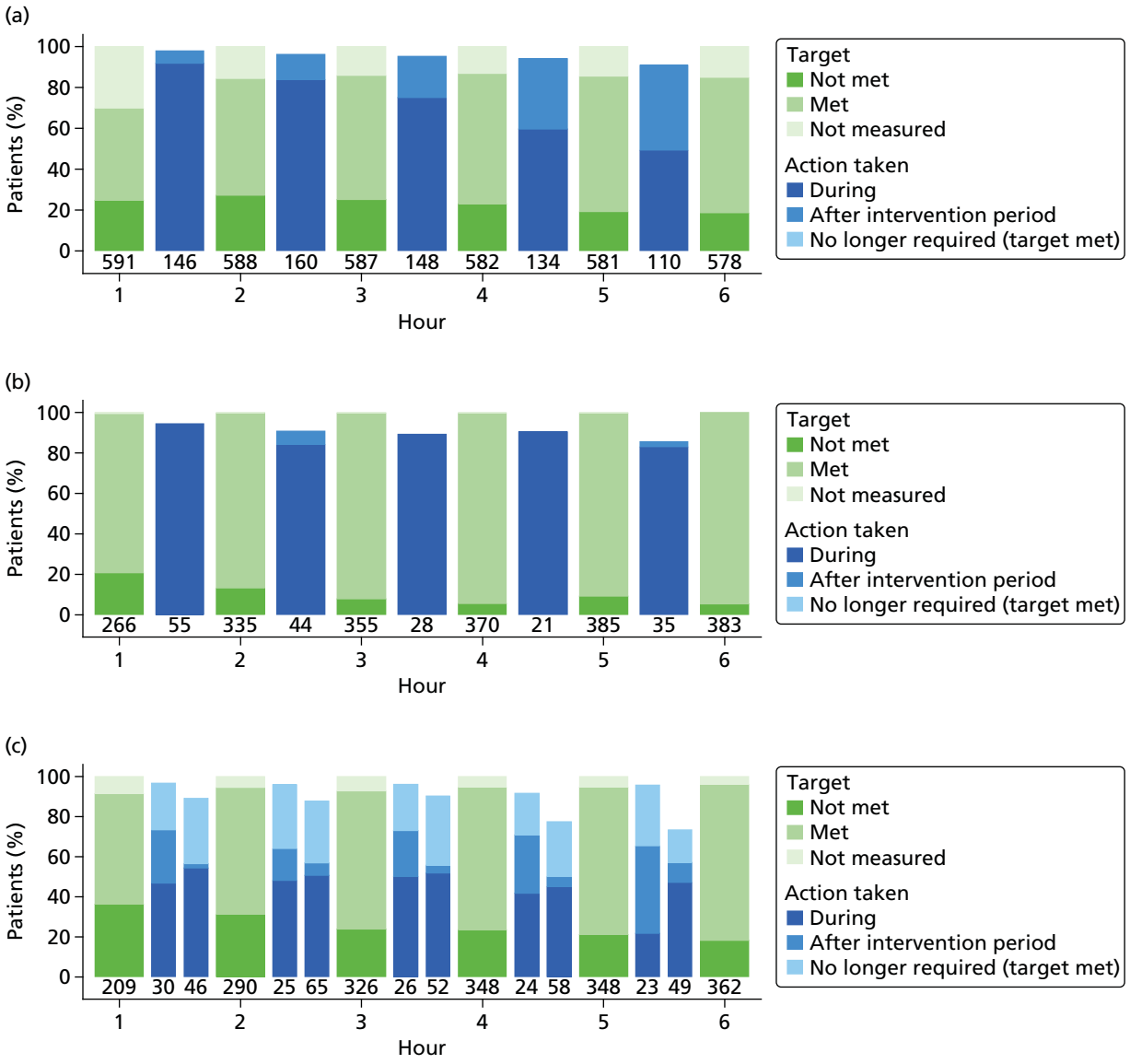

FIGURE 13 Adherence to the EGDT protocol. (a) Target: CVP; action: fluids; (b) target: MAP/SBP; action: vasopressors; and (c) target: $ScvO_2$; action: PRBC transfusion (L) or dobutamine (R). Numbers at the foot of each bar represent the denominator for the percentages in that bar. Each target is considered sequentially (i.e. those meeting the target for CVP become the denominator for MAP/SBP and those meeting the target for MAP/SBP become the denominator for $ScvO_2$). Of the two smaller bars, (L) denotes the left-hand bar and (R) denotes the right-hand bar. Thirty-two patients who no longer met eligibility criteria or declined the intervention were excluded from the evaluation of adherence. CVP, central venous pressure; MAP, mean arterial pressure; PRBC, packed red blood cells; SBP, systolic blood pressure.

Figure 14 reports the protocol adherence compared with ProCESS and ARISE, according to the adherence algorithms reported in their respective publications.[23,24] For the comparison with ProCESS, adherence was assessed at the end of the 6-hour intervention period only. Patients who died, were discharged or were withdrawn from the intervention prior to 6 hours were excluded (47/625, 7.5%, for ProMISe; 35/439, 8.0%, for ProCESS). Overall adherence among the evaluable patients was similar for the two trials (85.6% for ProMISe vs. 88.1% for ProCESS). The greatest difference was on failure to insert a central venous catheter with *Scv*O_2 monitoring capability; on all other measures, non-adherence for ProMISe was lower than for ProCESS. For the comparison with ARISE, adherence was assessed hourly as the percentage of patients meeting each physiological target (of those for whom the relevant physiological value was recorded) and, for those with physiological values recorded at 2 consecutive hours, the percentage who either met the target at the start or the end of the hour or received the associated action during the hour. The percentage of patients meeting the physiological targets at each hour, for ProMISe compared with ARISE, was similar for central venous pressure, higher for mean arterial pressure/systolic blood pressure and lower for *Scv*O_2. When reported as the percentage either meeting the target or receiving the associated action, adherence was extremely high (and similar to ARISE) for both receipt of intravenous fluids and receipt of vasopressors, but somewhat lower for receipt of packed red blood cells or dobutamine (although this did reach a level of 89% by the final hour of the intervention period).

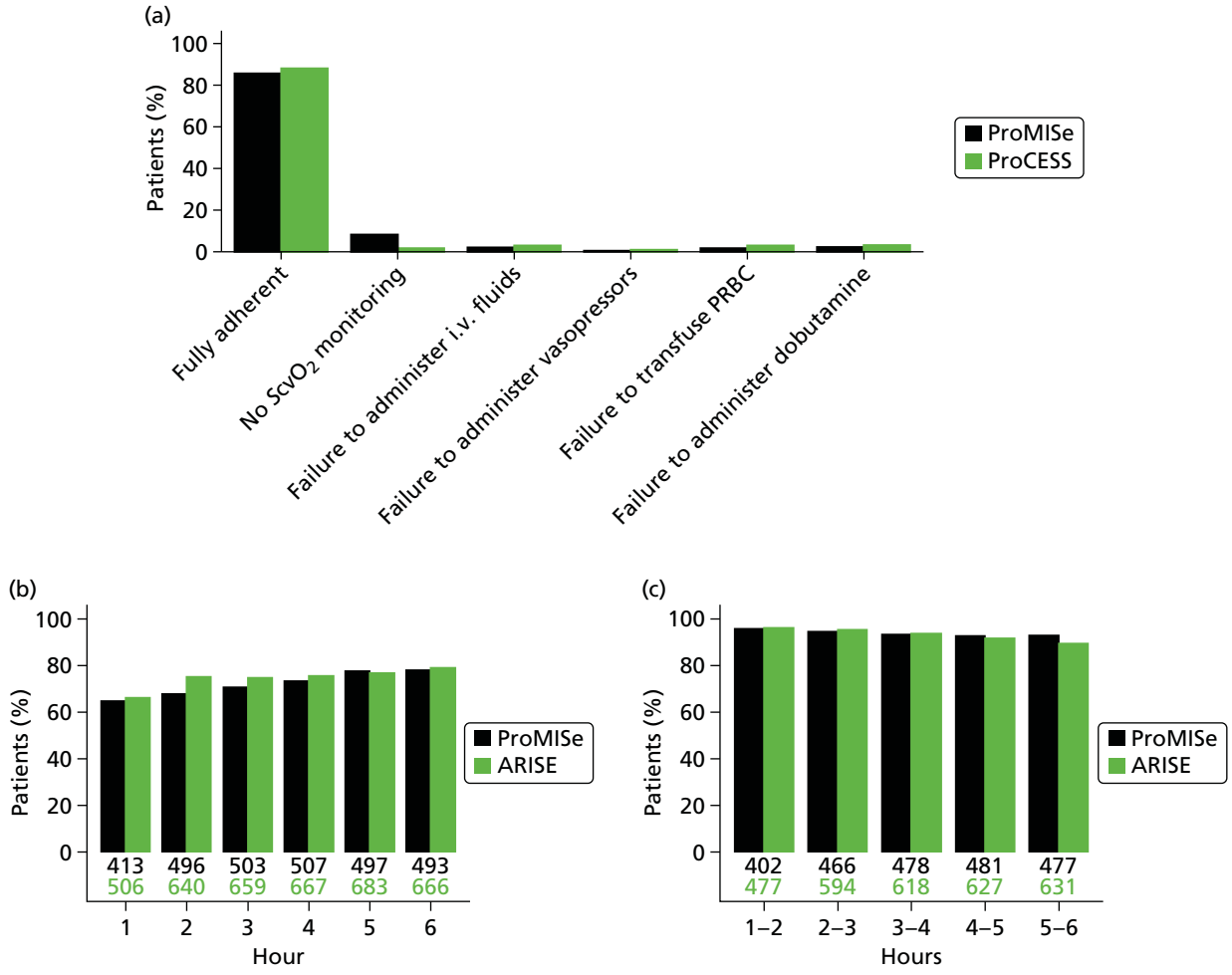

FIGURE 14 Protocol adherence compared with ProCESS (a) and ARISE [(b), CVP; (c) i.v. fluids; (d) MAP or SBP; (e) vasopressors; (f) *Scv*O_2; and (g) PRBC and/or dobutamine]. For the comparison with ProCESS, the numbers of evaluable patients were 578 (ProMISe) and 404 (ProCESS). For the comparison with ARISE, numbers at the foot of each bar represent the denominator for the percentages in that bar. CVP, central venous pressure; i.v., intravenous; MAP, mean arterial pressure; PRBC, packed red blood cells; SBP, systolic blood pressure. (*continued*)

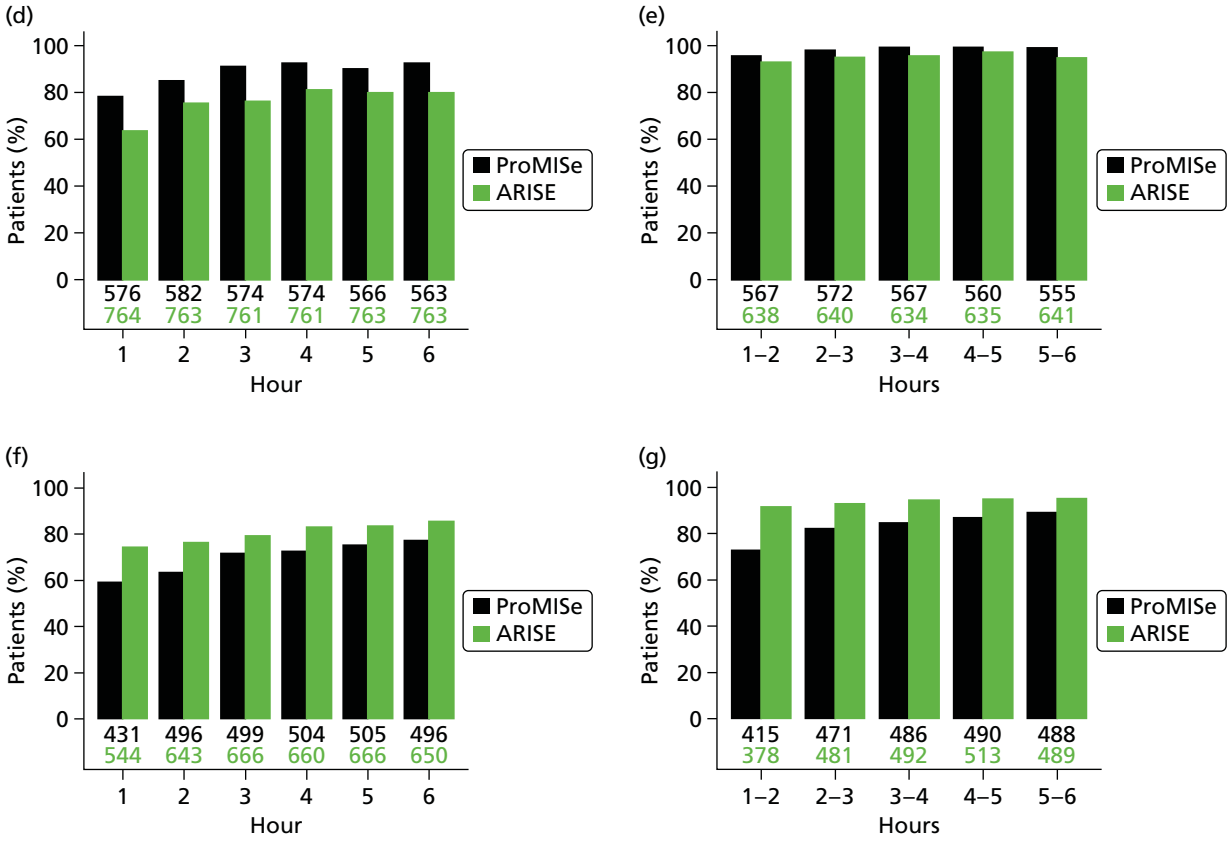

FIGURE 14 Protocol adherence compared with ProCESS (a) and ARISE [(b), CVP; (c) i.v. fluids; (d) MAP or SBP; (e) vasopressors; (f) $ScvO_2$; and (g) PRBC and/or dobutamine]. For the comparison with ProCESS, the numbers of evaluable patients were 578 (ProMISe) and 404 (ProCESS). For the comparison with ARISE, numbers at the foot of each bar represent the denominator for the percentages in that bar. CVP, central venous pressure; i.v., intravenous; MAP, mean arterial pressure; PRBC, packed red blood cells; SBP, systolic blood pressure.

Delivery of care by treatment group

During the 6-hour intervention period, patients randomised to EGDT received more intravenous fluid than those randomised to usual resuscitation (see *Table 9*). Hourly fluid volume decreased over the 6 hours but patients in the usual-resuscitation group received a greater volume initially (*Figure 15*). In both groups, crystalloid was used more frequently than colloid. More patients in the EGDT group received vasopressors and dobutamine. Although more patients in the EGDT group received packed red blood cell transfusions, larger volumes were transfused in the usual-resuscitation group. Administration of platelets and fresh-frozen plasma was similar, although volumes of both were higher in the EGDT group. Physiological values normalised slightly over the 6-hour intervention period in both groups (*Figure 16*). After 6 hours, central venous pressure, mean arterial pressure, systolic blood pressure and haemoglobin, where measured (with greater frequency in the EGDT group), were similar (*Table 10*).

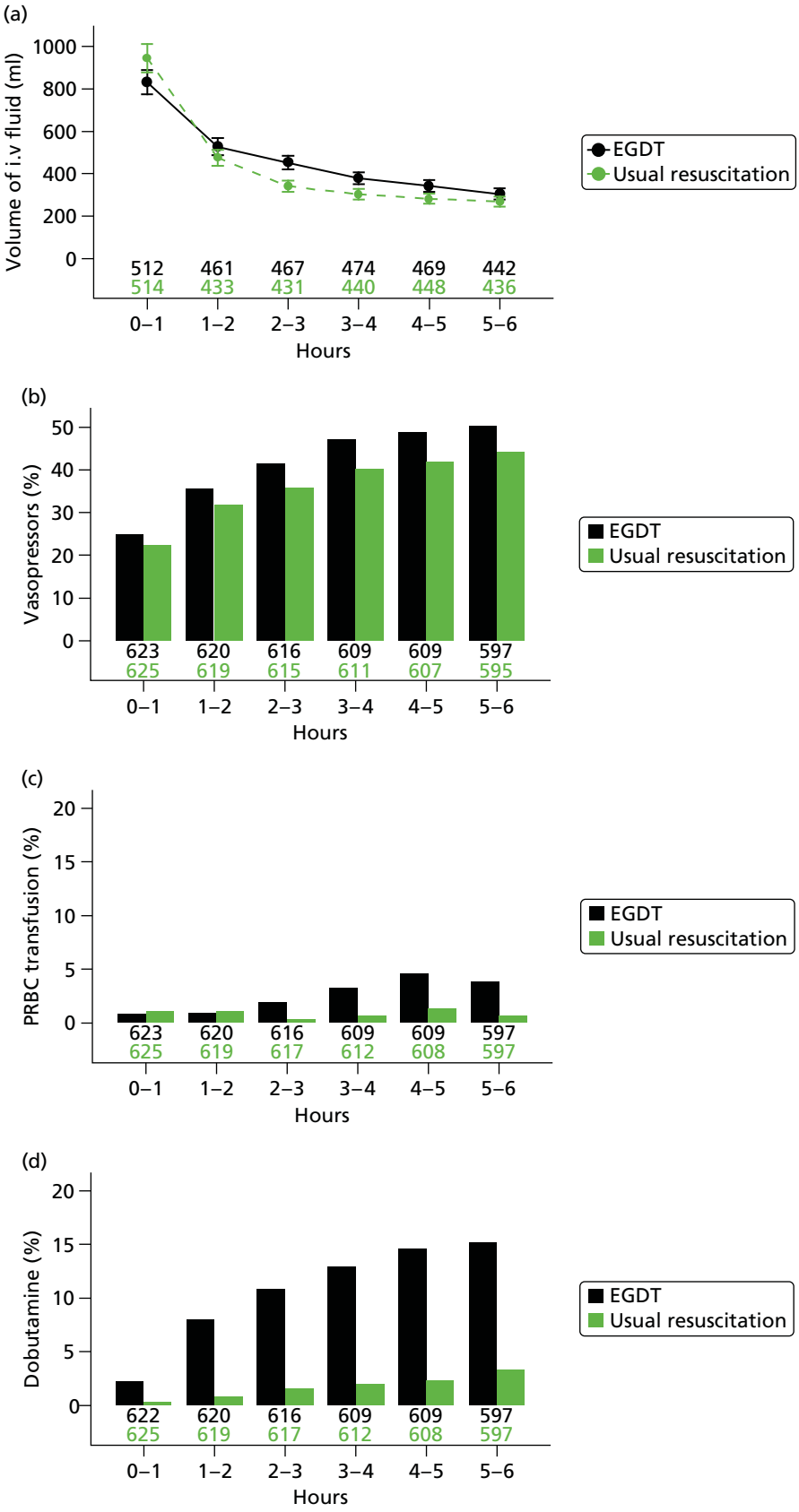

FIGURE 15 Interventions delivered during the intervention period. The values reported are the mean and 95% CI (volume of i.v. fluid) or percentage of patients receiving the intervention (all other panels) during each hour of the intervention period. The numbers at the foot of each bar represent the denominators for the means/percentages in that bar. (a) Volume of i.v. fluid; (b) vasopressors; (c) PRBC transfusion; (d) dobutamine; (e) sedatives; (f) neuromuscular blocking agents; and (g) mechanical ventilation. i.v., intravenous; PRBC, packed red blood cells. (*continued*)

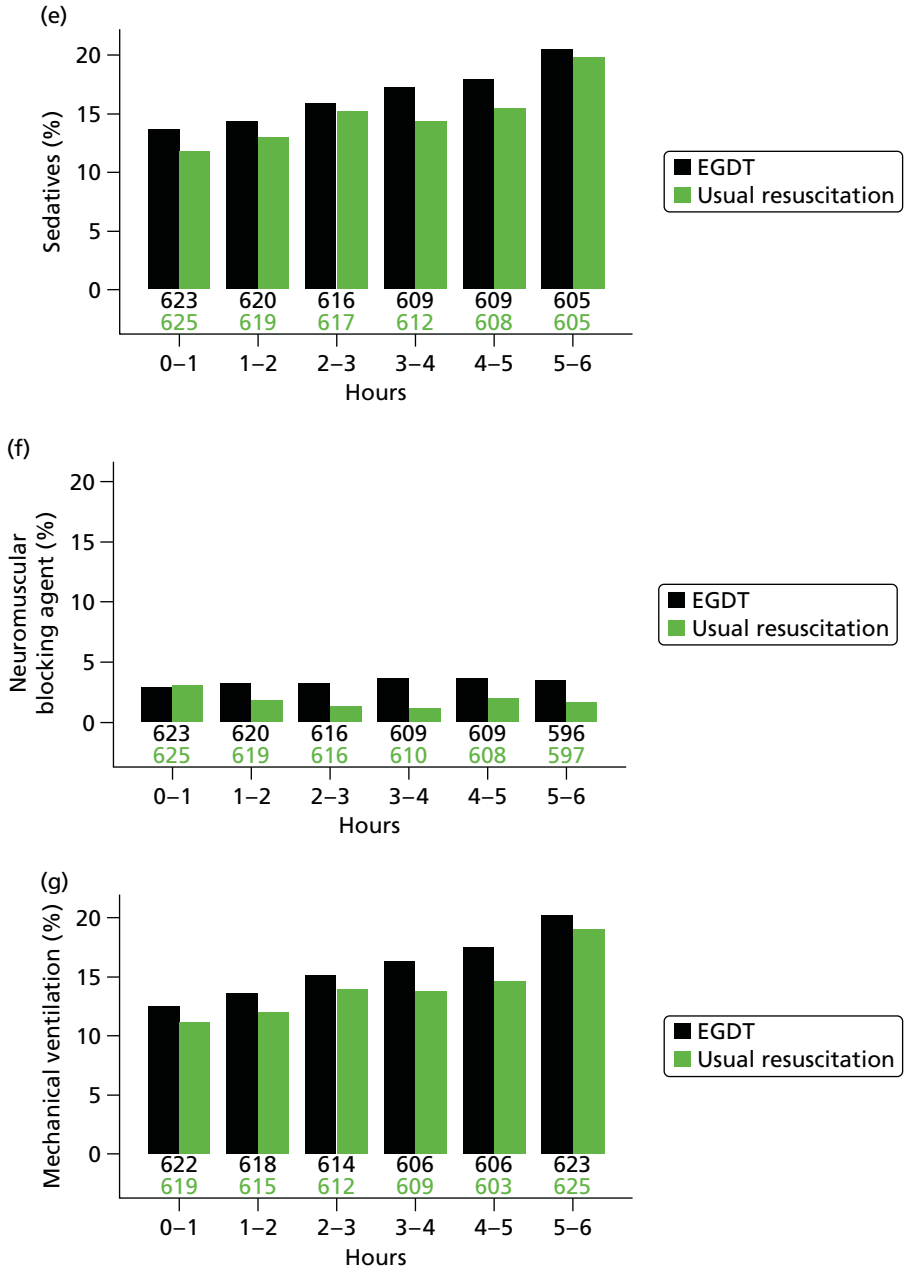

FIGURE 15 Interventions delivered during the intervention period. The values reported are the mean and 95% CI (volume of i.v. fluid) or percentage of patients receiving the intervention (all other panels) during each hour of the intervention period. The numbers at the foot of each bar represent the denominators for the means/percentages in that bar. (a) Volume of i.v. fluid; (b) vasopressors; (c) PRBC transfusion; (d) dobutamine; (e) sedatives; (f) neuromuscular blocking agents; and (g) mechanical ventilation. i.v., intravenous; PRBC, packed red blood cells.

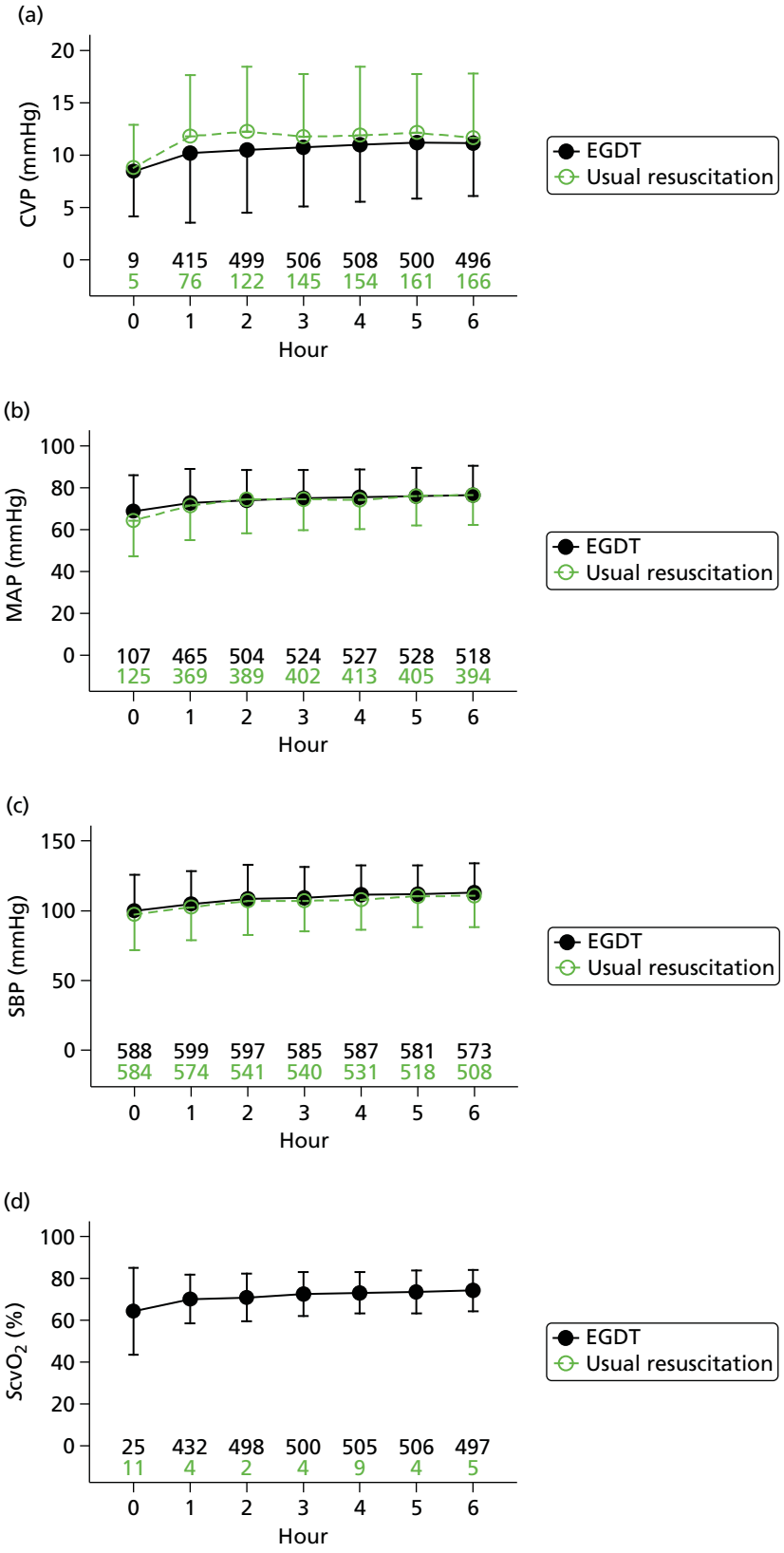

FIGURE 16 Physiology during the intervention period. (a) CVP; (b) MAP; (c) SBP; and (d) $ScvO_2$. The values reported are the mean plus/minus SD for values recorded within 15 minutes either side of the specified time point. For the EGDT group, first recorded values after insertion of the PreSep™ central venous oximetry catheter are at hour 1. $ScvO_2$ measurements are not reported for the usual-resuscitation group owing to very small numbers of patients for whom these were recorded. CVP, central venous pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

TABLE 10 Physiology measurements at the end of the intervention period

Physiology	EGDT ($n = 625$)	Usual resuscitation ($n = 626$)
CVP (mmHg), mean (SD)	11.2 (5.1) [496]	11.7 (6.1) [166]
MAP (mmHg), mean (SD)	76.5 (13.9) [518]	76.5 (14.3) [394]
SBP (mmHg), mean (SD)	113.1 (21.0) [573]	110.7 (22.4) [508]
$ScvO_2$ (%), mean (SD)	74.2 (9.8) [497]	–
Haemoglobin (g/dl), mean (SD)	11.0 (2.0) [384]	11.3 (2.3) [163]

CVP, central venous pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.
The numbers in square brackets denote the number of patients for whom the physiological value was recorded (within 15 minutes either side of hour 6).

Between 6 and 72 hours, use of intravenous fluids was similar but usual-resuscitation patients received higher volumes (*Table 11*). Intravenous colloid use was higher in the EGDT group but volumes were similar in the two groups, intravenous crystalloid use was similar but volumes were higher in the usual-resuscitation group and use of packed red blood cell transfusions was higher in the EGDT group but the volumes delivered were higher in the usual-resuscitation group. Although the use of platelets and fresh-frozen plasma was similar, the volume of platelets transfused was higher in the EGDT group and the volume of fresh-frozen plasma was higher in the usual-resuscitation group. Vasopressor and dobutamine use remained higher in the EGDT group. At 72 hours, physiological, biochemistry and SOFA values were similar (*Table 12*).

TABLE 11 Interventions delivered by time period

Interventions	Baseline		Hour 0 to hour 6		Hour 6 to hour 72		Hour 0 to hour 72	
	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 608)	Usual resuscitation (*N* = 607)	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)
Supplemental O_2,[a] *n*/*N* (%)	397/539 (73.7)	407/542 (75.1)	558/623 (89.6)	557/625 (89.1)	520/603 (86.2)	515/603 (85.4)	577/623 (92.6)	581/625 (93.0)
Any i.v. fluid,[b] *n*/*N* (%)	612/625 (97.9)	606/625 (97.0)	609/623 (97.8)	604/625 (96.6)	546/603 (90.5)	548/603 (90.9)	615/623 (98.7)	618/625 (98.9)
Volume (ml), mean (SD)	1890 (1105)	1965 (1149)	2226 (1443)	2022 (1271)	4215 (3068)	4366 (3114)	5946 (3740)	5844 (3651)
Volume (ml), median (IQR)	1950 (1000–2500)	2000 (1000–2500)	2000 (1150–3000)	1784 (1075–2775)	3623 (1800–6060)	3981 (1895–6291)	5587 (2915–8150)	5410 (3000–7970)
i.v. colloid,[b] *n*/*N* (%)	–	–	197/623 (31.6)	180/625 (28.8)	171/603 (28.4)	150/603 (24.9)	260/623 (41.7)	240/625 (38.4)
Volume (ml), mean (SD)	–	–	1062 (801)	913 (627)	1207 (1042)	1093 (1012)	1598 (1391)	1369 (1150)
Volume (ml), median (IQR)	–	–	1000 (500–1500)	750 (500–1000)	750 (500–1750)	750 (500–1500)	1000 (575–2000)	1000 (500–1750)
i.v. crystalloid,[b] *n*/*N* (%)	–	–	584/623 (93.7)	597/625 (95.5)	537/603 (89.1)	543/603 (90.0)	609/623 (97.8)	617/625 (98.7)
Volume (ml), mean (SD)	–	–	1963 (1357)	1767 (1178)	3909 (2869)	4136 (2914)	5323 (3518)	5317 (3435)
Volume (ml), median (IQR)	–	–	1750 (999–2750)	1500 (900–2380)	3403 (1576–5647)	3694 (1832–5911)	4864 (2520–7241)	4900 (2700–7408)
Vasopressors, *n*/*N* (%)	15/625 (2.4)	21/626 (3.4)	332/623 (53.3)	291/625 (46.6)	349/603 (57.9)	317/603 (52.6)	377/623 (60.5)	344/625 (55.0)
Dobutamine, *n*/*N* (%)	2/625 (0.3)	0/626 (0.0)	113/623 (18.1)	24/625 (3.8)	107/603 (17.7)	39/603 (6.5)	139/623 (22.3)	44/625 (7.0)
PRBC transfusion, *n*/*N* (%)	–	–	55/623 (8.8)	24/625 (3.8)	76/603 (12.6)	51/603 (8.5)	107/623 (17.2)	65/625 (10.4)
Volume (ml), mean (SD)	–	–	426 (209)	540 (294)	487 (335)	606 (403)	565 (393)	674 (506)
Volume (ml), median (IQR)	–	–	309 (285–577)	535 (305–607)	351 (291–579)	552 (317–620)	529 (298–602)	562 (317–660)

Interventions	Baseline		Hour 0 to hour 6		Hour 6 to hour 72		Hour 0 to hour 72	
	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 608)	Usual resuscitation (*N* = 607)	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)
Platelets, *n/N* (%)	–	–	11/623 (1.8)	10/625 (1.6)	23/603 (3.8)	25/603 (4.1)	31/623 (5.0)	30/625 (4.8)
Volume (ml), mean (SD)	–	–	286 (72)	242 (131)	314 (167)	278 (162)	325 (194)	315 (207)
Volume (ml), median (IQR)	–	–	315 (200–340)	180 (163–342)	274 (182–366)	187 (172–357)	290 (191–366)	250 (173–418)
Fresh-frozen plasma, *n/N* (%)	–	–	15/623 (2.4)	14/625 (2.2)	28/603 (4.6)	30/603 (5.0)	41/623 (6.6)	39/625 (6.2)
Volume (ml), mean (SD)	–	–	847 (383)	769 (285)	836 (721)	869 (507)	881 (658)	945 (533)
Volume (ml), median (IQR)	–	–	1007 (539–1095)	793 (526–1085)	587 (483–1000)	846 (528–1057)	791 (516–1095)	1025 (528–1140)
Mechanical ventilation, *n/N* (%)	40/625 (6.4)	28/626 (4.5)	126/623 (20.2)	119/625 (19.0)	147/603 (24.4)	153/603 (25.4)	171/623 (27.4)	178/625 (28.5)
Sedatives, *n/N* (%)	–	–	138/623 (22.2)	130/625 (20.8)	161/603 (26.7)	172/603 (28.5)	191/623 (30.7)	200/625 (32.0)
Neuromuscular blocking agent, *n/N* (%)	–	–	53/623 (8.5)	40/625 (6.4)	39/603 (6.5)	34/603 (5.6)	74/623 (11.9)	60/625 (9.6)
Co-interventions for the source of sepsis, *n/N* (%)								
Surgery	–	–	9/625 (1.4)	12/626 (1.9)	32/608 (5.3)	36/607 (5.9)	41/625 (6.6)	48/626 (7.7)
Activated Protein C	–	–	0/625 (0.0)	1/626 (0.2)	2/608 (0.3)	4/607 (0.7)	2/625 (0.3)	4/626 (0.6)
Steroids	31/625 (5.0)	25/626 (4.0)	73/625 (11.7)	72/626 (11.5)	133/608 (21.9)	128/607 (21.1)	142/625 (22.7)	136/626 (21.7)

i.v., intravenous; PRBC, packed red blood cells.

a At baseline, supplemental O_2 is based on recording of $FiO_2 > 0.21$.

b Includes i.v. crystalloid and colloid administration > 20 ml and all blood product administration at baseline. Includes i.v. crystalloid and colloid administration > 20 ml for all other time periods.

TABLE 12 Physiology by time period

Physiology	Baseline[a]		Hour 0 to hour 6		Hour 6 to hour 24		Hour 48 to hour 72	
	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 608)	Usual resuscitation (*N* = 607)	EGDT (*N* = 541)	Usual resuscitation (*N* = 529)
Lowest MAP (mmHg), mean (SD) [*n*]	69.0 (20.3) [145]	64.7 (17.2) [164]	64.7 (11.5) [566]	65.0 (14.3) [475]	64.0 (11.1) [439]	64.3 (11.9) [369]	68.9 (11.6) [282]	68.5 (13.7) [260]
Lowest SBP (mmHg), mean (SD) [*n*]	99.6 (26.0) [609]	97.0 (25.5) [602]	92.2 (19.3) [619]	91.4 (19.9) [616]	97.1 (19.1) [300]	97.9 (20.3) [344]	107.3 (19.5) [312]	107.9 (18.3) [308]
Haemoglobin[b] (g/dl), mean (SD) [*n*]	12.5 (2.5) [607]	12.7 (2.5) [613]	11.0 (2.0) [384]	11.3 (2.3) [163]	11.0 (1.8) [422]	10.9 (1.9) [374]	10.7 (1.7) [346]	10.7 (1.8) [331]
Blood lactate concentration[b] (mmol/l), mean (SD) [*n*]	5.2 (3.5) [608]	5.1 (3.5) [611]	3.3 (3.0) [392]	3.8 (3.2) [187]	2.7 (2.7) [382]	2.7 (2.6) [316]	2.0 (2.6) [229]	1.8 (1.7) [217]
Lowest PaO_2/FiO_2 (kPa), mean (SD) [*n*]	32.6 (26.1) [383]	33.9 (29.1) [416]	30.3 (25.2) [464]	30.9 (20.6) [432]	30.7 (20.3) [436]	30.4 (16.7) [393]	30.9 (21.7) [255]	28.4 (14.5) [225]
Highest creatinine (μmol/l), mean (SD) [*n*]	183.8 (141.5) [591]	192.7 (192.0) [586]	176.3 (135.0) [462]	196.3 (190.8) [422]	149.5 (102.1) [511]	174.4 (145.5) [476]	129.1 (98.9) [425]	140.8 (120.4) [413]
Highest bilirubin (μmol/l), mean (SD) [*n*]	24.7 (25.1) [491]	28.0 (37.6) [492]	24.2 (25.6) [408]	26.0 (37.5) [389]	26.6 (36.4) [436]	26.2 (39.6) [385]	24.8 (42.0) [324]	23.0 (37.2) [314]
Lowest platelet count (× 10^9/l), mean (SD) [*n*]	239.0 (131.5) [585]	236.1 (123.0) [585]	203.3 (113.5) [455]	208.7 (119.6) [415]	182.3 (100.2) [503]	181.7 (108.7) [469]	163.9 (98.1) [421]	164.9 (102.1) [411]
Lowest GCS score, mean (SD) [*n*]	13.8 (2.8) [593]	14.0 (2.2) [588]	13.3 (3.5) [578]	13.4 (3.4) [533]	13.2 (3.8) [492]	13.3 (3.7) [462]	13.4 (3.5) [422]	13.8 (3.2) [393]
SOFA respiratory dysfunction, *n* (%)	323 (51.7)	357 (57.0)	416 (66.6)	375 (59.9)	403 (66.3)	359 (59.1)	241 (44.5)	214 (40.5)
SOFA neurological dysfunction, *n* (%)	196 (31.4)	200 (31.9)	226 (36.2)	186 (29.7)	169 (27.8)	144 (23.7)	126 (23.3)	93 (17.6)

Physiology	Baseline[a]		Hour 0 to hour 6		Hour 6 to hour 24		Hour 48 to hour 72	
	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 625)	Usual resuscitation (*N* = 626)	EGDT (*N* = 608)	Usual resuscitation (*N* = 607)	EGDT (*N* = 541)	Usual resuscitation (*N* = 529)
SOFA cardiovascular dysfunction, *n* (%)	410 (65.6)	433 (69.2)	477 (76.3)	384 (61.3)	434 (71.4)	358 (59.0)	342 (63.2)	317 (59.9)
SOFA coagulation dysfunction, *n* (%)	144 (23.0)	144 (23.0)	152 (24.3)	134 (21.4)	209 (34.4)	201 (33.1)	197 (36.4)	203 (38.4)
SOFA hepatic dysfunction, *n* (%)	211 (33.8)	199 (31.8)	223 (35.7)	218 (34.8)	218 (35.9)	184 (30.3)	98 (18.1)	106 (20.0)
SOFA renal dysfunction,[c] *n* (%)	426 (68.2)	406 (64.9)	430 (68.8)	415 (66.3)	347 (57.1)	332 (54.7)	199 (36.8)	196 (37.1)
SOFA score,[c] median (IQR)	4 (2–5)	4 (3–6)	6 (3–9)	5 (3–8)	6 (3–9)	5 (2–9)	3 (1–6)	3 (1–6)

MAP, mean arterial pressure; SBP, systolic blood pressure.

a Baseline physiology values were based on the last recorded value prior to randomisation.

b Haemoglobin and blood lactate concentration were recorded at the end of the time period.

c At baseline, SOFA score was calculated using the last recorded physiology data prior to randomisation. SOFA renal score was based on plasma creatinine concentration only (i.e. did not include urine output). Patients for whom the variables for SOFA renal and coagulation scores were not recorded during hour 0 to hour 6 had these values carried forward from baseline, if recorded. Patients for whom the variables for SOFA renal and coagulation scores were not recorded during hour 6 to hour 24 had these values carried forward from hour 0 to hour 6, if recorded.

Numbers in square brackets denote the number of patients for whom the physiological value was recorded.

Primary outcome: clinical effectiveness

At 90 days following randomisation, 184 (29.5%) patients randomised to EGDT had died, compared with 181 (29.2%) patients randomised to usual resuscitation, corresponding to an absolute risk reduction of −0.3 (95% CI −5.4 to 4.7, $p = 0.90$) and a relative risk of 1.01 (95% CI 0.85 to 1.20; *Table 13*). This difference remained non-significant after adjustment for baseline characteristics (adjusted odds ratio 0.95, 95% CI 0.74 to 1.24; $p = 0.73$; unadjusted odds ratio 1.02, 95% CI 0.80 to 1.30).

TABLE 13 Primary and secondary outcomes: clinical effectiveness

Outcome	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)	Effect estimate (95% CI)	*p*-value
Primary outcome				
All-cause mortality at 90 days, *n*/*N* (%)	184/623 (29.5)	181/620 (29.2)	1.01 (0.85 to 1.20)[a]	0.90
			−0.3 (−5.4 to 4.7)[b]	
			1.02 (0.80 to 1.30)[c]	
			0.95 (0.74 to 1.24)[d]	0.73
Secondary outcomes				
SOFA score at 6 hours,[e] mean (SD)	6.4 (3.8)	5.6 (3.8)	0.8 (0.5 to 1.1)[f,g]	< 0.001
SOFA score at 72 hours,[e] mean (SD)	4.0 (3.8)	3.7 (3.6)	0.4 (−0.0 to 0.8)[f,g]	0.056
Receipt of advanced cardiovascular support, *n*/*N* (%)	230/622 (37.0)	190/614 (30.9)	1.19 (1.02 to 1.40)[a]	0.026
Receipt of advanced respiratory support, *n*/*N* (%)	179/620 (28.9)	175/615 (28.5)	1.01 (0.85 to 1.21)[a]	0.90
Receipt of renal support, *n*/*N* (%)	88/620 (14.2)	81/614 (13.2)	1.08 (0.81 to 1.42)[a]	0.62
Days alive and free from advanced cardiovascular support up to 28 days, mean (SD)	20.3 (11.9)	20.6 (11.8)	−0.3 (−1.6 to 1.0)[f]	0.65
Days alive and free from advanced respiratory support up to 28 days, mean (SD)	19.6 (12.1)	19.8 (12.0)	−0.2 (−1.5 to 1.1)[f]	0.75
Days alive and free from renal support up to 28 days, mean (SD)	20.6 (12.1)	20.6 (11.9)	0.0 (−1.3 to 1.4)[f]	0.96
ED length of stay (hours), median (IQR)	1.5 (0.4–3.1)	1.3 (0.4–2.9)	–	0.34
Survivors	1.4 (0.4–3.1)	1.3 (0.3–2.9)	–	0.38
Non-survivors	3.7 (2.4–4.1)	2.4 (1.2–5.9)	–	0.25

TABLE 13 Primary and secondary outcomes: clinical effectiveness (*continued*)

Outcome	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)	Effect estimate (95% CI)	*p*-value
Critical care length of stay (days), median (IQR)	2.6 (1.0–5.8)	2.2 (0.0–5.3)	–	0.006
Survivors	2.9 (1.0–6.1)	2.8 (0.0–5.9)	–	0.008
Non-survivors	1.6 (0.6–3.1)	1.2 (0.5–4.3)	–	0.85
Acute hospital length of stay (days), median (IQR)	9 (4–21)	9 (4–18)	–	0.46
Survivors	11 (7–25)	11 (7–22)	–	0.42
Non-survivors	2 (1–8)	2 (1–7)	–	0.44
All-cause mortality at 28 days, *n/N* (%)	155/625 (24.8)	152/621 (24.5)	1.01 (0.83 to 1.23)[a]	0.90
			0.95 (0.73 to 1.25)[d]	0.73
All-cause mortality at acute hospital discharge, *n/N* (%)	160/625 (25.6)	154/625 (24.6)	1.04 (0.86 to 1.26)[a]	0.74
			0.98 (0.75 to 1.29)[d]	0.90
All-cause mortality at 1 year, *n/N* (%)	224/558 (40.1)	233/558 (41.8)	0.96 (0.83 to 1.11)[a]	0.63
			0.85 (0.66 to 1.09)[d]	0.20

a Relative risk.
b Absolute risk reduction.
c Unadjusted odds ratio.
d Adjusted odds ratio.
e SOFA renal score was based on plasma creatinine concentration only. Patients for whom the variables for SOFA renal and coagulation scores were not recorded between randomisation and hour 6 had these values carried forward from baseline, if recorded. A total of 181 patients who died or were discharged before 48 hours (84 EGDT, 97 usual resuscitation) were not included in the SOFA score at 72 hours.
f Difference in means.
g Adjusted for baseline SOFA score.

Secondary outcomes: clinical effectiveness

For patients in the EGDT group, both the mean SOFA score at 6 hours ($p < 0.001$) and the proportion receiving advanced cardiovascular support ($p = 0.026$) were significantly higher than for patients in the usual-resuscitation group. The median total length of stay in critical care was significantly longer for patients in the EGDT group than the usual-resuscitation group ($p = 0.006$). There were no significant differences between the groups in any of the other secondary outcomes, including duration of survival (log-rank test, $p = 0.63$; Cox proportional hazards model, adjusted hazard ratio 0.94, 95% CI 0.79 to 1.11; $p = 0.46$) (*Figure 17* and see *Table 13*).

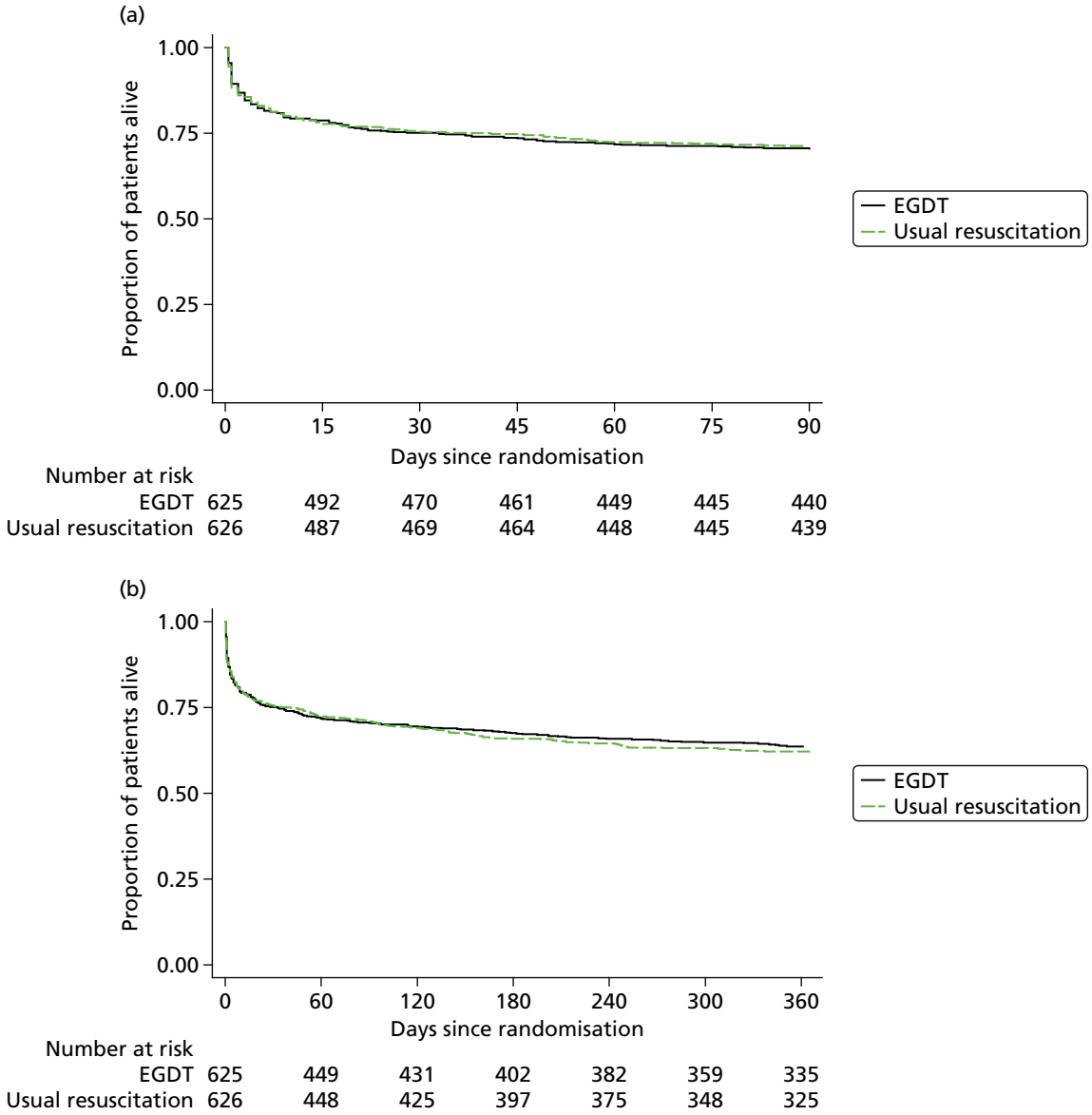

FIGURE 17 Kaplan–Meier curves for survival to (a) 90 days and (b) 1 year following randomisation.

Safety monitoring

Thirty (4.8%) patients in the EGDT group and 26 (4.2%) patients in the usual-resuscitation group experienced one or more serious adverse events within 30 days following randomisation (relative risk 1.16, 95% CI 0.69 to 1.93; $p = 0.58$; *Table 14*). The most commonly reported serious adverse events were pulmonary oedema (four patients in the EGDT group and seven patients in the usual-resuscitation group) and myocardial ischaemia (seven patients in the EGDT group and four patients in the usual-resuscitation group). Three serious adverse events associated with EGDT (two pulmonary oedema and one arrhythmia) were reported as probably related to the intervention, compared with four (in three patients) serious adverse events (two pneumothoraces and one pulmonary oedema probably related, and one ventricular fibrillation definitely related) reported as associated with usual resuscitation.

TABLE 14 Serious adverse events within 30 days following randomisation

Serious adverse events	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)
Any serious adverse event, *n* (%)	30 (4.8)	26 (4.2)
Specified serious adverse events, *n* (%)		
Pneumothorax	0 (0.0)	4 (0.6)
Haemo-pneumothorax	0 (0.0)	0 (0.0)
Bleeding	2 (0.3)	2 (0.3)
Thrombosis	2 (0.3)	0 (0.0)
Pulmonary embolus	4 (0.6)	2 (0.3)
Vascular catheter infection	0 (0.0)	0 (0.0)
Pulmonary oedema	4 (0.6)	7 (1.1)
Blood transfusion reaction	0 (0.0)	1 (0.2)
Myocardial ischaemia	7 (1.1)	4 (0.6)
Peripheral ischaemia	0 (0.0)	1 (0.2)
Unspecified serious adverse events, *n* (%)		
Cardiac arrest	5 (0.8)	4 (0.6)
Cerebrovascular event	4 (0.6)	1 (0.2)
Arrhythmia	1 (0.2)	2 (0.3)
Other[a]	5 (0.8)	5 (0.8)

a Other serious adverse events (one patient each) were bronchopleural fistula; encephalitis; fresh blood in endotracheal tube; hospital-acquired pneumonia; hypernatremia; myocardial infarction; perforation of ischaemic ileum; requirement for emergency splenectomy; respiratory failure; worsening lactate; and deranged liver function tests.
Numbers do not add as some patients experienced more than one serious adverse event.

Subgroup analyses of the primary outcome

There was no difference in the effect of EGDT on the primary outcome of all-cause mortality at 90 days following randomisation according to the pre-specified subgroups defined by the degree of protocolised care/usual resuscitation, age, MEDS score, SOFA score and time from ED presentation to randomisation (*p*-values for test of interaction 0.39 to 0.72; *Figure 18*).

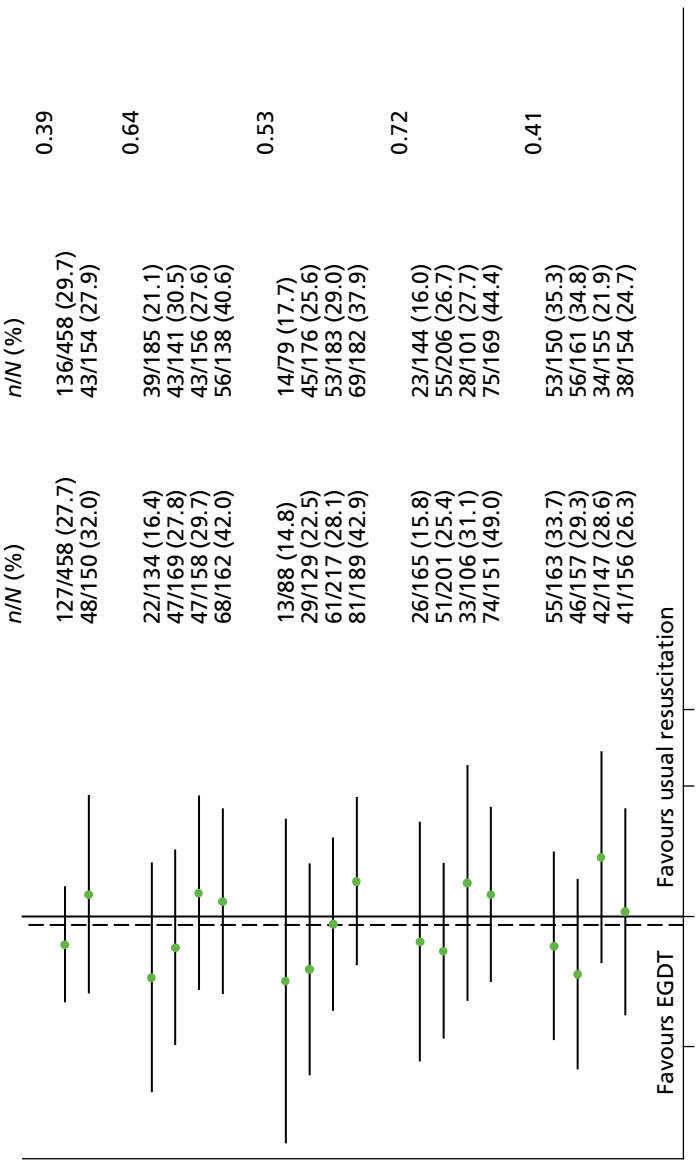

FIGURE 18 Subgroup analyses of the primary outcome. *p*-values are for tests of interaction. The *x*-axis is presented on a log scale. The solid line represents no difference between the groups and the dashed line represents the overall effect estimate (adjusted odds ratio).

Secondary analyses of the primary outcome

Eight patients were missing the primary outcome of all-cause mortality at 90 days following randomisation (two in the EGDT group and six in the usual-resuscitation group). The effect of missing data on the results was minimal. Sensitivity analyses making alternative extreme assumptions for the missing outcomes reported relative risks of 0.99 and 1.03 (*Table 15*). Although the learning curve analysis suggested increased odds of mortality for the first patient randomised to EGDT in each site, this effect was not significant ($p = 0.56$; *Figure 19* and see *Table 15*). Adjusting for non-adherence to the EGDT protocol resulted in minimal change to the relative risk (see *Table 15*).

TABLE 15 Secondary analyses of the primary outcome

Analysis	All-cause mortality at 90 days, *n*/*N* (%)			
	EGDT ($n = 625$)	Usual resuscitation ($n = 626$)	Incremental effect (95% CI)	*p*-value
Sensitivity analyses for missing data in the primary outcome				
EGDT survive, usual resuscitation die	184/625 (29.4)	187/626 (29.9)	0.99 (0.83 to 1.17)[a]	0.90
EGDT die, usual resuscitation survive	186/625 (29.8)	181/626 (28.9)	1.03 (0.87 to 1.22)[a]	0.76
Learning curve analysis				0.56[b]
Asymptotic adjusted odds ratio	–	–	0.89 (0.69 to 1.15)[c]	0.34
Adherence-adjusted analysis	–	–	1.02 (0.78 to 1.32)[a]	0.90

a Relative risk.
b *p*-value for test of nonlinearity (i.e. for presence of a learning-curve effect).
c Adjusted odds ratio.

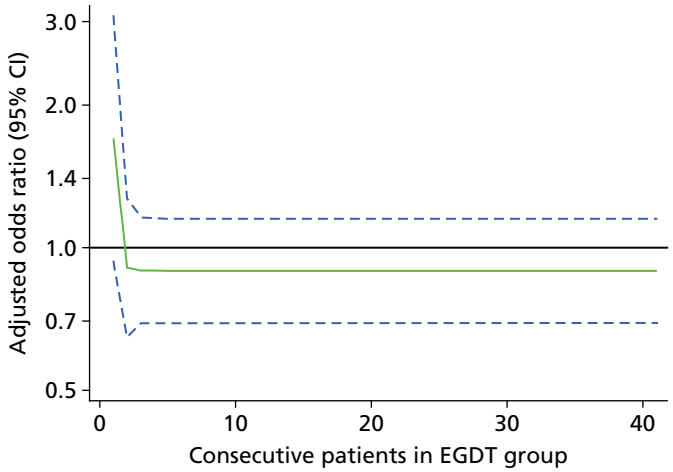

FIGURE 19 Learning curve for delivery of EGDT. The *y*-axis is presented on a log scale.

Comparison with other early goal-directed therapy studies

Comparing the usual-resuscitation group for ProMISe with that from the original randomised controlled trial of EGDT by Rivers *et al.*,[6] patients in ProMISe were randomised, on average, slightly later than those in the Rivers *et al.* trial (*Table 16*). Demographics were similar. Patients in ProMISe had slightly lower blood pressure, blood lactate measurements and APACHE II scores. Patients in the usual-resuscitation group in the Rivers *et al.*[6] trial received considerably more fluid and packed red blood cell transfusions, and were more likely to be mechanically ventilated; however, those in ProMISe received more vasopressors and dobutamine. Hospital mortality was substantially higher in the Rivers *et al.*[6] trial than in ProMISe.

Comparing the usual-resuscitation group for ProMISe with those from ProCESS[23] and ARISE,[24] time from ED presentation to randomisation was similar but patients in ProMISe had a shorter length of stay in the ED than those in ARISE (*Table 17*). Demographics were similar. The mean volume of fluid received prior to randomisation was higher for ARISE than for ProCESS or ProMISe. Blood pressure and blood lactate measurements were similar for ProMISe and ProCESS, but mean arterial pressure was slightly higher and blood lactate was slightly lower for ARISE. This lower severity of illness for patients in ARISE was also reflected in APACHE II scores, which were lowest for ARISE and highest for ProCESS. A greater proportion of patients in ProMISe met both the refractory hypotension and the hyperlactataemia inclusion criteria. To explore the hypothesis that the combination of both refractory hypotension and hyperlactataemia was associated with higher mortality than either alone, we examined data from the Case Mix Programme, the national clinical audit for adult critical care. Among 12,004 patients admitted to 183 adult general ICUs in

TABLE 16 Comparison of usual-resuscitation groups: Rivers *et al.*[6] and ProMISe

Characteristics	Rivers *et al.*[6]	ProMISe
Timing		
ED presentation to randomisation (hours), mean (SD)	1.5 (1.7)	2.8 (1.4)
Baseline characteristics		
Age (years), mean (SD)	64.4 (17.1)	64.3 (15.5)
Male (%)	50.4	58.6
SBP (mmHg), mean (SD)	109 (34)	97.0 (25.5)
MAP (mmHg), mean (SD)	76 (24)	64.7 (17.2)
Blood lactate concentration (mmol/l), mean (SD)	6.9 (4.5)	5.1 (3.5)
APACHE II score, mean (SD)	20.4 (7.4)	18.0 (7.1)
Interventions hour 0 to hour 6		
Total intravenous fluids (ml), mean (SD)	3499 (2438)	2022 (1271)
Vasopressors (%)	30.3	46.6
Packed red blood cell transfusion (%)	18.5	3.8
Dobutamine (%)	0.8	3.8
Mechanical ventilation (%)	53.8	19.0
Outcomes		
Hospital mortality (%)	46.5	24.6

MAP, mean arterial pressure; SBP, systolic blood pressure.

TABLE 17 Comparison of usual-resuscitation groups: ProCESS, ARISE and ProMISe

Characteristics	ProCESS[23]	ARISE[24]	ProMISe
Timing			
ED presentation to randomisation (hours), mean (SD)	3.0 (1.6)	–	2.8 (1.4)
ED presentation to randomisation (hours), median (IQR)	–	2.7 (2.0–3.9)	2.5 (1.8–3.5)
ED length of stay (hours), median (IQR)	–	2.0 (1.0–3.8)	1.3 (0.4–2.9)
Baseline characteristics			
Age (years), mean (SD)	62.0 (16.0)	63.1 (16.5)	64.3 (15.5)
Male (%)	57.9	59.3	58.6
Pre-randomisation fluids[a] (l), mean (SD)	2.1 (1.4)	2.6 (1.3)	2.0 (1.1)
SBP (mmHg), mean (SD)	99.9 (29.5)	–	97.0 (25.5)
MAP (mmHg), mean (SD)	64.7 (15.6)	70.5 (16.0)	64.7 (17.2)
Blood lactate concentration (mmol/l), mean (SD)	4.9 (3.1)	4.2 (2.8)	5.1 (3.5)
Refractory hypotension only (%)	39.3	53.5	36.3
Hyperlactataemia only (%)	46.7	30.2	44.4
Both refractory hypotension and hyperlactataemia (%)	14.0	16.3	19.3
APACHE II score, mean (SD)	20.7 (7.5)	15.8 (6.5)	18.0 (7.1)
Interventions hour 0 to hour 6			
Intravenous fluids[b] (ml), mean (SD)	2279 (1881)	1713 (1401)	2022 (1271)
Vasopressors[c] (%)	44.1	57.8	46.6
Dobutamine (%)	0.9	2.6	3.8
Packed red blood cell transfusion (%)	7.5	7.0	3.8
Mechanical ventilation[d] (%)	21.7	22.4	19.0
CVC insertion[e] (%)	57.9	61.9	50.9
Outcomes			
Hospital mortality (%)	–	15.7	24.6
Discharge home[f] (%)	51.5	79.6	82.2
28-day mortality (%)	–	15.9	24.5
90-day mortality (%)	33.7	18.8	29.2

CVC, central venous catheter; MAP, mean arterial pressure; SBP, systolic blood pressure.
a ProMISe includes intravenous crystalloid and colloid administration > 20 ml and all blood product administration; ProCESS includes intravenous crystalloid, colloid and blood product administration.
b ProMISe and ARISE include intravenous crystalloid and colloid administration > 20 ml.
c ARISE includes vasopressor infusion at any dose for ≥ 30 minutes.
d ProCESS includes mechanical ventilation from ED presentation.
e ProCESS and ARISE include CVC insertion from ED presentation.
f ProCESS discharge home is reported at 60 days (two patients remained in hospital).

England between February 2011 and June 2014 (the recruitment period of ProMISe) direct from the ED with infection, meeting two or more SIRS criteria during the first 24 hours following admission, and with hypotension (lowest systolic blood pressure < 90 mmHg) and/or hyperlactataemia (highest blood lactate ≥ 4 mmol/l), acute hospital mortality was around 30% for patients meeting a single criterion but almost double for patients meeting both the refractory hypotension and the hyperlactataemia criteria (*Table 18*).

During the intervention period, the mean volume of fluid received by patients in the usual-resuscitation group was highest for ProCESS and lowest for ARISE (see *Table 17*); however, a greater proportion of patients in ARISE received vasopressors. Dobutamine use was highest in ProMISe and lowest in ProCESS and the proportions of usual-resuscitation group patients receiving packed red blood cell transfusions in ProCESS and ARISE were approximately double that in ProMISe. In all three trials, around 20% of patients received mechanical ventilation, and the central venous catheter insertion rates varied from 51% in ProMISe to 62% in ARISE. Reflecting the pattern seen in severity of illness scores, 90-day mortality for usual-resuscitation group patients in ProCESS was slightly higher than in ProMISe (34% vs. 29%), whereas for those in ARISE it was substantially lower (19%). Mortality in ARISE was similarly lower at other comparable time points. Of patients discharged alive from hospital in both ProMISe and ARISE, approximately 80% were discharged home, compared with only just over 50% of similar patients in ProCESS.

TABLE 18 Acute hospital mortality for patients admitted to ICU from the ED with severe sepsis and refractory hypotension and/or hyperlactataemia

Criteria met	Admissions, *n* (%)	Acute hospital mortality, *n* (%)
Refractory hypotension only	2186 (18.2)	687 (31.4)
Hyperlactataemia only	5339 (44.5)	1397 (26.2)
Both refractory hypotension and hyperlactataemia	4479 (37.3)	2485 (55.5)

Based on 12,004 patients admitted to 183 adult general ICUs in England participating in the Case Mix Programme between February 2011 and June 2014.

Chapter 5 Results: cost-effectiveness

Cost-effectiveness at 90 days following randomisation

Resource use up to 90 days

The average duration for the delivery of the EGDT protocol for the EGDT group was 5.8 hours in total, of which 2.0 were in the ED. The delivery of the EGDT protocol used resources specific to the intervention with respect to catheter insertion (PreSep™ central venous oximetry catheter and arterial catheter), packed red blood cell transfusion, infusion of dobutamine and additional staff time required to implement the protocol in the ED (*Table 19*). For the index hospital episode, the mean length of stay in critical care and

TABLE 19 Resource use up to 90 days following randomisation

Resource use up to 90 days	EGDT ($n = 625$)	Usual resuscitation ($n = 626$)
Interventions[a]		
PreSep™ central venous oximetry catheter, *n* (%)	545 (87)	2 (0)
Standard CVC, *n* (%)	48 (8)	316 (50)
Arterial catheter, *n* (%)	462 (74)	389 (62)
Blood products		
Packed red blood cells (ml)	97 (267)	70 (262)
Platelets (ml)	16 (82)	15 (79)
Fresh-frozen plasma (ml)	58 (275)	59 (264)
Dobutamine total dose (mg)	183 (592)	88 (489)
Duration of protocol delivered in ED (hours)	2.0 (1.9)	–
Duration of protocol delivered in total (hours)	5.8 (0.8)	–
Additional staff time		
Catheter insertion and monitor set-up (hours)	1.2 (0.3)	0.5 (0.4)
Monitoring (hours)	0.3 (0.3)	–
Training (hours)	0.3 (0)	–
Acute hospital length of stay *Index hospital admission*[a]		
Length of stay in ED (hours)	2.3 (3.2)	1.9 (2.1)
Length of stay in critical care (days)	4.9 (7.8)	4.7 (8.9)
Length of stay on general medical ward (days)	10.5 (15.0)	9.6 (13.5)
Acute hospital readmissions,[b] *n* (%)	28 (4)	30 (5)
Length of stay in critical care (days)	0.3 (2.5)	0.4 (3.2)
Length of stay on general medical ward (days)	0.7 (4.2)	0.7 (4.5)
Total acute hospital length of stay up to 90 days	16.7 (19.2)	15.5 (17.8)

CVC, central venous catheter.
a Source: ProMISe data set.
b Source: Case Mix Programme database.[32]
Values are mean (SD), unless stated otherwise.

on general medical wards was higher in the EGDT group than the usual-resuscitation group. The proportion of patients who were readmitted and the mean length of stay following readmission were similar between the treatment groups (see *Table 19*). The mean total length of stay in acute hospital up to 90 days following randomisation was 16.7 days in the EGDT group versus 15.5 days in the usual-resuscitation group.

Table 20 summarises the resource use reported from responses to the Health Services Questionnaire administered at 90 days following randomisation for all patients randomised to each treatment group. The mean number of inpatient days reported from admissions other than those involving critical care was 4.6 days for the EGDT group and 3.8 days for the usual-resuscitation group. The mean numbers of outpatient visits and community care contacts up to 90 days were similar between the groups. Patients in both groups reported low use of community health services over the 90 days following randomisation.

Total costs up to 90 days

The net effect of the higher average length of stay in critical care and on general medical wards was that the EGDT group had higher mean total costs per patient than the usual-resuscitation group (*Table 21*). At 90 days, the mean total costs per patient were £12,414 for the EGDT group and £11,424 for the usual-resuscitation group.

TABLE 20 Resource use from the Health Services Questionnaire between discharge from hospital and 90 days following randomisation

Resource use	EGDT ($N = 625$), mean (SD)	Usual resuscitation ($N = 626$), mean (SD)
Inpatient days (general medical)	4.6 (8.5)	3.8 (7.0)
Outpatient visits	0.9 (2.6)	1.1 (2.4)
GP contacts	1.2 (2.4)	1.1 (2.3)
Nurse contacts	0.7 (2.0)	0.7 (2.0)
Occupational therapist contacts	0.2 (1.4)	0.3 (2.2)
Health visitor contacts	0.2 (1.6)	0.4 (2.4)
Clinical psychologist contacts	0.02 (0.2)	0.01 (0.3)
Speech therapist contacts	0.01 (0.3)	0.04 (2.7)
Physiotherapist contacts	0.4 (2.3)	0.4 (2.7)
Dietitian contacts	0.1 (0.9)	0.1 (0.5)

GP, general practitioner.
For patients with missing values who were known to be alive at 90 days, we applied imputed means for each item of resource use.

TABLE 21 Costs (£) up to 90 days following randomisation

Resource use categories	EGDT ($N = 625$), mean (SD)	Usual resuscitation ($N = 626$), mean (SD)
Intervention[a]		
Monitor and consumables	206 (70)	33 (26)
Blood products	83 (208)	66 (207)
Drugs (dobutamine)	8 (24)	4 (19)
Additional staff time costs		
Catheter insertion and monitor set-up	64 (18)	29 (21)
Monitoring	16 (16)	–
Training	17 (0)	–
Hospital costs *Index hospital admission*[a]		
ED	62 (85)	53 (56)
Critical care	7255 (12,045)	6852 (13,529)
General medical ward	2788 (3983)	2532 (3586)
Readmission costs		
Critical care[b]	467 (3577)	626 (4500)
General medical[b,c]	196 (1132)	178 (1187)
Outpatient and community costs[c,d]	1252 (2848)	1051 (2660)
Total costs up to 90 days[d]	12,414 (14,970)	11,424 (15,727)

a Source: ProMISe data set.
b Source: Case Mix Programme database.[32]
c Source: Health Services Questionnaire.
d Results reported after applying multiple imputation to handle missing data.

Health-related quality of life at 90 days

The distribution of responses to each dimension of the EQ-5D questionnaires, administered at 90 days following randomisation, is reported by treatment group in *Table 22*. The distribution of responses was similar between the groups. The resultant mean EQ-5D utility scores and QALYs were also similar between the treatment groups (*Table 23*).

Cost-effectiveness at 90 days

The incremental QALY gain for EGDT versus usual resuscitation was negative, but with 95% CIs that included zero (see *Table 23*). The average costs were higher for the EGDT group, but this difference was not statistically significant. The INB for EGDT versus usual resuscitation was negative at −£1000 (95% CI −£2720 to £720; see *Table 23*).

When the uncertainty in the incremental costs and QALYs is represented on the cost-effectiveness plane, the majority of the points are in those quadrants that show EGDT has, on average, higher costs (*Figure 20*). The probability that EGDT is more cost-effective than usual resuscitation, given the data, is never greater than 20%, irrespective of how much society is willing to pay for a QALY gain (*Figure 21*).

TABLE 22 Health-related quality of life (EQ-5D-5L) responses for patients who were alive and fully completed the questionnaire at 90 days following randomisation

EQ-5D-5L dimension	EGDT ($N = 339$[a]), *n* (%)	Usual resuscitation ($N = 332$[a]), *n* (%)
Mobility		
No problems	101 (30)	102 (31)
Slight problems	44 (13)	51 (15)
Moderate problems	86 (25)	71 (21)
Severe problems	75 (22)	74 (22)
Extreme problems	33 (10)	34 (10)
Self-care		
No problems	173 (51)	171 (52)
Slight problems	44 (13)	40 (12)
Moderate problems	68 (20)	71 (21)
Severe problems	30 (9)	25 (8)
Extreme problems	24 (7)	25 (8)
Usual activities		
No problems	81 (24)	87 (26)
Slight problems	61 (18)	62 (19)
Moderate problems	83 (24)	82 (25)
Severe problems	62 (18)	51 (15)
Extreme problems	52 (15)	50 (15)
Pain/discomfort		
No problems	93 (27)	95 (29)
Slight problems	91 (27)	81 (24)
Moderate problems	81 (24)	89 (27)
Severe problems	50 (15)	53 (16)
Extreme problems	24 (7)	14 (4)
Anxiety/depression		
No problems	152 (45)	146 (44)
Slight problems	74 (22)	79 (24)
Moderate problems	72 (21)	70 (21)
Severe problems	23 (7)	22 (7)
Extreme problems	18 (5)	15 (5)

a Results are presented for patients with complete information; the numbers of complete responses/eligible patients at 90 days are as follows: EGDT 339/441 (77%), usual resuscitation 332/445 (75%).

TABLE 23 Cost-effectiveness at 90 days

End point	EGDT ($n = 625$), mean (SD)	Usual resuscitation ($n = 626$), mean (SD)	Incremental effect (unadjusted), mean (95% CI)	*p*-value
EQ-5D-5L utility score (survivors)	0.609 (0.319)	0.613 (0.312)	−0.004 (−0.051 to 0.044)	0.88
QALYs	0.054 (0.048)	0.054 (0.048)	−0.001 (−0.006 to 0.005)	0.85
Costs (£)	12,414 (14,970)	11,424 (15,727)	989 (−726 to 2705)	0.26
Incremental net benefit (£)[a]			−1000 (−2720 to 720)	0.25

Results are reported after applying multiple imputation to handle missing data.
a Incremental net benefit is calculated, according to NICE methods guidance, by multiplying the mean QALY gain (or loss) by £20,000, and subtracting from this the incremental cost.

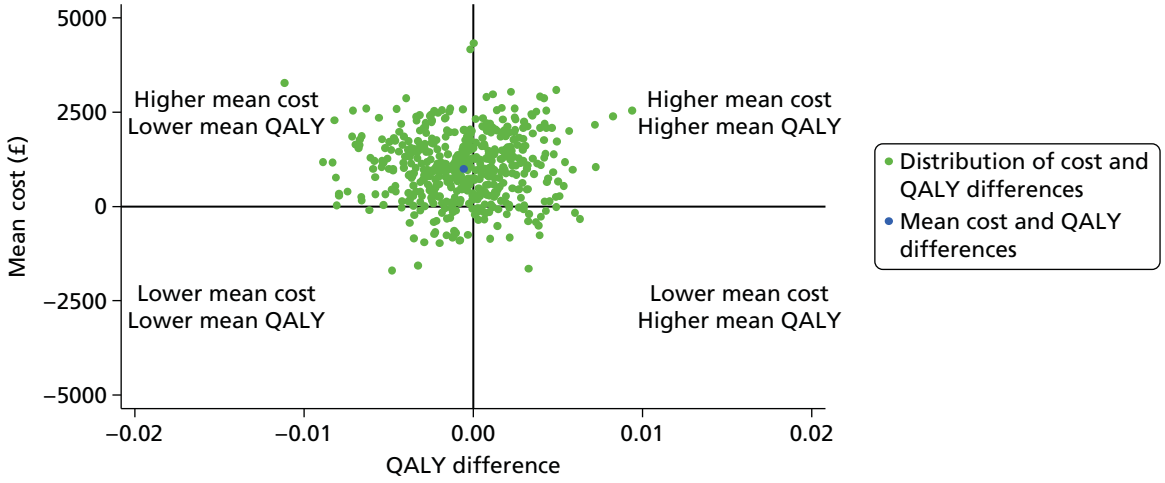

FIGURE 20 Uncertainty in the mean costs (£) and QALY differences at 90 days and their distribution for EGDT vs. usual resuscitation.

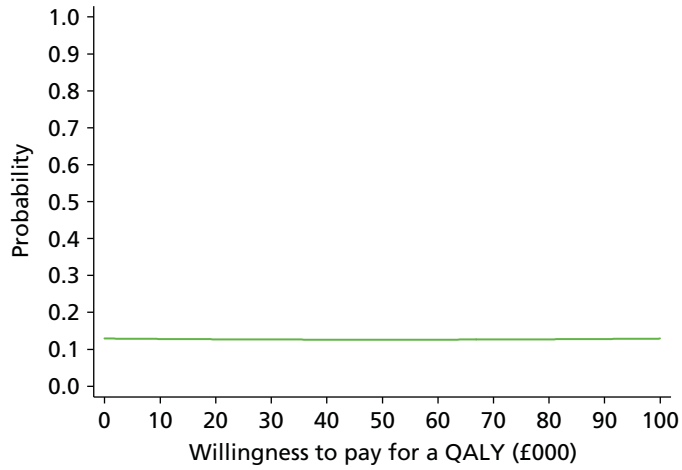

FIGURE 21 Cost-effectiveness acceptability curve reporting the probability that EGDT is cost-effective at 90 days at alternative willingness to pay.

The estimated INB were similar for the scenarios considered in the sensitivity analyses (*Figure 22*). For example, the INB remains around −£1000 whether EGDT is provided in the ED or in critical care. Similarly, excluding readmissions that were reported from responses to the Health Services Questionnaire, to avoid any risk of double counting, had only a small impact on the mean INB (−£800 vs. −£1000).

The results of the subgroup analyses are presented in *Table 24*, and show that the incremental QALYs were similar across all subgroups. Although there were some subgroups for which the incremental costs of EGDT were negative and hence the INBs were positive, the statistical uncertainty surrounding these findings was high. Hence for each subgroup, as for the overall results, the 95% CIs around the INB included zero. Adjusting for adherence to the EGDT protocol decreased the INB to −£1438, but the 95% CI still included zero (see *Table 24*).

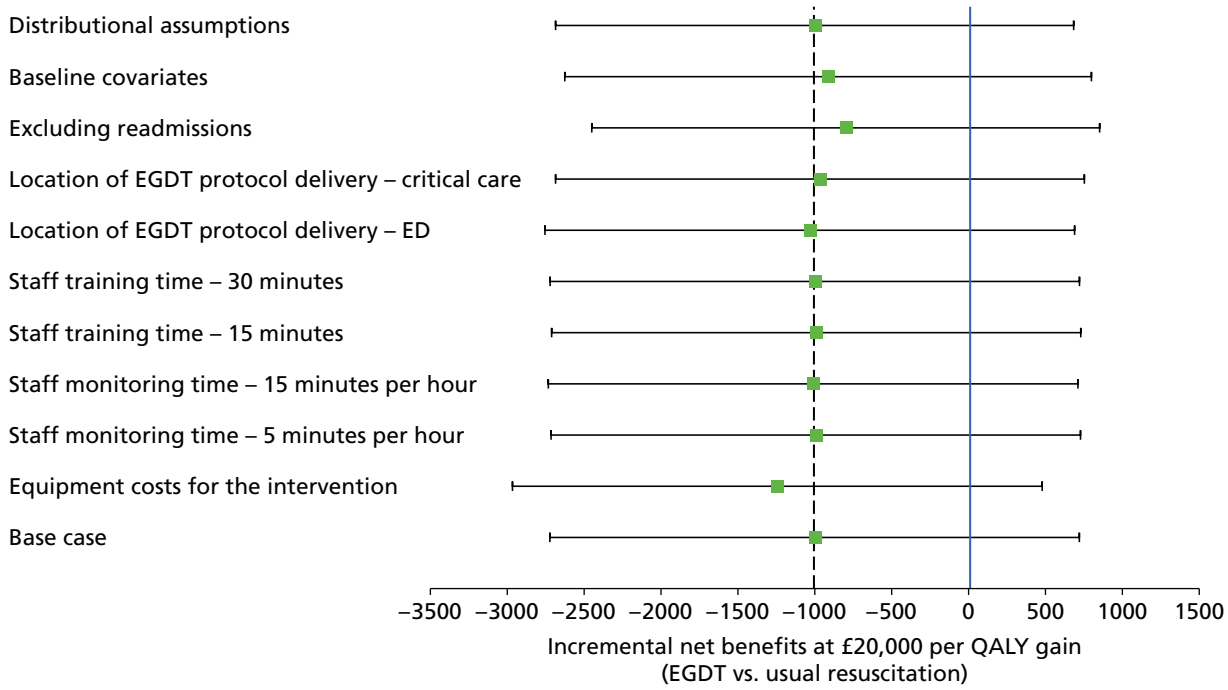

FIGURE 22 Sensitivity analyses for the incremental net benefit at 90 days following randomisation according to alternative assumptions, compared with the base case. The vertical dashed line indicates incremental net benefit in the base-case analysis. The solid vertical line indicates no difference in net monetary benefits between the treatment groups.

TABLE 24 Cost-effectiveness at 90 days: subgroup and secondary analyses

Subgroup	Incremental cost (£) (95% CI)	Incremental QALYs (95% CI)	Incremental net benefit (£) (95% CI)
Degree of protocolised resuscitation in usual-resuscitation group			
Low	806 (–1213 to 2825)	0.002 (–0.004 to 0.009)	–765 (–2789 to 1259)
High	1655 (–1822 to 5131)	–0.005 (–0.017 to 0.006)	–1764 (–5247 to 1719)
Age (years)			
18–56	3253 (–155 to 6662)	–0.001 (–0.012 to 0.011)	–3265 (–6684 to 154)
57–67	398 (–3021 to 3818)	0.003 (–0.008 to 0.014)	–329 (–3758 to 3100)
68–77	–1511 (–4884 to 1862)	–0.003 (–0.015 to 0.008)	1444 (–1943 to 4831)
78–95	2359 (–1112 to 5830)	0.003 (–0.008 to 0.015)	–2296 (–5777 to 1185)
MEDS score			
0–4	2129 (–2644 to 6902)	0.002 (–0.014 to 0.018)	–2089 (–6864 to 2686)
5–6	2700 (–815 to 6215)	0.002 (–0.009 to 0.014)	–2652 (–6173 to 869)
7–9	–250 (–3308 to 2807)	0.005 (–0.005 to 0.015)	351 (–2715 to 3417)
10–20	196 (–2934 to 3326)	–0.009 (–0.019 to 0.001)	–377 (–3514 to 2760)
SOFA score			
0–2	1947 (–1482 to 5375)	0.002 (–0.009 to 0.014)	–1898 (–5327 to 1531)
3–4	623 (–2351 to 3598)	0.001 (–0.009 to 0.011)	–603 (–3580 to 2374)
5	–1506 (–5705 to 2692)	–0.007 (–0.021 to 0.006)	1359 (–2848 to 5566)
6–14	2658 (–701 to 6016)	–0.004 (–0.014 to 0.007)	–2736 (–6099 to 627)
Time from ED presentation to randomisation (hours)			
0.2–1.8	1291 (–2114 to 4697)	–0.002 (–0.013 to 0.009)	–1322 (–4734 to 2090)
1.8–2.5	2849 (–515 to 6214)	0.004 (–0.007 to 0.015)	–2776 (–6147 to 595)
2.5–3.5	1123 (–2344 to 4590)	–0.003 (–0.014 to 0.009)	–1179 (–4655 to 2297)
3.5 +	–1453 (–4882 to 1976)	–0.001 (–0.012 to 0.01)	1426 (–2008 to 4860)
Adherence adjusted analysis	1423 (–1042 to 3888)	–0.001 (–0.009 to 0.007)	–1438 (–3909 to 1033)

Cost-effectiveness at 1 year following randomisation (primary outcome)

Resource use up to 1 year

Acute hospital length of stay up to 1 year following randomisation is presented in *Table 25*. A higher proportion of patients in the EGDT group had an index hospital admission or readmission that continued beyond day 90. Between 90 days and 1 year following randomisation, the mean number of days in critical care, on general medical wards and in total was lower for the EGDT group than for the usual-resuscitation group. The mean total acute hospital length of stay up to 1 year following randomisation was 18.7 days in the EGDT group, compared with 18.2 days in the usual-resuscitation group.

Table 26 reports results from responses to the Health Services Questionnaire administered at 1 year following randomisation, concerning resource use between 90 days and 1 year. The mean number of inpatient days reported from admissions other than those involving critical care was 6.3 days for the EGDT

TABLE 25 Acute hospital length of stay up to 1 year following randomisation

Acute hospital length of stay up to 1 year	EGDT ($N = 625$)	Usual resuscitation ($N = 626$)
Total acute hospital length of stay up to 90 days[a,b]	16.7 (19.2)	15.5 (17.8)
Acute hospital length of stay 90 days to 1 year		
Continuing index hospital admission,[a] *n* (%)	13 (2.1)	9 (1.4)
Length of stay in critical care (days)	0 (0)	0.01 (0.1)
Length of stay on general medical ward (days)	0.5 (5.6)	0.6 (10.0)
Acute hospital readmissions,[b] *n* (%)	40 (6.4)	46 (7.3)
Length of stay in critical care[c] (days)	0.2 (1.5)	0.3 (2.0)
Length of stay on general medical ward[c] (days)	1.3 (6.6)	1.8 (10.3)
Total acute hospital length of stay up to 1 year	18.7 (24.5)	18.2 (26.8)

Values are mean (SD), unless stated otherwise.
a Source: ProMISe data set.
b Source: Case Mix Programme database.[32]
c Results reported after applying multiple imputation to handle missing data.

TABLE 26 Resource use from the Health Services Questionnaire between 90 days and 1 year following randomisation

Resource use	EGDT ($n = 625$), mean (SD)	Usual resuscitation ($n = 626$), mean (SD)
Inpatient days (general medical)	6.3 (9.0)	6.6 (11.9)
Outpatient visits	1.6 (3.7)	1.8 (4.5)
GP contacts	1.7 (3.3)	1.6 (3.4)
Nurse contacts	1.5 (4.1)	1.7 (4.8)
Occupational therapist contacts	0.2 (1.0)	0.3 (1.2)
Health visitor contacts	0.3 (4.1)	0.2 (1.6)
Clinical psychologist contacts	0.03 (0.3)	0.04 (0.4)
Speech therapist contacts	0.05 (0.6)	0.05 (0.5)
Physiotherapist contacts	0.4 (2.0)	0.6 (3.2)
Dietitian contacts	0.1 (0.7)	0.2 (1.1)

GP, general practitioner.
For patients with missing values who were known to be alive at 1 year, we applied imputed means for each item of resource use.

group and 6.6 days for the usual-resuscitation group. The mean numbers of outpatient visits and community care contacts between 90 days and 1 year were similar between the groups. Overall, both groups reported low use of community health services over 1 year following randomisation.

Total costs up to 1 year

Table 27 reports the total costs up to 1 year following randomisation, across all of the resource use items recorded. At 1 year, the mean total costs per patient were £15,139 for the EGDT group and £14,375 for the usual-resuscitation group.

Health-related quality of life at 1 year

The distribution of responses to each dimension of the EQ-5D questionnaires, administered at 1 year following randomisation, is reported by treatment group in *Table 28*. At 1 year, a lower proportion of patients in the EGDT group than in the usual-resuscitation group reported 'no problems' for each dimension of the EQ-5D, with a higher proportion of patients in the EGDT group reporting 'severe problems' or 'extreme problems' for each dimension of health. The mean EQ-5D utility score of those patients who were alive at 1 year post randomisation was higher in the usual-resuscitation group (0.653) than in the EGDT group (0.620; *Table 29*).

Cost-effectiveness at 1 year

At 1 year following randomisation, a slightly higher proportion of patients in the EGDT group were alive than in the usual-resuscitation group (see *Secondary outcomes: clinical effectiveness*). The net effect of the EGDT group having higher survival but a lower average EQ-5D utility score resulted in similar 1-year QALYs between the treatment groups (see *Table 29*). The mean total cost was higher in the EGDT group, with an incremental cost of £764 (95% CI −£1402 to £2930). Hence the INB for EGDT versus usual resuscitation was negative at −£725 (95% CI −£3000 to £1550). The distribution of incremental costs and QALYs in the cost-effectiveness plane is shown in *Figure 23*.

TABLE 27 Costs (£) up to 1 year following randomisation

Resource use categories	EGDT ($n = 625$), mean (SD)	Usual resuscitation ($n = 626$), mean (SD)
Total costs up to 90 days[a,b,c,d]	12,414 (14,970)	11,424 (15,727)
Hospital costs 90 days to 1 year *Continuing index hospital admission*[a]		
Critical care	0 (0)	15 (281)
General medical ward	144 (1471)	148 (2666)
Acute hospital readmissions		
Critical care[b]	607 (2233)	575 (2678)
General medical ward[b,c]	340 (1740)	490 (2727)
Outpatient and community costs[c,d]	1634 (3546)	1722 (4406)
Total costs up to 1 year[d]	15,139 (18,345)	14,375 (19,179)

a Source: ProMISe data set.
b Source: Case Mix Programme database.[32]
c Source: Health Services Questionnaire.
d Results reported after applying multiple imputation to handle missing data.

TABLE 28 Health-related quality of life (EQ-5D-5L) responses for patients that were alive and fully completed the questionnaire at 1 year following randomisation

EQ-5D-5L dimension	EGDT ($N = 244$[a]), *n* (%)	Usual resuscitation ($N = 236$[a]), *n* (%)
Mobility		
No problems	65 (26.6)	81 (34.3)
Slight problems	40 (16.4)	38 (16.1)
Moderate problems	69 (28.3)	47 (19.9)
Severe problems	49 (20.1)	55 (23.3)
Extreme problems	21 (8.6)	15 (6.4)
Self-care		
No problems	124 (50.8)	141 (59.8)
Slight problems	33 (13.5)	27 (11.4)
Moderate problems	49 (20.1)	38 (16.1)
Severe problems	21 (8.6)	22 (9.3)
Extreme problems	17 (7.0)	8 (3.4)
Usual activities		
No problems	69 (28.3)	88 (37.3)
Slight problems	49 (20.1)	42 (17.8)
Moderate problems	55 (22.5)	50 (21.2)
Severe problems	46 (18.9)	39 (16.5)
Extreme problems	25 (10.3)	17 (7.2)
Pain/discomfort		
No problems	71 (29.1)	81 (34.3)
Slight problems	50 (20.5)	45 (19.1)
Moderate problems	71 (29.1)	57 (24.2)
Severe problems	41 (16.8)	43 (18.2)
Extreme problems	11 (4.5)	10 (4.2)
Anxiety/depression		
No problems	104 (42.6)	120 (50.9)
Slight problems	57 (23.4)	50 (21.2)
Moderate problems	55 (22.5)	39 (16.5)
Severe problems	19 (7.8)	22 (9.3)
Extreme problems	9 (3.7)	5 (2.1)

a Results are presented for patients with complete information; the numbers of complete responses/eligible patients at 1 year are as follows: EGDT 244/334 (73%), usual resuscitation 236/325 (73%).

TABLE 29 Cost-effectiveness at 1 year (primary outcome)

End point	EGDT ($n = 625$)	Usual resuscitation ($n = 626$)	Incremental effect (unadjusted), mean (95% CI)	*p*-value
EQ-5D-5L utility score (survivors)	0.620 (0.307)	0.653 (0.323)	–0.032 (–0.085 to 0.020)	0.23
QALYs	0.352 (0.323)	0.351 (0.329)	0.002 (–0.036 to 0.040)	0.92
Costs (£)	15,139 (18,345)	14,375 (19,179)	764 (–1402 to 2930)	0.49
Incremental net benefit (£)[a]			–725 (–3000 to 1550)	0.53

a Incremental net benefit is calculated, according to NICE methods guidance, by multiplying the mean QALY gain (or loss) by £20,000, and subtracting from this the incremental cost.
Values are mean (SD), unless stated otherwise. Results are reported after applying multiple imputation to handle missing data.

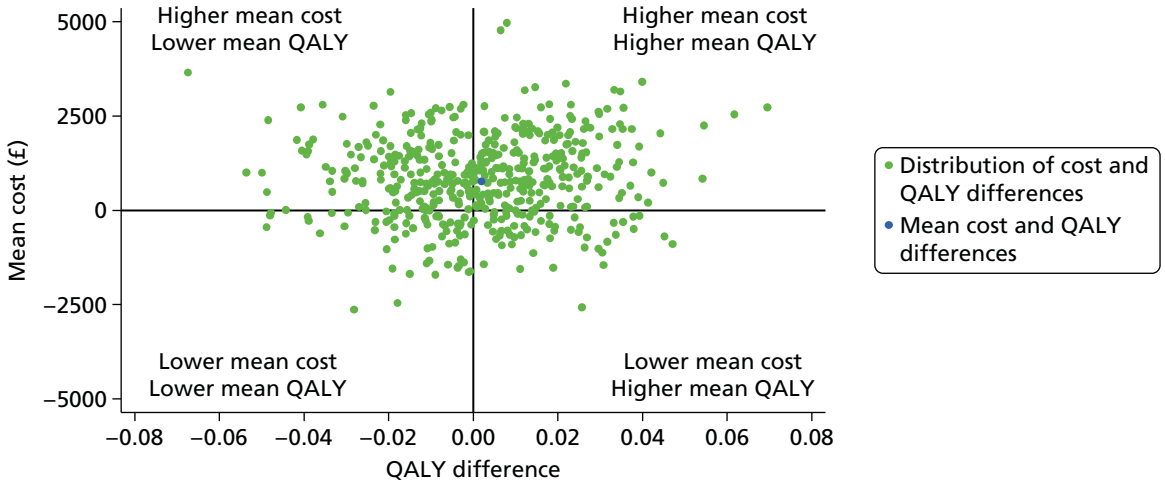

FIGURE 23 Uncertainty in the mean costs (£) and QALY differences at 1 year and their distribution for EGDT vs. usual resuscitation.

The cost-effectiveness acceptability curve (*Figure 24*) shows that at 1 year the probability that EGDT is more cost-effective than usual resuscitation, given the data, is below 30% at the £20,000 willingness-to-pay threshold stipulated by NICE.

The estimated INBs were similar for the scenarios considered in the sensitivity analyses (*Figure 25*). This shows that the base-case results are robust to alternative assumptions.

The estimated INBs were similar across all pre-specified subgroups (*Table 30*). Although there were some subgroups for whom EGDT was cost-saving and hence their INBs were positive, there was high statistical uncertainty around surrounding these findings. Hence for each subgroup, as for the overall results, there is high statistical uncertainty surrounding INBs.

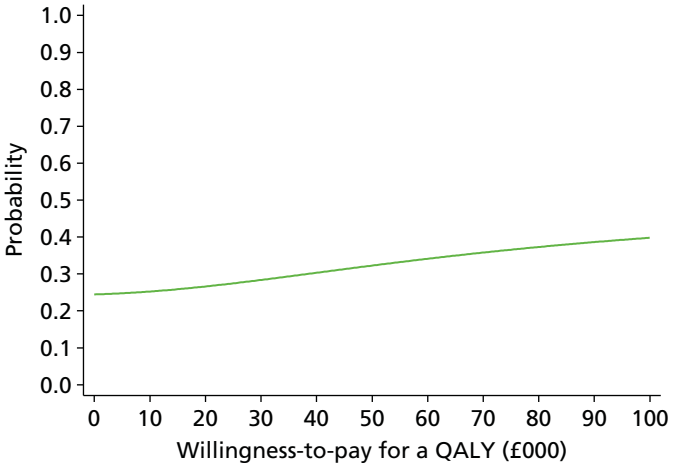

FIGURE 24 Cost-effectiveness acceptability curve reporting the probability that EGDT is cost-effective at 1 year at alternative levels of willingness to pay.

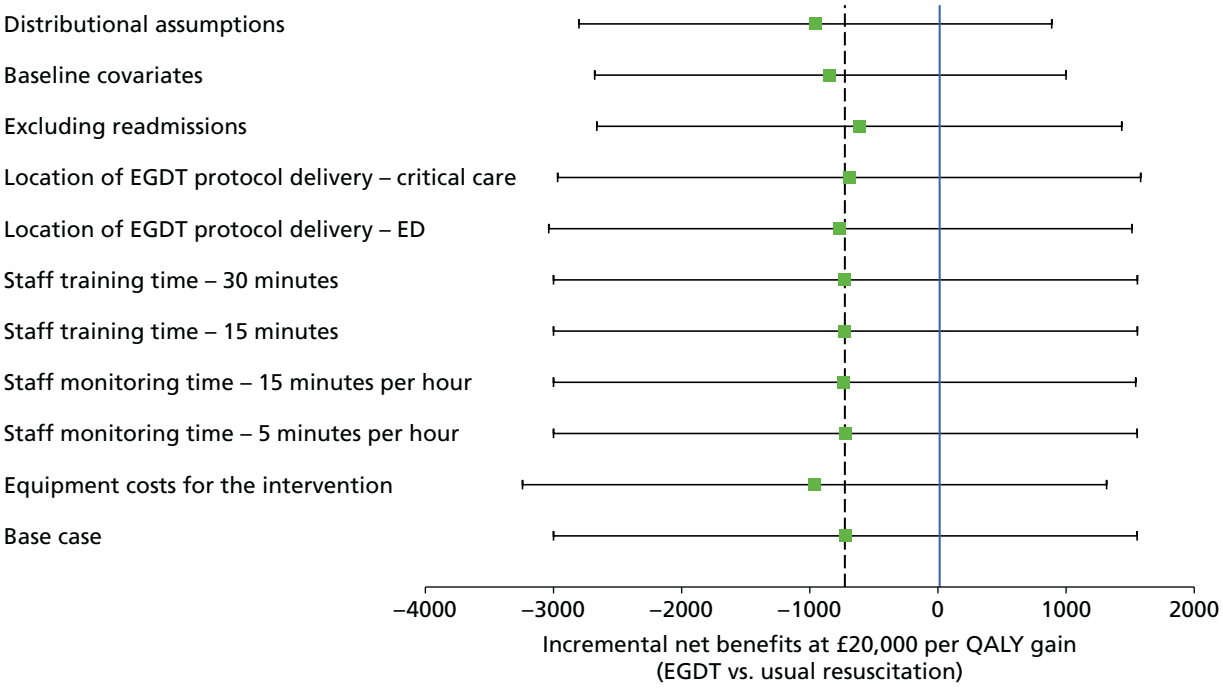

FIGURE 25 Sensitivity analyses for the incremental net benefit at 1 year following randomisation according to alternative assumptions, compared with the base case. The vertical dashed line indicates incremental net benefit in the base-case analysis. The solid vertical line indicates no difference in net monetary benefits between the treatment groups.

TABLE 30 Cost-effectiveness at 1 year: subgroup and secondary analyses

Subgroup	Incremental cost (£) (95% CI)	Incremental QALYs (95% CI)	Incremental net benefit (£) (95% CI)
Degree of protocolised resuscitation in usual-resuscitation group			
Low	801 (–1718 to 3319)	0.014 (–0.03 to 0.058)	–525 (–3172 to 2122)
High	739 (–3562 to 5040)	–0.017 (–0.093 to 0.059)	–1084 (–5578 to 3410)
Age (years)			
18–56	3643 (–626 to 7913)	0.011 (–0.064 to 0.086)	–3422 (–7932 to 1088)
57–67	257 (–3977 to 4490)	0.025 (–0.049 to 0.098)	238 (–4234 to 4710)
68–77	–1924 (–6101 to 2252)	–0.028 (–0.104 to 0.047)	1357 (–3042 to 5756)
78–95	2038 (–2227 to 6302)	0.041 (–0.035 to 0.116)	–1226 (–5720 to 3268)
MEDS score			
0–4	1972 (–3966 to 7909)	0.015 (–0.088 to 0.118)	–1670 (–7866 to 4526)
5–6	2401 (–1931 to 6733)	0.008 (–0.068 to 0.084)	–2241 (–6789 to 2307)
7–9	–909 (–4684 to 2866)	0.045 (–0.022 to 0.112)	1806 (–2160 to 5772)
10–20	615 (–3305 to 4534)	–0.047 (–0.114 to 0.021)	–1551 (–5636 to 2534)
SOFA score			
0–2	1579 (–2755 to 5913)	0.020 (–0.055 to 0.095)	–1183 (–5694 to 3328)
3–4	696 (–3033 to 4425)	0.007 (–0.059 to 0.072)	–566 (–4450 to 3318)
5	–2836 (–8057 to 2384)	–0.036 (–0.127 to 0.056)	2118 (–3332 to 7568)
6–14	2769 (–1401 to 6939)	–0.016 (–0.087 to 0.055)	–3097 (–7446 to 1252)
Time from ED presentation to randomisation (hours)			
0.2–1.8	1739 (–2507 to 5985)	–0.010 (–0.085 to 0.065)	–1940 (–6387 to 2507)
1.8–2.5	3576 (–633 to 7786)	0.032 (–0.043 to 0.107)	–2934 (–7350 to 1482)
2.5–3.5	1111 (–3225 to 5446)	–0.005 (–0.082 to 0.071)	–1215 (–5785 to 3355)
3.5 +	–3535 (–7762 to 692)	–0.007 (–0.083 to 0.068)	3388 (–1037 to 7813)
Adherence adjusted analysis	1099 (–2013 to 4211)	0.003 (–0.051 to 0.057)	–1042 (–4312 to 2228)

Lifetime incremental cost-effectiveness

Long-term survival

The Kaplan–Meier survival curves show that when the time horizon was extended beyond 1 year, for those with survival data available, the probability of survival remained similar between treatment groups (*Figure 26*).

To calculate QALYs over 20 years, the long-term survival for each patient was estimated by combining the observed survival for each patient up to 1 year with their predicted survival from 1 year to 20 years. We compared alternative parametric extrapolation approaches to predict longer-term survival of patients recruited to ProMISe. *Figure 27* considers alternative parametric extrapolations for survival, using the observed survival data after day 30. The survival data were pooled across the treatment groups, given that there was no evidence of an effect of treatment group on survival. Of the alternative survival functions, log-normal appeared to fit the observed data best in that it reported the lowest Akaike information criteria and Bayesian information criteria (*Table 31*). However, the Gompertz function offered the most plausible projections of future survival (see *Figure 27* and *Table 31*), in that the levels of survival remained constant

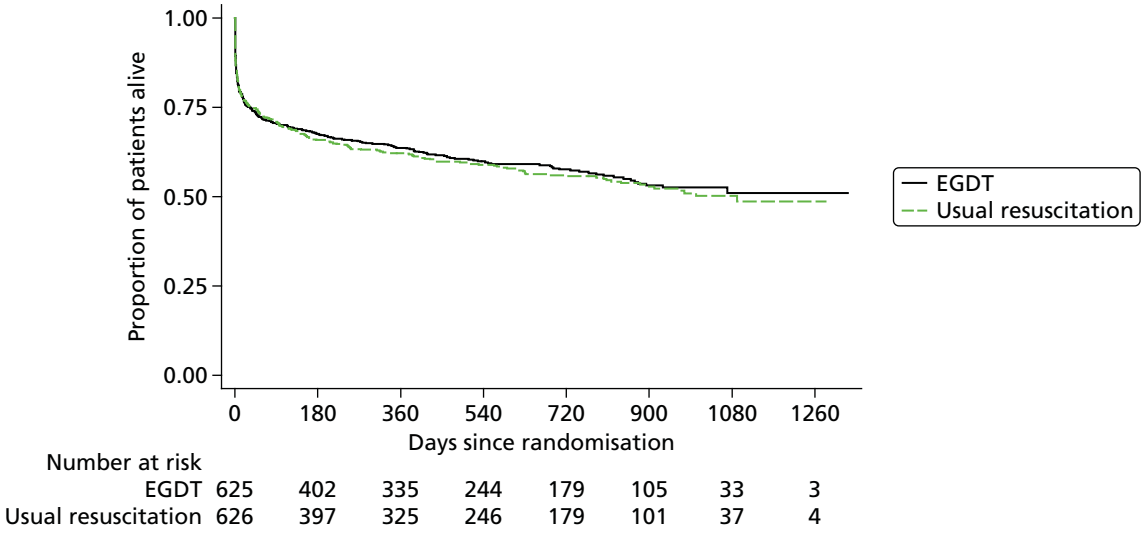

FIGURE 26 Kaplan–Meier survival curves for long-term survival.

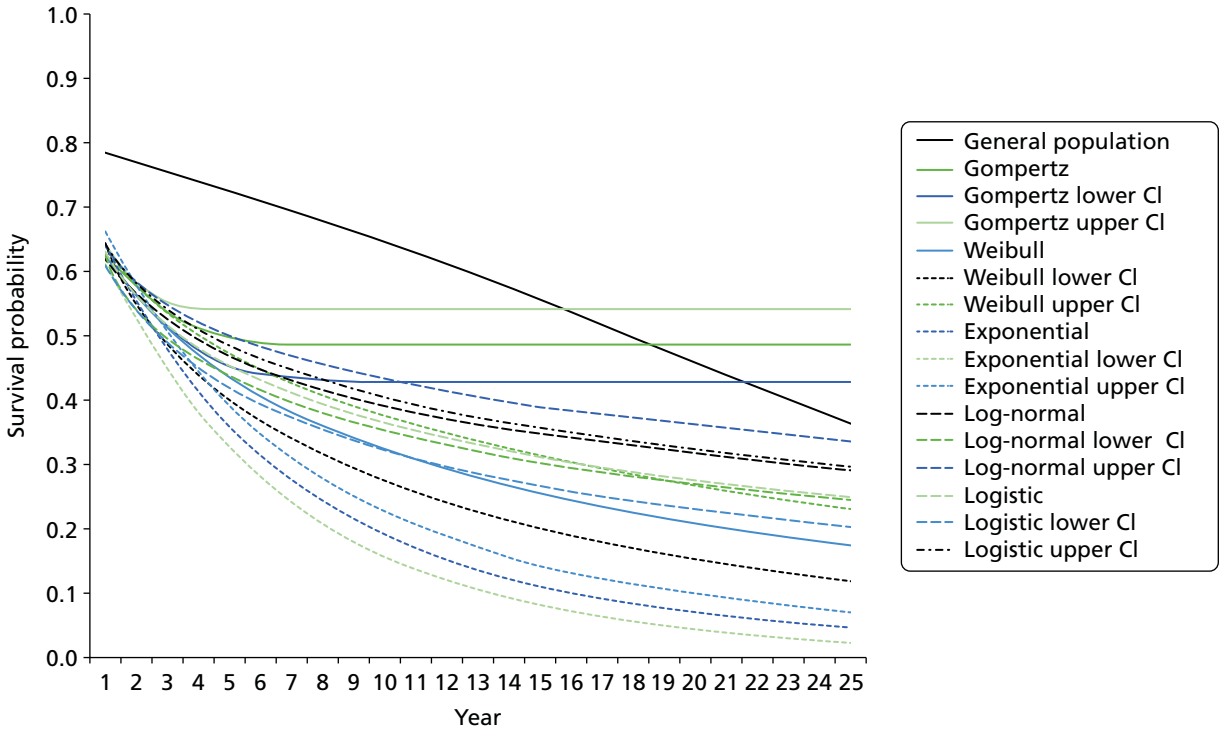

FIGURE 27 Comparison of alternative parametric extrapolations of survival.

TABLE 31 Fit of alternative parametric survival functions applied to the ProMISe data set after day 30

Distribution	AIC	BIC
Gompertz	1658.0	1687.1
Log-normal	1642.4	1671.5
Logistic	1644.5	1673.5
Weibull	1645.8	1674.8
Exponential	1691.0	1715.2

AIC, Akaike information criterion; BIC, Bayesian information criterion.

over time from 5 years following randomisation onwards. The parametric models predicted excess mortality in patients recruited to ProMISe compared with the age-/sex-matched general population. In the base case, we applied death rates according to the most plausible parametric model (i.e. Gompertz) between year 2 and year 15. At year 16, predicted survival overlaps with age-/sex-matched survival and, therefore, from year 16 onwards we applied age-/sex-matched general population death rates.

Long-term health-related quality of life

The lifetime cost-effectiveness analysis required health-related quality of life to be estimated over time. We used health-related quality of life from ProMISe and also from the age-/sex-matched general population to predict the long-term quality of life of patients recruited to ProMISe. There was a difference in the mean quality of life between the treatment groups at 1 year (0.62 for EGDT and 0.65 for usual resuscitation), which was maintained for the period over which the excess rate of mortality was applied (years 2–15). In the base case, we applied age-/sex-matched general population quality of life for years 2–15, but applying decrements of 21% (EGDT) and 17% (usual resuscitation) to allow for the relative differences in quality of life observed between the treatment groups at 1 year to be maintained.

Long-term costs

To project lifetime costs attributable to the initial episode of severe sepsis, we considered mean inpatient, outpatient and community costs up to 1 year estimated from the Health Services Questionnaires.

The mean cost for each intervention group was calculated for those patients who survived at least up to 1 year. These mean costs were used to impute mean costs between year 1 and year 15. For each group, these mean costs were similar (£4221 for EGDT and £4216 for usual resuscitation). After year 15 it was assumed that there were no further readmission costs that were attributable to the original episode of severe sepsis.

Lifetime incremental cost-effectiveness

Table 32 presents the resultant lifetime QALYs, lifetime costs and INB according to the base-case assumptions. Overall, at the NICE-stipulated threshold of £20,000 per QALY the INB was negative, but with a wide 95% CI that included zero. The distribution of incremental costs and QALYs in the cost-effectiveness plane is shown in *Figure 28*.

The cost-effectiveness acceptability curve shows that that the probability of EGDT of being cost-effective compared with usual resuscitation is never > 50% irrespective of how much society is willing to pay for a QALY gain (*Figure 29*).

The sensitivity analyses on the long-term results suggest that these findings are robust to alternative assumptions including those applied to extrapolation of long-term survival, quality of life for survivors and costs (*Figure 30*). For example, a large versus smaller decrement in quality of life over 15 years had only marginal impact on the mean INB.

TABLE 32 Lifetime cost-effectiveness

End point	EGDT ($n = 625$)	Usual resuscitation ($n = 626$)	Incremental effect (unadjusted), mean (95% CI)	p-value
QALYs	4.584 (3.546)	4.582 (3.720)	0.002 (–0.411 to 0.414)	0.99
Costs (£)	33,620 (25,012)	32,142 (25,798)	1478 (–1434 to 4390)	0.32
Incremental net benefit (£)[a]			–1446 (–8102 to 5210)	0.67

a Incremental net benefit is calculated according to NICE methods guidance, by multiplying the mean QALY gain (or loss) by £20,000, and subtracting from this the incremental cost.
Values are mean (SD), unless stated otherwise. Results are reported after applying multiple imputation to handle missing data.

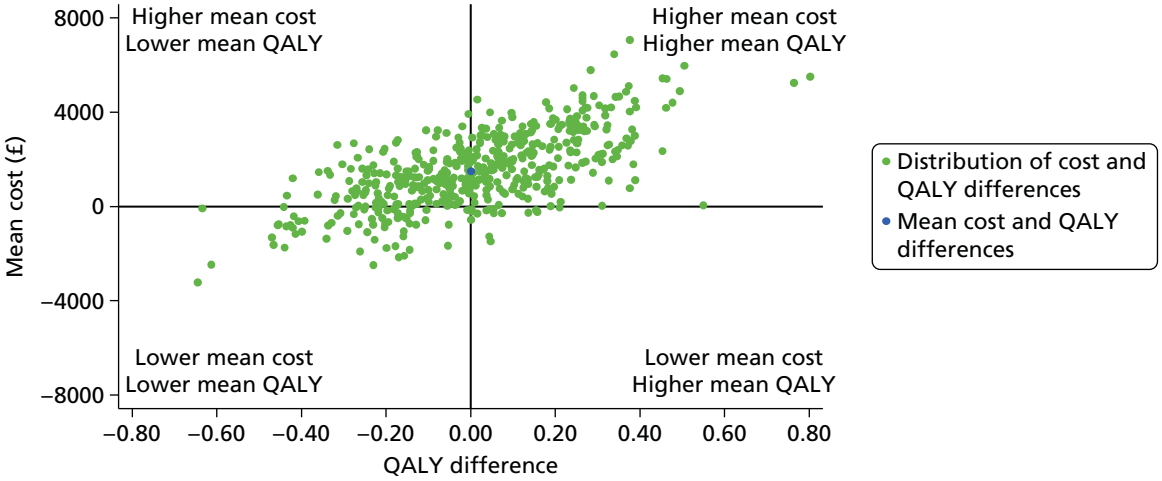

FIGURE 28 Uncertainty in the mean costs (£) and QALY differences at 1 year and their distribution for EGDT vs. usual resuscitation.

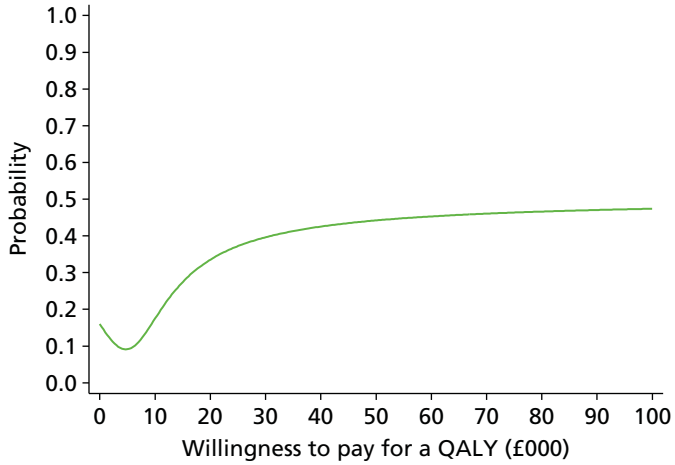

FIGURE 29 Cost-effectiveness acceptability curve reporting the probability that the EGDT is cost-effective (at lifetime) at alternative levels of willingness to pay.

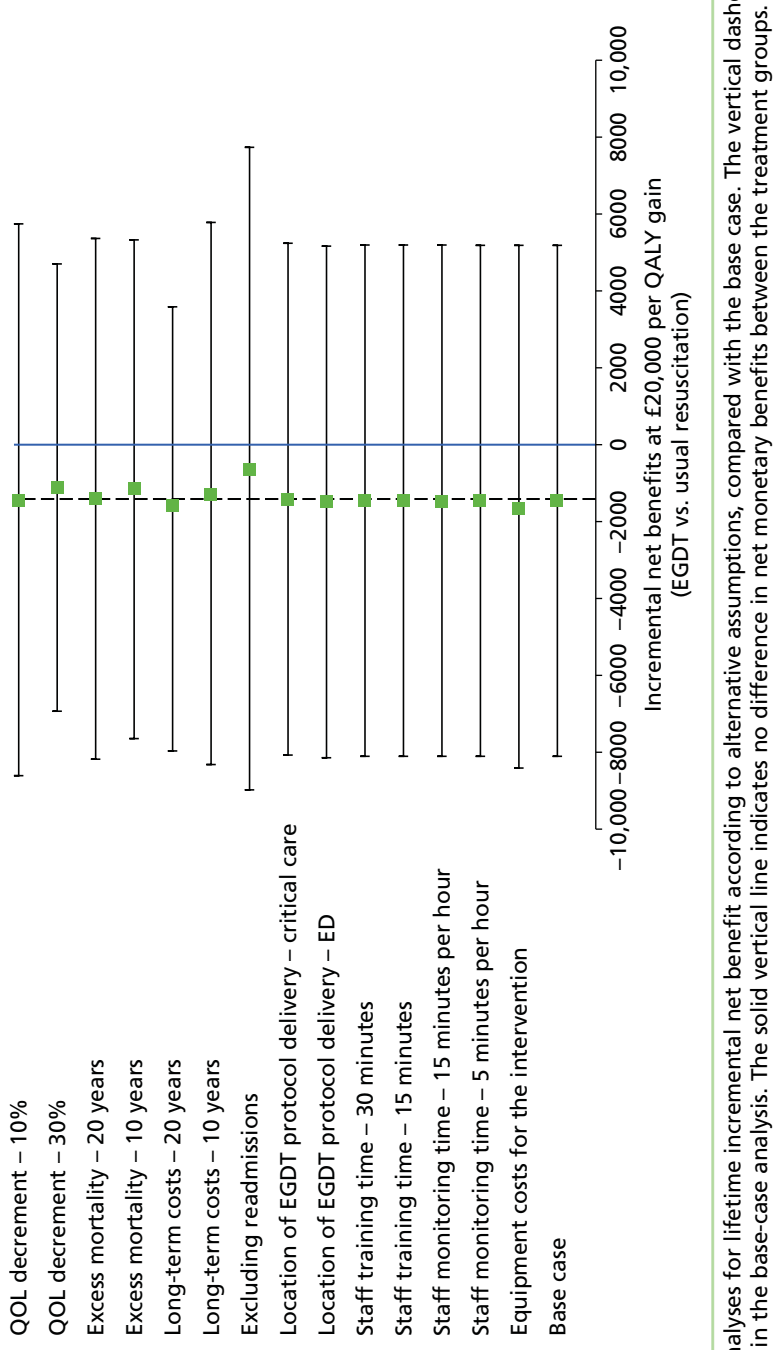

FIGURE 30 Sensitivity analyses for lifetime incremental net benefit according to alternative assumptions, compared with the base case. The vertical dashed line indicates incremental net benefit in the base-case analysis. The solid vertical line indicates no difference in net monetary benefits between the treatment groups. QOL, quality of life.

The results of the subgroup analysis presented in *Table 33* show that there were some differences in the direction of mean incremental effects but high statistical uncertainty surrounds these findings. Across subgroups, incremental QALYs were small. Although there were some subgroups of patients for whom the incremental costs of EGDT were negative, and hence the INBs were positive, 95% CIs around these INBs included zero. Hence for each subgroup, as for the overall result, cost-effectiveness estimates were surrounded by high statistical uncertainty.

TABLE 33 Lifetime incremental cost-effectiveness: subgroup and secondary analyses

Subgroup	Incremental cost (£) (95% CI)	Incremental QALYs (95% CI)	Incremental net benefit (£) (95% CI)
Degree of protocolised resuscitation in usual-resuscitation group			
Low	1905 (–1495 to 5305)	0.104 (–0.38 to 0.587)	168 (–7630 to 7966)
High	965 (–4874 to 6805)	–0.131 (–0.968 to 0.706)	–3589 (–17,056 to 9878)
Age (years)			
18–56	4881 (–736 to 10,498)	0.096 (–0.715 to 0.907)	–2957 (–16,236 to 10,322)
57–67	1357 (–4289 to 7003)	0.114 (–0.692 to 0.919)	915 (–12,166 to 13,996)
68–77	–1945 (–7570 to 3681)	–0.201 (–1.007 to 0.606)	–2069 (–15,097 to 10,959)
78–95	4635 (–1113 to 10,383)	0.521 (–0.309 to 1.351)	5787 (–7640 to 19,214)
MEDS score			
0–4	3344 (–4654 to 11,343)	0.139 (–1.006 to 1.284)	–560 (–19,050 to 17,930)
5–6	3759 (–2120 to 9638)	0.139 (–0.700 to 0.977)	–985 (–14,470 to 12,500)
7–9	819 (–4262 to 5900)	0.280 (–0.441 to 1.001)	4788 (–6840 to 16,416)
10–20	–140 (–5456 to 5176)	–0.361 (–1.104 to 0.383)	–7077 (–18,979 to 4825)
SOFA score			
0–2	3008 (–2798 to 8814)	0.151 (–0.661 to 0.963)	4 (–13,077 to 13,085)
3–4	1886 (–3143 to 6915)	0.114 (–0.591 to 0.819)	386 (–10,938 to 11,710)
5	–3279 (–10,351 to 3793)	–0.312 (–1.300 to 0.677)	–2952 (–18,774 to 12,870)
6–14	1792 (–3854 to 7439)	–0.369 (–1.163 to 0.426)	–9164 (–21,917 to 3589)
Time from ED presentation to randomisation (hours)			
0.2–1.8	2471 (–3280 to 8223)	0.005 (–0.819 to 0.829)	–2371 (–15,643 to 10,901)
1.8–2.5	6390 (707 to 12,073)	0.523 (–0.276 to 1.323)	4074 (–8777 to 16,925)
2.5–3.5	693 (–5140 to 6525)	–0.279 (–1.130 to 0.571)	–6275 (–20,079 to 7529)
3.5 +	–3759 (–9472 to 1953)	–0.230 (–1.052 to 0.591)	–847 (–14,099 to 12,405)
Adherence adjusted analysis	2126 (–2056 to 6307)	0.002 (–0.591 to 0.595)	–2079 (–11,654 to 7496)

Chapter 6 Discussion and conclusions

Principal findings

Among adults identified with early signs of septic shock presenting to the ED of one of 56 NHS hospitals in England and receiving 6 hours of protocolised resuscitation, there was no significant difference in mortality at 90 days when compared with usual resuscitation (relative risk 1.01, 95% CI 0.85 to 1.20). Although mortality was lower than anticipated, our results rule out, with 95% confidence, a relative risk reduction with EGDT of > 15%. On average, EGDT increased costs and, given similar QALYs across groups, INB at 1 year was negative (−£725, 95% CI −£3000 to £1550). The probability that EGDT is cost-effective (at a willingness to pay of £20,000 per QALY) is below 30%. Sensitivity analyses found that this conclusion is robust to alternative assumptions to those made in the base-case analysis.

There was no significant interaction between treatment effect and mortality at 90 days across pre-specified subgroups on the basis of degree of protocolisation of usual resuscitation, age, MEDS score, SOFA score or time to randomisation. More patients receiving EGDT were admitted to ICU, resulting in significantly more days spent in critical care in this group. Treatment intensity was greater for the EGDT group, driven by adherence to the protocol, and indicated by the increased use of central venous catheters, intravenous fluids, vasoactive drugs and packed red blood cell transfusions. Increased treatment intensity was reflected by significantly higher SOFA scores and more advanced cardiovascular support days in critical care for the EGDT group. There were no significant differences in any other secondary outcomes including health-related quality of life, measured in health-state utility values, which was substantially poorer in this severely ill patient group at both 90 days (0.61) and 1 year (0.62–0.65) than for the age-/sex-matched general population (0.80).[58] At 12 months post randomisation, approximately 30% of responders reported 'severe' or 'extreme' problems with mobility or undertaking usual activities, indicating substantial ongoing morbidity for this patient group.

Strengths

ProMISe was set in a real-world context, in a large, representative, mixed sample of approximately one-quarter of NHS hospitals in England, and was pragmatic, with staff and locations for delivery of the protocol determined locally, as would be the case if the intervention were to be adopted into routine NHS care. Site set-up was rapid, resulting in our trial recruiting its full sample of 1260 patients over a relatively shorter time period than the two similar studies already reported from the USA and Australasia; minimising the potential for other changes in treatments to impact on the trial.

Loss to follow-up was minimal and all analyses were conducted according to a pre-specified, published statistical analysis plan including, given the complex intervention, adjusted analyses to address the degree of adherence to EGDT and the possibility of the existence of a learning curve for its delivery.

Unlike the previous studies, our trial reported on quality of life at 90 days and 1 year post randomisation and our results include an integrated analysis of the cost-effectiveness of EGDT. This prospectively designed economic evaluation ensured that resource use data were collected on both primary admissions and readmissions for each patient randomised. The resource use measurement harnessed information from three sources: the case report forms, linked data from the Case Mix Programme database and responses to follow-up Health Service Questionnaires. This approach enabled detailed resource use measurement for those events that were anticipated to be the key drivers of the incremental costs of EGDT versus usual

resuscitation. The cost-effectiveness analysis also measured quality of life with the EQ-5D-5L;[59] this version of the EQ-5D instrument was anticipated to be sensitive to differences in health status between the treatment groups. To address missing data, we undertook the recommended approach of multiple imputation and imputed missing values, conditional on all the information observed.

Limitations

As with all studies enrolling patients presenting as emergencies, recruitment was more challenging at weekends and out-of-office hours. As a result of this, together with other logistical issues, only around one-third of eligible patients were recruited. However, there were no important differences in baseline characteristics between patients recruited during usual working hours or at weekends and out-of-office hours. In addition, exclusion by a clinician was comparatively rare.

With recruitment rates much lower – and eligible patients missed – at nights and at weekends, alongside a number of sites undergoing a period of suspension or closing early to recruitment owing to lack of available resources, the trial recruited behind the planned schedule. Owing to the short time-windows to recruit and commence treatment in randomised controlled trials in emergency and critical care settings, it is vital that research infrastructure within the NHS is delivered 24 hours per day, 7 days per week.

The intervention could not be blinded to those caring for patients but the risk of bias was minimised through central randomisation to ensure allocation concealment and the use of a primary outcome not subject to observer bias. The mortality observed in the usual-resuscitation group was lower than anticipated as the basis for the sample size calculation (29.2% vs. 40%). This was also true for both ProCESS (60-day in-hospital mortality, 18.9% observed, 30–46% anticipated[23]) and ARISE (90-day mortality, 18.8% observed, 38% anticipated[24]). However, unlike both ProCESS and ARISE, based on the 95% CI, our results were able to rule out with 95% confidence, in our setting of NHS EDs, the relative risk reduction in 90-day mortality of 20% that was the basis for our sample size calculation. Although able to provide, relatively, the most precise overall estimate of effect, we have limited power to address many important subgroups for either the clinical effectiveness or the cost-effectiveness.

The long-term cost-effectiveness analysis was inevitably required to make assumptions, in particular about the mortality, quality of life and cost in the time period beyond the observed data. The study made maximum use of the available trial data to inform these assumptions. For example, the analysis of the mortality data found that mortality was similar between the treatment groups at each time point, and that there was excess mortality versus the age-/sex-matched general population for up to 15 years post randomisation. These findings informed the assumptions made in the base-case analysis concerning the long-term survival extrapolation. The study made these and other requisite structural assumptions transparent and subjected them to extensive sensitivity analyses.

Our findings in context

Rivers et al.[6]

Unlike the original Rivers *et al.* trial,[6] we did not observe a significant reduction in mortality at hospital discharge. There are many possible reasons for this. First, there may be bias in a small, single-centre trial, leading to an inflated effect. Second, in the intervening years, both presenting patients and usual resuscitation has changed; all patients in our trial received antibiotics prior to randomisation and, comparing the usual-resuscitation groups, patients in our trial appeared less sick (with lower baseline serum lactate, lower APACHE II scores and a lower rate of initiation of mechanical ventilation in the first 6 hours), received much lower volumes of fluid, more vasoactive drugs and experienced lower hospital mortality.

ProCESS and ARISE

Our results, both for adherence and outcomes, are comparable with those from the ProCESS[23] and ARISE[24] studies from the USA and Australasia, respectively. Of note is that a greater proportion of patients in our trial met the inclusion criteria for both refractory hypotension and hyperlactataemia, associated with higher mortality, than met either criterion alone. The rate of death at 90 days in our trial was slightly lower than ProCESS but higher than ARISE.

Economic evaluation

Previous cost-effectiveness analyses have reported that EGDT is cost-effective relative to usual resuscitation.[9,11,54,60,61] However, almost all these studies relied solely on observational data,[9,11,60,61] and so the finding that EGDT was associated with improved survival, and higher QALYs, could reflect confounding by indication. Neither ProCESS nor ARISE undertook a fully integrated cost-effectiveness analysis. A key advantage is that individual-level data on quality of life and resource use were collected prospectively. The quality-of-life data were collected at 90 days and 1 year following randomisation with EQ-5D-5L[59] and hence the cost-effectiveness analysis was able to incorporate any differences in quality of life between the treatment groups into the final measures of cost-effectiveness.

A previous cost-effectiveness analysis, based on the mortality reduction reported in the Rivers' trial,[6] projected that EGDT would lead to a gain in QALYs and a reduction in hospital costs of 22%.[54] In contrast, our analysis of the individual patient resource use data from the trial found that EGDT led to a small average increase in both intervention costs and the use of critical care and general medical ward resources. Our cost analysis also allowed for the additional training and monitoring costs of providing EGDT in the NHS – relatively minor costs. When combined with no difference in patient outcomes this led to a very low probability of EGDT being cost-effective. The quality-of-life estimates were similar to previous estimates for patients surviving sepsis and sepsis shock,[62,63] and to a previous study of general ICU survivors.[64]

Trends in outcomes

Mortality for patients with severe sepsis has been reported to be decreasing in a number of settings.[3,65–67] Although this may, in part, be a dilution effect due to increased recognition and changes in clinical coding,[68,69] it is also likely that increased global awareness and a focus on early identification and treatment, for example, early administration of antibiotics, have contributed to improved outcomes. It is of note, however, that the reported downwards trend in mortality has been ongoing since before the Rivers *et al.*[6] trial and Surviving Sepsis Campaign,[70] and that similar trends have been reported among critically ill patients without sepsis.[3]

Implications for health care

Our results suggest that usual resuscitation has evolved over the fifteen years since the Rivers *et al.*[6] trial; NHS hospitals now achieve similar levels of in-hospital survival to those achieved with EGDT in the Rivers *et al.*[6] trial for patients with septic shock identified early and receiving intravenous antibiotics and adequate fluid resuscitation. The addition of continuous $ScvO_2$ monitoring and strict protocolisation of care was, on average, more costly and did not improve outcomes.

Although adherence to the EGDT protocol in ProMISe was similar in most respects with both ProCESS and ARISE, it is of note that the adherence with administration of packed red blood cells was generally low and occurred considerably slower than for other interventions. The lower adherence may reflect concerns over the relatively high haemoglobin threshold for blood transfusion in the EGDT protocol, as more recent research evidence suggests that lower transfusion thresholds may be preferable,[71] but the long time lag from reaching the transfusion threshold to administration of blood may warrant local investigation to ensure adequate processes are in place for rapid provision of blood products when required.

Recommendations for research

Recommendation 1: an individual patient data meta-analysis of the three completed trials should be conducted

Our results complete the planned trio of evaluations of EGDT across the USA, Australasia and England. These three large studies, each with their own strengths and weaknesses, have indicated that EGDT is not superior to usual resuscitation. Recognising that each of the three individual, large trials has limited power for evaluating potentially important subgroups, the harmonised approach adopted provides the opportunity to conduct an individual patient data meta-analysis, enhancing both knowledge and generalisability.

Recommendation 2: further research to consider alternative definitions of adherence to the resuscitation protocol should be conducted

Both the clinical effectiveness and cost-effectiveness analyses reported estimates that were adherence-adjusted as part of pre-specified secondary analyses. However, further research to consider alternative definitions of adherence to the EGDT resuscitation protocol are warranted. In particular, future research could apply differential weights for adherence to the different elements of the EGDT resuscitation protocol, or to particular time points within the 6-hour intervention period. Hence subsequent research could report whether EGDT was clinically effective or cost-effective when these alternative definitions of adherence were met.

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Contributions of authors

Paul R Mouncey (senior trial manager) managed the trial, contributed to the design of the trial, contributed to the acquisition, analysis and interpretation of the data, and drafted and critically reviewed the manuscript.

Dr Tiffany M Osborn (associate professor) contributed to the design of the trial, the analysis and interpretation of the data, and drafted and critically reviewed the manuscript.

G Sarah Power (statistician) contributed to the analysis and interpretation of the data, and drafted and critically reviewed the manuscript.

Dr David A Harrison (senior statistician and honorary senior lecturer in medical statistics) contributed to the design of the trial, the analysis and interpretation of the data, and drafted and critically reviewed the manuscript.

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Power GS, Harrison DA, Mouncey PR, Osborn TM, Harvey SE, Rowan KM. The Protocolised Management in Sepsis (ProMISe) trial statistical analysis plan. *Crit Care Resusc* 2013;**15**:311–17.

Huang DT, Angus DC, Barnato A, Gunn SR, Kellum JA, Stapleton DK, *et al.* Harmonizing international trials of early goal directed resuscitation for severe sepsis and septic shock: methodology of ProCESS, ARISE, and ProMISe. *Intensive Care Med* 2013;**39**:1760–75.

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Data sharing statement

Data can be obtained from the corresponding author.

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Appendix 1 Patient information sheet

[To go on your hospital Trust's Headed paper]

Patient Information Sheet

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

Introduction

We would like to invite you to take part in a clinical trial which considers the benefit of early, goal-directed, protocolised resuscitation compared to usual resuscitation in patients with severe sepsis or septic shock.

Before you decide, it is important that you understand why the trial is being done and what it involves. One of our team will go through the information sheet with you and answer any questions you have. Please feel free to talk to others about the trial if you wish and please don't hesitate to ask us if there is anything that is unclear.

Background

The usual resuscitation for severe sepsis in the United Kingdom involves treatment with antibiotics, fluids given into a vein, and medication to support the blood pressure, the heart and lung function. In the United States (US), a trial performed at one hospital found that usual resuscitation for severe sepsis worked better with a treatment plan guided by central blood oxygen levels during the first six hours of hospital treatment. This treatment plan is early, goal-directed, protocolised resuscitation.

What is the purpose of this trial?

When a person has a severe infection, their body may react by producing an 'inflammatory response', which can damage important organs, such as the heart and lungs to the point where they no longer function properly. When infection causes organ failure, it is called severe sepsis. If severe sepsis results in low blood pressure, it is referred to as septic shock.

The purpose of this trial is to investigate whether early, goal-directed, protocolised resuscitation results in more people recovering from severe sepsis or septic shock when compared with usual resuscitation. Early, goal-directed, protocolised resuscitation is a structured series of steps or elements that must be initiated as soon as possible, and completed over a six-hour period. This is referred to as the 'trial protocol' in the rest of the document. Usual resuscitation is less structured in that the doctor may provide some of the same elements, but does not necessarily follow a structured series of steps or elements in a time dependent manner.

The trial, which took place in the US (see background), showed that early, goal-directed, protocolised resuscitation is better than usual resuscitation, but this trial only involved a small number of patients, and therefore, more research is needed. Doctors don't know if early, goal-directed, protocolised resuscitation will be better than usual resuscitation, so this trial will help to determine if early, goal-directed, protocolised resuscitation should be used routinely in this country.

Why have I been asked to take part in the trial?

You are eligible to participate in this trial because you have severe sepsis or septic shock, and have been admitted through the Emergency Department in your hospital.

Do I have to take part?

Joining the trial is entirely voluntary. Once you have read this information sheet, if you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason, and this will not affect the standard of care you receive.

What will happen to me if I take part?

In order to find out which of the resuscitation methods is best, each patient will be put into one of two groups (early, goal-directed, protocolised resuscitation or usual resuscitation). The results will be compared to see which one is better.

ProMISe is a 'randomised controlled trial', which means that, each patient is randomly put into one of the two groups. The groups are selected by a computer that will decide on a chance basis (as if it were tossing a coin) whether you will receive early, goal-directed, protocolised resuscitation or usual resuscitation. Your progress will be closely followed to see which resuscitation method turns out to be the most beneficial. There is equal likelihood that you will receive either early, goal-directed, protocolised resuscitation or usual resuscitation. Neither you nor the doctor can decide which resuscitation method you will receive.

Whether you receive early, goal-directed, protocolised resuscitation or usual resuscitation, you will be provided with all other standard care as necessary, such as antibiotics or surgery. We will collect information about your progress throughout your hospital stay.

Many people who develop severe sepsis or septic shock routinely require a central venous catheter (CVC). This involves a doctor inserting a tube (catheter) into a large vein, usually in the neck, or near the collarbone to provide drugs, fluids or other products required during standard sepsis treatment. Treatment can include giving fluid into the vein; medications to support the blood pressure and heart; and a possible blood transfusion. The patient may also have an arterial catheter, which is a smaller tube that will be inserted into your artery in the wrist or groin and connected to a monitor to measure blood pressure. Additional treatment to support breathing may include supplemental oxygen and a machine to help the patient breathe.

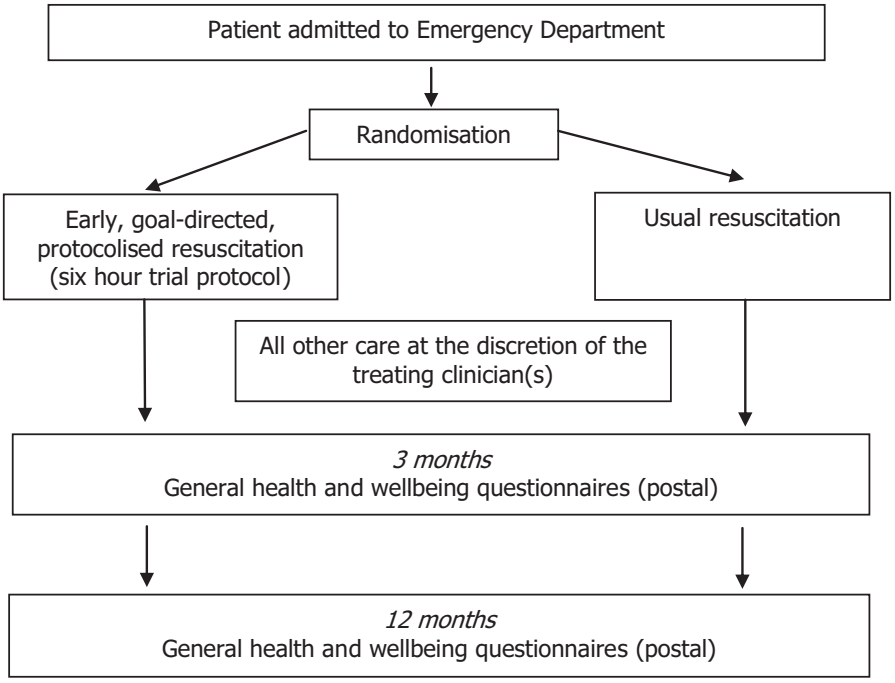
Early, goal-directed, protocolised resuscitation

If you are assigned to receive early, goal-directed, protocolised resuscitation, you will be cared for by the hospital's ProMISe Trial Team in conjunction with the team who will provide your ongoing care. You will receive resuscitation which follows the trial protocol for six hours. All patients will have a specialised CVC placed. The specialised CVC measures the oxygen level in blood returning from the tissues to the heart (central blood oxygen levels). These levels are monitored and treated accordingly. This specialised central catheter is used routinely. Many patients may have an arterial catheter to monitor blood pressure. The treating clinician(s) will use the information from these to treat you, and will include many of the standard sepsis treatments mentioned above, but according to the trial protocol. Each element in the trial protocol is to be given at the discretion of the treating clinician(s). Once a total of six hours of early, goal-directed, protocolised resuscitation has been completed, you will be given standard care at the discretion of the treating clinician(s) in accordance with current best practice.

Usual resuscitation

If you are assigned to receive usual resuscitation, you will continue to be monitored and treated by the hospital's usual clinical team in accordance with the hospital's current standard resuscitation practice. You will often have a CVC and an arterial catheter placed, if the treating clinician(s) deems this is needed for your treatment.

ProMISe patient schedule



What are the possible disadvantages and risks of taking part?

All medical procedures, regardless of trial participation, involve some risk of injury. In addition, there may be risks associated with this trial that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this trial. The most predictable risks are from the insertion of a CVC and an arterial catheter. These catheters are commonly inserted as part of usual resuscitation, but the CVC will always be inserted, and the arterial catheter will often be inserted, as part of early, goal-directed, protocolised resuscitation.

CVC complications

The most common complication is infection which occurs in less than one in 20 patients. The most serious complications are puncture of the lung, causing collection of air into the chest, or puncture of an artery causing blood to collect in the chest. These are rare and occur in less than one in a hundred patients. Other complications include injury to the blood vessel causing bruising and/ or bleeding or a blood clot inside the blood vessel (thrombosis). These are treatable and all patients will be assessed for the presence of any of these complications.

Arterial catheter complications

Complications from arterial catheters are rare, but may include bleeding, infection or a lack of blood flow to tissue supplied by the artery, which is nearly always correctable by removal of the catheter.

Other trial treatments

There are specific risks associated with each of the individual standard treatments used routinely for patients with severe sepsis or septic shock. These treatments are commonly used in critically ill patients and side effects can include:

Fluid infusions: giving fluid into a vein can cause 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, discontinuation, and sometimes by giving other medications.

Blood transfusion: can contribute to fluid overload, cause a reaction to the blood itself (rare) and spread viral disease. All blood is screened prior to administration.

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

All patients are monitored closely for development of any side effects from treatments, which will be immediately treated by decreasing the dose or stopping the treatment altogether.

What are the possible benefits of taking part?

We cannot promise that participation in the trial will benefit you during your hospital stay but the information we get from this trial may help improve the way in which we care for patients with severe sepsis or septic shock in the future.

If you receive early, goal-directed, protocolised resuscitation you will be cared for by the hospital's ProMISe Trial Team in conjunction with the team who will provide your ongoing care and may receive closer observation and additional nursing attention. Early, goal-directed protocolised resuscitation may or may not improve your chances of recovery when compared to usual resuscitation; at present there is no evidence to suggest that early, goal-directed, protocolised resuscitation is harmful.

What happens when the trial stops?

Once the trial has finished you will receive usual medical care up to and following discharge from hospital. However, at 3 months and 12 months after recruitment to the trial you will be contacted by post, by a researcher from ICNARC, to ask that you complete some questions on your general health and wellbeing. These questionnaires will take around 15-20 minutes to complete.

What if something goes wrong?

If you are harmed due to someone's negligence or wish to complain about any aspect of the wa you have been approached or treated during the course of this trial, contact the Hospital's Patien Advice & Liaison Service (PALS) for further information.

Will my taking part in this trial be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All information that is collected about you during the course of the trial will be kept strictly confidential. Where possible, any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. As some patients may lose touch with their hospital, we will need to collect important basic information from national records held by the NHS Medical Research Information Service (MRIS). To ensure we identify you correctly on the MRIS database, we will ask the hospital staff for your name, date of birth, post code and NHS number. In addition, ICNARC will also be given your address and telephone number, in order to send the questionnaires (mentioned above) to your home. Your GP will also be notified that you have agreed to participate in this trial. The information will be stored securely and in strict confidence at ICNARC. Procedures for handling, processing, storing and destroying data [add relevant NHS Trust here] and at ICNARC are compliant with the Data Protection Act 1998.

What will happen to the results of the trial?

The trial is estimated to take two years, commencing in late 2010. It is hoped to publish the results by mid 2014. If you would like a copy of the published results, please contact the Principal Local Investigator (details below).

Funding and organisation of the trial

This trial is being funded by the National Institute for Health Research, Health Technology Assessment programme. The trial is being Sponsored and managed by ICNARC.

Who has reviewed the trial

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given a favourable opinion by the North West London Research Ethics Committee 1.

Thank you for taking the time to read this information:

Local research contact details:

Please contact the Consultant leading the trial at your unit for further information:

- [Insert name and contact number of Local Principal Investigator]

Alternate contacts include:

- [Nurse – name and contact]
- ProMISe Team @ ICNARC – 020 7269 9277

Appendix 2 Short patient information sheet

[To go on your hospital Trust's Headed paper]

Patient Information Sheet - short

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

Introduction

When a person has a severe infection, their body may react by producing an 'inflammatory response', which can damage important organs, such as the heart and lungs to the point where they no longer function properly. When infection causes organ failure, it is called severe sepsis. If severe sepsis results in low blood pressure, it is referred to as septic shock. The usual resuscitation for severe sepsis in the United Kingdom involves treatment with antibiotics, fluids given into a vein, and medication to support the blood pressure, the heart and lung function. In the United States, a small trial performed at one hospital found that usual resuscitation for severe sepsis worked better with a treatment plan guided by central blood oxygen levels during the first six hours of hospital treatment. This treatment plan is early, goal-directed, protocolised resuscitation. This trial only involved a small number of people and more research is needed.

What is the purpose of the ProMISe trial?

We would like you to take part in a clinical trial to investigate whether early, goal-directed, protocolised resuscitation results in more people recovering from severe sepsis or septic shock when compared with usual resuscitation. Early, goal-directed, protocolised resuscitation is a structured series of steps or elements that must be initiated as soon as possible, and completed over a six-hour period. Usual resuscitation is less structured in that the doctor may provide some of the same elements, but does not necessarily follow a structured series of steps or elements in a time dependent manner.

Why have I been asked to take part in the trial?

You are eligible to participate in this trial because you have severe sepsis or septic shock, and have been admitted through the Emergency Department in your hospital. Joining the trial is entirely

voluntary. Once you have read this information sheet, if you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason, and this will no affect the standard of care you receive.

What will happen to me if I take part?

In order to find out which of the resuscitation methods is best, each patient will be randomly put into one of two groups (early, goal-directed, protocolised resuscitation or usual resuscitation) – as i tossing a coin. The results will be compared to see which one is better. There is equal likelihood that you will receive either early, goal-directed, protocolised resuscitation or usual resuscitation. Neither you nor the doctor can decide which resuscitation method you will receive. Whether you receive early, goal-directed, protocolised resuscitation or usual resuscitation (details below), you will be provided with all other standard care as necessary, such as antibiotics or surgery. We will collect information about your progress throughout your hospital stay.

- **Early, goal-directed, protocolised resuscitation:** you will receive resuscitation which follows the trial protocol for six hours. All patients will have a specialised central venous catheter (CVC) placed into a large vein, usually in the neck, to measure the oxygen level in the blood. These levels are monitored and treated accordingly. This specialised CVC is used routinely. You may also have an arterial catheter (a small tube) inserted into an artery in your wrist or groin to monitor blood pressure. Once a total of six hours of early, goal-directed, protocolised resuscitation has been completed, you will be given standard care at the discretion of the treating clinician(s) in accordance with current best practice.

- **Usual resuscitation**: you will continue to be monitored and treated by the hospital's usual clinical team in accordance with the hospital's current standard resuscitation practice. You may have a CVC and an arterial catheter inserted if the treating clinician(s) deems this is needed for your treatment.

What are the possible disadvantages and risks of taking part?

All medical procedures, regardless of trial participation, involve some risk of injury. In addition, there may be risks associated with this trial that are presently unknown or unforeseeable.

- **CVC complications:** the most common complication is infection which occurs in less than one in 20 patients. The most serious complications are puncture of the lung, causing collection of air into the chest, or puncture of an artery causing blood to collect in the chest. These are rare and occur in less than one in a hundred patients. Other complications include injury to the blood vessel causing bruising and/ or bleeding or a blood clot inside the blood vessel (thrombosis). These are treatable and all patients will be assessed for the presence of any of these complications.

- **Arterial catheter complications:** these are rare, but may include bleeding, infection or a lack of blood flow to tissues supplied by the artery, which is nearly always correctable by removal of the catheter.

What are the possible benefits of taking part?

We cannot promise that participation in the trial will benefit you during your hospital stay but the information we get from this trial may help improve the way in which we care for patients with severe sepsis or septic shock in the future.

What if something goes wrong?

If you are harmed due to someone's negligence or wish to complain about any aspect of the way you have been approached or treated during the course of this trial, contact the Hospital's Patient Advice & Liaison Service (PALS) for further information.

Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given a favourable opinion by the North West London Research Ethics Committee 1.

Please also read the ProMISe Patient Information Sheet which has more detailed information about the ProMISe Trial.

Appendix 3 Case report form

Randomisation - Eligibility

ProMISe

Time of presentation at ED

Presentation at ED: Today (1) Yesterday (2) Time: H H : M M (24-hour clock)

Inclusion

Met once, in any order, within six hours from presentation at ED

Known or presumed infection: Yes (Y)

Two, or more SIRS criteria: Yes (Y)

Refractory hypotension or hypoperfusion: Yes (Y)

You now have two hours to consent and randomise the patient

Exclusion

Transferred from another in-hospital setting: No (N)

Requirement for immediate surgery: No (N)

Age less than 18 years: No (N)

Do-Not-Attempt-Resuscitation (DNAR) status: No (N)

Advanced directives restricting implementation of the protocol: No (N)

Attending physician deems aggressive care unsuitable: No (N)

Contraindication to central venous catheterisation: No (N)

Contraindication to blood transfusion: No (N)

Known history of AIDS: No (N)

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: No (N)

Haemodynamic instability due to active gastrointestinal haemorrhage: No (N)

Known pregnancy: No (N)

Not able to complete six hours of protocol treatment from commencement: No (N)

Not able to commence protocol within one hour of randomisation: No (N)

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

Treatment limitations

Does the patient have any other treatment limitations? *(see: overleaf for guidance)* Yes (Y) No (N) ***Not requested in call to Randomisation Service***

If yes, please specify

Time met physiological inclusion criteria

Time met final physiological inclusion criteria: H H : M M (24-hour clock)

Consent

Consent process used: Patient consent (1) Personal Consultee (2) Professional Consultee (3) Emergency consent (4)

Antimicrobial(s)

Antimicrobial(s) initiated: Yes (Y)

Randomisation

Trial number:

Treatment allocation: Early, goal-directed, protocolised resuscitation (E) Usual resuscitation (U)

Randomisation (T_0) Date: D D / M M / 2 0 Y Y Time: H H : M M (24-hour clock)

First "golden" hour (T_1) Date: D D / M M / 2 0 Y Y Time: H H : 0 0 (24-hour clock)

Completed by: **Signature:**

ProMISe CRF booklet v3.1, 10/09/2013 promise@icnarc.org

Randomisation – Eligibility

Overleaf, to be completed once consent/agreement is obtained and before calling the Randomisation Service

Time of presentation at ED

- Presentation at ED – day the patient physically presented at ED
- Time – time the patient physically presented at ED

Inclusion

All should be ticked 'Yes' to be eligible

- Two, or more SIRS criteria

SIRS criteria		Results
Core temperature	≤ 36°C or ≥ 38°C	
Heart rate	≥ 90 beats min^{-1}	
Respiratory rate	≥ 20 breaths min^{-1}	
or Hyperventilaton	$PaCO_2$ < 4.3 kPa **or** mechanical ventilation for acute process	
White blood cell count	≤ $4x10^9$ l^{-1} **or** ≥ $12×10^9$ l^{-1}	
or Immature neutrophils (bands)	> 10%	

- Refractory hypotension or hypoperfusion

Physiology		Results
Refractory hypotension	MAP < 65 mmHg **or** SBP < 90 mmHg	
or Hypoperfusion	blood lactate ≥ 4 mmol l^{-1}	

Exclusion

All should be ticked 'No' to be eligible

Treatment limitations

- Does the patient have any other treatment limitations? – these are treatment limitations which do not prevent delivery of the early, goal-directed, protocolised resuscitation (obviously, ones that do, exclude the patient from ProMISe), e.g.
  - a patient whose treatment limitation precludes the use of inotropic agents would be excluded from ProMISe
  - a patient whose treatment limitation precludes the use of mechanical ventilation would be eligible for ProMISe, because the early, goal-directed, protocolised resuscitation requires that mechanical ventilation only be considered

Consent

- Consent process used –
  - Patient consent – the patient provided informed consent
  - Personal Consultee – a relative or friend provided agreement
  - Professional Consultee – an Independent Mental Capacity Advocate provided agreement
  - Emergency consent – an independent doctor was consulted and agreed

Antimicrobial(s)

- Antimicrobial(s) initiated – first dose must be initiated before randomisation

---

Randomisation

Randomisation Service – 020 8099 7784
Study number – 2016
Investigator number – XXX

- Trial number – provided by the Randomisation Service
- Treatment allocation – provided by the Randomisation Service
- Randomisation (T_0) – complete date and time provided by the Randomisation Service
- First "golden" hour (T_1) – date and time provided by the Randomisation Service

ProMISe

icnarc intensive care national audit & research centre

Protocolised Management In Sepsis

A multi-centre, randomised controlled trial
of the clinical and cost-effectiveness of
early, goal-directed, protocolised resuscitation
for emerging septic shock

Case Report Form

Investigator number

Trial number

Treatment allocation

Early, goal-directed, protocolised resuscitation (E)

Usual resuscitation (U)

Randomisation (T_0)

Date: D D / M M / 2 0 Y Y Time: H H : M M

T_1

Date: D D / M M / 2 0 Y Y Time: H H : 0 0

ProMISe

Trial number: ☐☐☐☐

Randomisation - Inclusion criteria

(results confirming inclusion criteria)

Inclusion criteria

Blood pressure (after fluid challenge) - MAP: ☐☐☐ mmHg **or** SBP: ☐☐☐ mmHg

Lactate: ☐☐ · ☐ mmol l^{-1}

Known or presumed infection: Yes (Y) No (N)

Temperature: ☐☐ · ☐ °C

Heart rate: ☐☐☐ beats min^{-1}

Respiratory rate: ☐☐☐ breaths min^{-1}

$PaCO_2$: ☐☐☐ · ☐ kPa (K) mmHg (M)

Mechanical ventilation: Yes (Y) No (N)

White blood count: ☐☐☐ · ☐ 10^9 l^{-1}

Immature neutrophils (bandforms): ☐☐ %

For SIRS criteria

First dose of IV antimicrobial(s) initiated: Yes (Y) No (N)

IV antimicrobial(s) initiated: ☐

Care location

Would patient be admitted direct to ICU from ED if not enrolled into ProMISe? Yes (Y) No (N)

Comments

Completed by: ☐

Signature: ☐ **Date completed:** D D / M M / 2 0 Y Y

PrOMISe

Trial number: | | | | |

Baseline - Contact details

Patient details

Title:

First name:

Surname:

Gender: Male (M) Female (F)

Date of birth: D D / M M / 1 9 Y Y

or Estimated age:

NHS number:

Hospital number:

House number/name:

Postcode:

Address 1:

Address 2:

City:

County:

Country:

If address not known

Residence/status: Abroad (A) Military (M) Homeless (H) No fixed abode (N)

Telephone number:

Mobile number:

Other number:

Primary care details

Initials:

Surname:

Practice name:

House number/name:

Postcode:

Address 1:

Address 2:

City:

County:

Country:

Clinician details

Treating clinician responsible for patient

Title:

First name:

Surname:

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

Baseline - Physiology/Interventions

(last result prior to randomisation)

ProMISe

Trial number: ☐☐☐☐

Physiology

Not recorded (NR)

Temperature: ☐☐·☐ °C (NR)

MAP: ☐☐☐ mmHg **or** (NR)

SBP/DBP: ☐☐☐/☐☐☐ mmHg

Heart rate: ☐☐☐ beats min^{-1} (NR)

Respiratory rate: ☐☐☐ breaths min^{-1} (NR)

Mechanical ventilation: Yes (Y) No (N)

FiO_2: ☐·☐☐ (NR)

PaO_2: ☐☐☐·☐ kPa (K) mmHg (M) (NR)

$PaCO_2$: ☐☐☐·☐ kPa (K) mmHg (M) (NR)

Arterial pH: ☐·☐☐ (NR)

CVP: ☐☐ mmHg (NR)

SpO_2: ☐☐☐ % (NR)

$ScvO_2$: ☐☐☐ % (NR)

Not recorded (NR)

Sodium: ☐☐☐ mmol l^{-1} (NR)

Potassium: ☐☐·☐ mmol l^{-1} (NR)

Lactate: ☐☐·☐ mmol l^{-1} (NR)

Creatinine: ☐☐☐☐ µmol l^{-1} (NR)

Bilirubin: ☐☐☐·☐ µmol l^{-1} (NR)

Platelets: ☐☐☐☐ x10^9 l^{-1} (NR)

Haemoglobin: ☐☐·☐ g dl^{-1} (NR)

White blood count: ☐☐☐·☐ x10^9 l^{-1} (NR)

Immature neutrophils (bandforms): ☐☐ % (NR)

Glasgow Coma Score (GCS)

Pre-sedation: Yes (Y) No (N)

Not recorded: (NR)

Total GCS: ☐☐

Eye opening response

Spontaneous: (4)

To speech: (3)

To painful stimuli: (2)

No response: (1)

Motor response

Obeys commands: (6)

Localises to painful stimuli: (5)

Withdrawal to painful stimuli: (4)

Abnormal flexion: (3)

Extends to painful stimuli: (2)

No response: (1)

Verbal response

Oriented: (5)

Confused: (4)

Inappropriate words: (3)

Incomprehensible sounds: (2)

No response: (1)

Interventions

Vasoactives administered: Yes (Y) No (N)

If yes

Dobutamine: Yes (Y)

Dopamine: Yes (Y) Rate →

- ≤5 µg kg^{-1} min^{-1} (L)
- >5 µg kg^{-1} min^{-1} (M)
- >15 µg kg^{-1} min^{-1} (U)

Epinephrine: Yes (Y) Rate →

- ≤0.1 µg kg^{-1} min^{-1} (L)
- >0.1 µg kg^{-1} min^{-1} (U)

Norepinephrine: Yes (Y) Rate →

- ≤0.1 µg kg^{-1} min^{-1} (L)
- >0.1 µg kg^{-1} min^{-1} (U)

IV fluid (total volume)

Pre-hospital: ☐☐☐☐☐ ml → ED presentation to randomisation: ☐☐☐☐☐ ml

Blood products (total volume)

Pre-hospital: ☐☐☐☐ ml → ED presentation to randomisation: ☐☐☐☐ ml

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

ProMISe

Trial number:

Baseline - Comorbidities

(last six months prior to ED presentation)

Comorbidities

Does the patient have any of the listed comorbidities? Yes (Y) No (N)

If yes

Liver

Cirrhosis: (Y)

Portal hypertension: (Y)

Upper GI bleeding (due to portal hypertension): (Y)

Hepatic failure or encephalopathy: (Y)

Haematological/oncological

AIDS: (Y)

Lymphoma: (Y)

Leukaemia: (Y)

Myeloma: (Y)

Metastatic disease: (Y)

Renal

Chronic renal replacement therapy for irreversible renal disease: (Y)
(haemodialysis, haemofiltration and peritoneal dialysis)

Respiratory

Shortness of breath with light activity: (Y)

Home ventilation: (Y)

Cardiovascular

Fatigue, claudication, dyspnoea or angina at rest: (Y)
(New York Heart Association Functional Class IV)

Neurological

Altered mental state: (Y)

Immunological

Therapy supressing resistance to infection: (Y)
(e.g. steroids, chemotherapy, radiotherapy, etc.)

Other

Admitted from a Nursing Home: (Y)

Other: (Y)

Specify other:

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

PrOMISe

Trial number: | | | | |

Resuscitation - Lines

Lines

CVC with $ScvO_2$ monitoring capability: Yes (Y) No (N) PreSep catheter batch number: | | | | | | | | |

If yes

Date of insertion: D D / M M / 2 0 Y Y

Time of insertion: H H : M M (24-hour clock)

CVC without $ScvO_2$ monitoring capability: Yes (Y) No (N)

If yes

Date of insertion: D D / M M / 2 0 Y Y

Time of insertion: H H : M M (24-hour clock)

Arterial line: Yes (Y) No (N)

If yes

Date of insertion: D D / M M / 2 0 Y Y

Time of insertion: H H : M M (24-hour clock)

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

PrOMISe

Resuscitation - T0 → T1

T1*: H H : 0 0 (24-hour clock)

Trial number:

Interventions T0 → T1*

Supplemental O_2: Yes (Y) → [ ] l min^{-1} No (N)

Highest FiO_2: [ ] . [ ]

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → [ ] ml

Crystalloid: Yes (Y) → [ ] ml

Vasoactive agents: Yes (Y) No (N)

If yes

Max. infusion rate

Dopamine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Phenylephrine Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Other: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Specify other: [ ]

PRBC: Yes (Y) → [ ] ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → [ ] ml

FFP: Yes (Y) → [ ] ml

Albumin (20%): Yes (Y) → [ ] ml

Other: Yes (Y) → [ ] ml

Specify other: [ ]

Max. infusion rate

Dobutamine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other: [ ]

Neuromuscular blocking agent: Yes (Y) No (N)

Physiology at T1*

Not recorded (NR)

CVP: [ ] mmHg (NR)

MAP: [ ] mmHg (NR)

SBP: [ ] mmHg (NR)

Not recorded (NR)

$ScvO_2$: [ ] % (NR)

Haemoglobin: [ ] . [ ] g dl^{-1} (NR)

*T1

T0 = time of randomisation and T1 = time of randomisation plus one "golden" hour
e.g. patient randomised at 18:25, T1 = 20:00, patient randomised at 19:04, T1 = 21:00

Completed by: [ ]

Signature: [ ] **Date completed:** D D / M M / 2 0 Y Y

PrOMISe

Resuscitation – T1 → T2

T2: H H : 0 0 (24-hour clock)

Trial number: ☐☐☐☐

Interventions T1 → T2

Supplemental O_2: Yes (Y) → ☐☐ l min^{-1} No (N)

Highest FiO_2: ☐ . ☐☐

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → ☐☐☐☐ ml

Crystalloid: Yes (Y) → ☐☐☐☐☐ ml

Vasoactive agents: Yes (Y) No (N)

If yes

Max. infusion rate

Dopamine: Yes (Y) → ☐☐ . ☐ μg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → ☐ . ☐ μg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → ☐ . ☐☐ μg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → ☐ . ☐☐ μg kg^{-1} min^{-1}

Phenylephrine: Yes (Y) → ☐☐ . ☐ μg kg^{-1} min^{-1}

Other: Yes (Y) → ☐☐ . ☐☐ μg kg^{-1} min^{-1}

Specify other: ☐

PRBC: Yes (Y) → ☐☐☐☐ ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → ☐☐☐ ml

FFP: Yes (Y) → ☐☐☐☐ ml

Albumin (20%): Yes (Y) → ☐☐☐☐ ml

Other: Yes (Y) → ☐☐☐☐ ml

Specify other: ☐

Max. infusion rate

Dobutamine: Yes (Y) → ☐☐ . ☐ μg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other: ☐

Neuromuscular blocking agent: Yes (Y) No (N)

Physiology at T2

Not recorded (NR)

CVP: ☐☐ mmHg (NR)

MAP: ☐☐☐ mmHg (NR)

SBP: ☐☐☐ mmHg (NR)

Not recorded (NR)

$ScvO_2$: ☐☐☐ % (NR)

Haemoglobin: ☐☐ . ☐ g dl^{-1} (NR)

Comments

Completed by: ☐

Signature: ☐ **Date completed:** D D / M M / 2 0 Y Y

PROMISE

Resuscitation – T2 → T3

T3: H H : 0 0 (24-hour clock)

Trial number: ____

Interventions T2 → T3

Supplemental O_2: Yes (Y) → ____ l min^{-1} No (N)

Highest FiO_2: ____ . ____

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → ____ ml

Crystalloid: Yes (Y) → ____ ml

Vasoactive agents: Yes (Y) No (N)

If yes

Max. infusion rate

Dopamine: Yes (Y) → ____ . ____ µg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → ____ . ____ µg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → ____ . ____ µg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → ____ . ____ µg kg^{-1} min^{-1}

Phenylephrine Yes (Y) → ____ . ____ µg kg^{-1} min^{-1}

Other: Yes (Y) → ____ . ____ µg kg^{-1} min^{-1}

Specify other: ____

PRBC: Yes (Y) → ____ ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → ____ ml

FFP: Yes (Y) → ____ ml

Albumin (20%): Yes (Y) → ____ ml

Other: Yes (Y) → ____ ml

Specify other: ____

Max. infusion rate

Dobutamine: Yes (Y) → ____ . ____ µg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other: ____

Neuromuscular blocking agent: Yes (Y) No (N)

Physiology at T3

Not recorded (NR)

CVP: ____ mmHg (NR)

MAP: ____ mmHg (NR)

SBP: ____ mmHg (NR)

Not recorded (NR)

$ScvO_2$: ____ % (NR)

Haemoglobin: ____ . ____ g dl^{-1} (NR)

Comments

Completed by: ____

Signature: ____ **Date completed:** D D / M M / 2 0 Y Y

PROMISE

Resuscitation – T3 → T4

T4: H H : 0 0 (24-hour clock)

Trial number: ☐☐☐☐

Interventions T3 → T4

Supplemental O_2: Yes (Y) → ☐☐ l min^{-1} No (N)

Highest FiO_2: ☐ . ☐☐

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → ☐☐☐☐ ml

Crystalloid: Yes (Y) → ☐☐☐☐☐ ml

Vasoactive agents: Yes (Y) No (N)

If yes

Max. infusion rate

Dopamine: Yes (Y) → ☐☐ . ☐ μg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → ☐ . ☐ μg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → ☐ . ☐☐ μg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → ☐ . ☐☐ μg kg^{-1} min^{-1}

Phenylephrine Yes (Y) → ☐☐ . ☐ μg kg^{-1} min^{-1}

Other: Yes (Y) → ☐☐ . ☐☐ μg kg^{-1} min^{-1}

Specify other: ☐

PRBC: Yes (Y) → ☐☐☐☐ ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → ☐☐☐ ml

FFP: Yes (Y) → ☐☐☐☐ ml

Albumin (20%): Yes (Y) → ☐☐☐☐ ml

Other: Yes (Y) → ☐☐☐☐ ml

Specify other: ☐

Max. infusion rate

Dobutamine: Yes (Y) → ☐☐ . ☐ μg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other: ☐

Neuromuscular blocking agent: Yes (Y) No (N)

Physiology at T4

Not recorded (NR)

CVP: ☐☐ mmHg (NR)

MAP: ☐☐☐ mmHg (NR)

SBP: ☐☐☐ mmHg (NR)

Not recorded (NR)

$ScvO_2$: ☐☐☐ % (NR)

Haemoglobin: ☐☐ . ☐ g dl^{-1} (NR)

Comments

Completed by: ☐

Signature: ☐ **Date completed:** D D / M M / 2 0 Y Y

ProMISe

Resuscitation – T4 → T5

T5: H H : 0 0 (24-hour clock)

Trial number:

Interventions T4 → T5

Supplemental O_2: Yes (Y) → l min^{-1} No (N)

Highest FiO_2: .

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → ml

Crystalloid: Yes (Y) → ml

Vasoactive agents: Yes (Y) No (N)

If yes

Max. infusion rate

Dopamine: Yes (Y) → . µg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → . µg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → . µg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → . µg kg^{-1} min^{-1}

Phenylephrine Yes (Y) → . µg kg^{-1} min^{-1}

Other: Yes (Y) → . µg kg^{-1} min^{-1}

Specify other:

PRBC: Yes (Y) → ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → ml

FFP: Yes (Y) → ml

Albumin (20%): Yes (Y) → ml

Other: Yes (Y) → ml

Specify other:

Max. infusion rate

Dobutamine: Yes (Y) → . µg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other:

Neuromuscular blocking agent: Yes (Y) No (N)

Physiology at T5

Not recorded (NR)

CVP: mmHg (NR)

MAP: mmHg (NR)

SBP: mmHg (NR)

Not recorded (NR)

$ScvO_2$: % (NR)

Haemoglobin: . g dl^{-1} (NR)

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

PrOMISe

Resuscitation – T5 → T6

T6: H H : 0 0 (24-hour clock)

Trial number:

Interventions T5 → T6

Supplemental O_2: Yes (Y) → [ ] l min^{-1} No (N)

Highest FiO_2: [ ] . [ ]

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → [ ] ml

Crystalloid: Yes (Y) → [ ] ml

Vasoactive agents: Yes (Y) No (N)

If yes

Max. infusion rate

Dopamine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Phenylephrine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Other: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1}

Specify other: [ ]

PRBC: Yes (Y) → [ ] ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → [ ] ml

FFP: Yes (Y) → [ ] ml

Albumin (20%): Yes (Y) → [ ] ml

Other: Yes (Y) → [ ] ml

Specify other: [ ]

Max. infusion rate

Dobutamine: Yes (Y) → [ ] . [ ] µg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other: [ ]

Neuromuscular blocking agent: Yes (Y) No (N)

Physiology at T6

Not recorded (NR)

CVP: [ ] mmHg (NR)

MAP: [ ] mmHg (NR)

SBP: [ ] mmHg (NR)

Not recorded (NR)

$ScvO_2$: [ ] % (NR)

Haemoglobin: [ ] . [ ] g dl^{-1} (NR)

Lactate: [ ] . [ ] mmol l^{-1} (NR)

Comments

Completed by: [ ]

Signature: [ ]

Date completed: D D / M M / 2 0 Y Y

ProMISe

Trial number: ☐☐☐☐

Resuscitation – T0 → T6

Doctor T0 → T6

Most senior doctor to review patient (T0® T6):

- Foundation Year 1/2 (F)
- Specialty Registrar (year 1 – 7) (R)
- Consultant (C)
- Clinical Fellow (L)
- Staff or Associate Specialist (S)
- Other (O)

Specify: ☐

Speciality of most senior doctor:

- Emergency Medicine (E)
- Intensive Care Medicine (I)
- Acute Medicine (A)
- Surgery (S)
- Other (O)

Specify: ☐

Physiology T0 → T6

Lowest P/F ratio:

PaO_2: ☐☐☐ · ☐ kPa (K) mmHg (M) (NR)

FiO_2: ☐ · ☐☐

P/F ratio on mechanical ventilation: Yes (Y) No (N)

Not recorded (NR)

Lowest platelets: ☐☐☐☐ $x10^9 l^{-1}$ (NR)

Highest bilirubin: ☐☐☐ · ☐ µmol l^{-1} (NR)

Highest creatinine: ☐☐☐☐ µmol l^{-1} (NR)

Glasgow Coma Score (GCS) T0 → T6

Pre-sedation: Yes (Y) No (N)

Not recorded: (NR)

Lowest total GCS: ☐☐

Eye opening response

- Spontaneous: (4)
- To speech: (3)
- To painful stimuli: (2)
- No response: (1)

Motor response

- Obeys commands: (6)
- Localises to painful stimuli: (5)
- Withdrawal to painful stimuli: (4)
- Abnormal flexion: (3)
- Extends to painful stimuli: (2)
- No response: (1)

Verbal response

- Oriented: (5)
- Confused: (4)
- Inappropriate words: (3)
- Incomprehensible sounds: (2)
- No response: (1)

End of resuscitation protocol

End of early, goal-directed, protocolised resuscitation (if randomised to)

Date: D D / M M / 2 0 Y Y Time: H H : M M (24-hour clock)

Completed by: ☐

Signature: ☐ **Date completed:** D D / M M / 2 0 Y Y

PROMISE

Trial number: | | | | |

T6 → T24 - Interventions

T24

Date: D D / M M / 2 0 Y Y Time: H H : 0 0 (24-hour clock)

Interventions T6 → T24

Supplemental O_2: Yes (Y) → | | l min^{-1} No (N)

Highest FiO_2: | | . | |

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → | | | | ml

Crystalloid: Yes (Y) → | | | | | ml

Vasoactive agents: Yes (Y) No (N)

If yes Max. infusion rate

Dopamine: Yes (Y) → | | . | | μg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → | | . | | μg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → | | . | | | μg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → | | . | | μg kg^{-1} min^{-1}

Phenylephrine Yes (Y) → | | . | | μg kg^{-1} min^{-1}

Other: Yes (Y) → | | . | | μg kg^{-1} min^{-1}

Specify other:

PRBC: Yes (Y) → | | | | ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → | | | ml

FFP: Yes (Y) → | | | | ml

Albumin (20%): Yes (Y) → | | | | ml

Other: Yes (Y) → | | | | ml

Specify other:

Max. infusion rate

Dobutamine: Yes (Y) → | | . | | μg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other:

Neuromuscular blocking agent: Yes (Y) No (N)

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

T6 → T24 - Physiology

PrOMISe
Trial number:

Physiology T6 → T24

Lowest P/F ratio:

Not recorded (NR)

PaO_2: ___ . ___ kPa (K) mmHg (M) (NR)

FiO_2: ___ . ___

P/F ratio on mechanical ventilation: Yes (Y) No (N)

Lowest MAP: ___ mmHg **or**

Lowest SBP/DBP: ___ / ___ mmHg (NR)

Not recorded (NR)

Lowest platelets: ___ x10^9 l^{-1} (NR)

Highest bilirubin: ___ . ___ µmol l^{-1} (NR)

Highest creatinine: ___ µmol l^{-1} (NR)

Glasgow Coma Score (GCS) T6 → T24

Pre-sedation: Yes (Y) No (N)

Not recorded: (NR)

Lowest total GCS: ___

Eye opening response

- Spontaneous: (4)
- To speech: (3)
- To painful stimuli: (2)
- No response: (1)

Motor response

- Obeys commands: (6)
- Localises to painful stimuli: (5)
- Withdrawal to painful stimuli: (4)
- Abnormal flexion: (3)
- Extends to painful stimuli: (2)
- No response: (1)

Verbal response

- Oriented: (5)
- Confused: (4)
- Inappropriate words: (3)
- Incomprehensible sounds: (2)
- No response: (1)

Physiology at T24

Not recorded (NR)

Lactate: ___ . ___ mmol l^{-1} (NR)

Not recorded (NR)

Haemoglobin: ___ . ___ g dl^{-1} (NR)

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

PROMISE

Trial number: ☐☐☐☐

T24 → T72 – Interventions/Physiology

T72

Date: D D / M M / 2 0 Y Y Time: H H : 0 0 (24-hour clock)

Interventions T24 → T72

Supplemental O_2: Yes (Y) → ☐☐ l min^{-1} No (N)

Highest FiO_2: ☐ · ☐☐

Mechanical ventilation: Yes (Y) No (N)

IV fluid(s): Yes (Y) No (N)

If yes

Colloid: (exclude blood products) Yes (Y) → ☐☐☐☐ ml

Crystalloid: Yes (Y) → ☐☐☐☐☐ ml

Vasoactive agents: Yes (Y) No (N)

If yes

Max. infusion rate

Dopamine: Yes (Y) → ☐☐ · ☐ μg kg^{-1} min^{-1}

Dopexamine: Yes (Y) → ☐ · ☐ μg kg^{-1} min^{-1}

Epinephrine: Yes (Y) → ☐ · ☐☐ μg kg^{-1} min^{-1}

Norepinephrine Yes (Y) → ☐ · ☐☐ μg kg^{-1} min^{-1}

Phenylephrine Yes (Y) → ☐☐ · ☐ μg kg^{-1} min^{-1}

Other: Yes (Y) → ☐☐ · ☐☐ μg kg^{-1} min^{-1}

Specify other: ☐

PRBC: Yes (Y) → ☐☐☐☐ ml No (N)

Other blood products: Yes (Y) No (N)

If yes

Platelets: Yes (Y) → ☐☐☐ ml

FFP: Yes (Y) → ☐☐☐☐ ml

Albumin (20%): Yes (Y) → ☐☐☐☐ ml

Other: Yes (Y) → ☐☐☐☐ ml

Specify other: ☐

Max. infusion rate

Dobutamine: Yes (Y) → ☐☐ · ☐ μg kg^{-1} min^{-1} No (N)

Sedated: Yes (Y) No (N)

If yes

Sedative(s): Benzodiazepine: (B) Propofol: (P) Opioid: (D) Other: (O)

Specify other: ☐

Neuromuscular blocking agent: Yes (Y) No (N)

Physiology at T72

Lactate: ☐☐ · ☐ mmol l^{-1} (NR) Not recorded (NR)

Haemoglobin: ☐☐ · ☐ g dl^{-1} (NR) Not recorded (NR)

Completed by: ☐

Signature: ☐ **Date completed:** D D / M M / 2 0 Y Y

T48 → T72 – Interventions/Physiology/Infection

ProMISe
Trial number:

Interventions T48 → T72

Vasoactives administered: Yes (Y) No (N)

If yes

Dobutamine: Yes (Y)

Dopamine: Yes (Y) Max. rate → ≤5 µg kg^{-1} min^{-1} (L); >5 µg kg^{-1} min^{-1} (M); >15 µg kg^{-1} min^{-1} (U)

Epinephrine: Yes (Y) Max. rate → ≤0.1 µg kg^{-1} min^{-1} (L); >0.1 µg kg^{-1} min^{-1} (U)

Norepinephrine: Yes (Y) Max. rate → ≤0.1 µg kg^{-1} min^{-1} (L); >0.1 µg kg^{-1} min^{-1} (U)

Physiology T48 → T72

Lowest P/F ratio:

Not recorded (NR)

PaO_2: ____ . ____ kPa (K) mmHg (M) (NR)

FiO_2: ____ . ____

P/F ratio on mechanical ventilation: Yes (Y) No (N)

Lowest MAP: ____ mmHg **or**

Lowest SBP/DBP: ____ / ____ mmHg (NR)

Not recorded (NR)

Lowest platelets: ____ x10^9 l^{-1} (NR)

Highest bilirubin: ____ . ____ µmol l^{-1} (NR)

Highest creatinine: ____ µmol l^{-1} (NR)

Glasgow Coma Score (GCS) T48 → T72

Pre-sedation: Yes (Y) No (N)

Not recorded: (NR)

Lowest total GCS: ____

Eye opening response

- Spontaneous: 4
- To speech: 3
- To painful stimuli: 2
- No response: 1

Motor response

- Obeys commands: 6
- Localises to painful stimuli: 5
- Withdrawal to painful stimuli: 4
- Abnormal flexion: 3
- Extends to painful stimuli: 2
- No response: 1

Verbal response

- Oriented: 5
- Confused: 4
- Inappropriate words: 3
- Incomprehensible sounds: 2
- No response: 1

Infection (for source of sepsis)

Site:

- Lungs: (L)
- Soft tissue: (S)
- Abdomen: (A)
- Urinary tract: (U)
- Blood: (B)
- Other: (O)
- Central nervous system: (C)
- Specify: ____

Organism:

- Gram positive coccus: (C)
- Fungus/yeast: (F)
- Gram positive rod: (R)
- Parasite: (P)
- Gram negative coccus: (K)
- Virus: (V)
- Gram negative rod: (D)
- Other: (O)
- Specify: ____

Has the antimicrobial(s) changed since ED presentation? Yes (Y) No (N)

If yes

Specify new antimicrobial(s): ____

Completed by: ____

Signature: ____ **Date completed:** D D / M M / 2 0 Y Y

PrOMISe

Trial number: | | | | |

Acute hospital – Location/Discharge

Change of location in your hospital

From ED ®

Location*:	Start date:	Start time: (24-hour clock)
	D D / M M / 2 0 Y Y	H H : M M
	D D / M M / 2 0 Y Y	H H : M M
	D D / M M / 2 0 Y Y	H H : M M
	D D / M M / 2 0 Y Y	H H : M M
	D D / M M / 2 0 Y Y	H H : M M
	D D / M M / 2 0 Y Y	H H : M M

***Location:** A=Acute Admissions Unit (or equivalent), W=Ward, I=ICU or ICU/HDU, H=HDU, E=Emergency Department, T=Theatre*

Discharge

Acute hospital discharge status (from your hospital): Alive (A) Dead (D)

If alive

Date of discharge: D D / M M / 2 0 Y Y

Discharge location:

- Home: (H)
- Nursing Home: (N)
- Transfer to other hospital: (T)
- Other: (O)
- Specify:

If dead

Date of death: D D / M M / 2 0 Y Y

Time of death: H H : M M

Ultimate discharge from acute hospital:

Status: Alive (A) Dead (D)

Date: D D / M M / 2 0 Y Y

Note: Please obtain Retrospective Consent prior to discharge

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

Acute hospital – Organ support/Co-interventions

PrOMISe
Trial number: | | | | |

Organ support in your critical care location

	Total calendar days:		Total calendar days:
Advanced respiratory:		Gastrointestinal:	
Basic respiratory:		Liver:	
Advanced cardiovascular:		Dermatological:	
Basic cardiovascular:		Level 2:	
Renal:		Level 3:	
Neurological:			

Co-interventions (for source of sepsis)

Surgery: Yes (Y) No (N)

If yes Started: D D / M M / 2 0 Y Y H H : M M (24-hour clock)

APC: Yes (Y) No (N)

If yes Started: D D / M M / 2 0 Y Y H H : M M (24-hour clock)
Finished: D D / M M / 2 0 Y Y H H : M M (24-hour clock)

Steroids: Yes (Y) No (N)

If yes Started: D D / M M / 2 0 Y Y H H : M M (24-hour clock)
Finished: D D / M M / 2 0 Y Y H H : M M (24-hour clock)

Comments

Completed by:

Signature: **Date completed:** D D / M M / 2 0 Y Y

PrOMISe

Trial number: | | | | |

Safety monitoring (SOP 016)

(adverse events from randomisation ® 30 days)

Adverse events (specified)

	Severity[1]:	Start date:	Start time: (24-hour clock)	Related[2]:
Pneumothorax:		D D / M M / 2 0 Y Y	H H : M M	
Haemo-pneumothorax:		D D / M M / 2 0 Y Y	H H : M M	
Bleeding:		D D / M M / 2 0 Y Y	H H : M M	
Thrombosis:		D D / M M / 2 0 Y Y	H H : M M	
Pulmonary emboli:		D D / M M / 2 0 Y Y	H H : M M	
Vascular catheter infection:		D D / M M / 2 0 Y Y	H H : M M	
Pulmonary oedema:		D D / M M / 2 0 Y Y	H H : M M	
Blood transfusion reaction:		D D / M M / 2 0 Y Y	H H : M M	
Myocardial ischaemia:		D D / M M / 2 0 Y Y	H H : M M	
Peripheral ischaemia:		D D / M M / 2 0 Y Y	H H : M M	

Adverse events (other)

Adverse event:	Severity[1]:	Start date:	Start time: (24-hour clock)	Related[2]:
		D D / M M / 2 0 Y Y	H H : M M	
		D D / M M / 2 0 Y Y	H H : M M	
		D D / M M / 2 0 Y Y	H H : M M	
		D D / M M / 2 0 Y Y	H H : M M	
		D D / M M / 2 0 Y Y	H H : M M	

[1]*Severity:* *0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, 5=Fatal*

[2]*Related (to trial treatment):* *0=None, 1=Unlikely, 2=Possibly, 3=Probably, 4=Definitely*

Note: If Severity 3 or more, complete the Serious Adverse Event Reporting Form and fax to ICNARC CTU

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

PrOMISe

Trial number:

Retrospective consent

Retrospective consent

Regained mental capacity: Yes (Y) No (N)

Retrospective consent:

- Obtained (O)
- Part-obtained (P)
- Refused (R)
- Not sought (N)

Date: D D / M M / 2 0 Y Y

If part-obtained/ not sought

Details:

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

PrOMISe

Trial number: | | | | |

Investigator number: | | |

Death notification

Death

Date of death: D D / M M / 2 0 Y Y

If completed, return to ICNARC CTU

By fax: [redacted]
By email: [redacted]
By post: [redacted]

Comments

Completed by:

Signature:

Date completed: D D / M M / 2 0 Y Y

PrOMISe

Withdrawal of consent/agreement

Trial number: | | | | |

Investigator number: | | | |

Withdrawal of consent/agreement

Date of withdrawal: D D / M M / 2 0 Y Y

Reason (if available):

Consent/agreement withdrawn by:

- Patient 1
- Personal Consultee 2
- Professional Consultee 3

If completed, return to ICNARC CTU

By fax:
By email:
By post:

[redacted]

Comments

Completed by:

Signature: **Date completed:** D D / M M / 2 0 Y Y

Appendix 4 Severity of illness scores

Acute Physiology And Chronic Health Evaluation version II

The APACHE II Acute Physiology Score consists of weightings for 12 physiological parameters to give a total score ranging from 0 to 60, with higher scores indicating greater severity of illness.[33] The 12 physiological parameters are as follows:

- temperature
- mean arterial pressure
- heart rate
- respiratory rate
- alveolar–arterial gradient (if $FiO_2 \geq 0.5$) or PaO_2 (if $FiO_2 < 0.5$)
- arterial pH (or serum bicarbonate if no arterial blood gas recorded)
- serum sodium
- serum potassium
- serum creatinine (with double weighting for acute renal failure)
- haematocrit (estimated from haemoglobin)
- white blood cell count
- GCS score (assumed to be normal for patients sedated or paralysed).

The APACHE II score comprises the Acute Physiology score plus additional weightings for age and severe comorbidities in the past medical history to give a total score ranging from 0 to 71. Severe comorbidities must have been present and documented in the past medical history within the 6 months prior to presentation at hospital and are defined as follows:

- severe liver condition – presence of portal hypertension, biopsy proven cirrhosis or hepatic encephalopathy
- severe cardiovascular condition – presence of fatigue, claudication, dyspnoea or angina at rest (New York Heart Association Functional Class IV)
- severe respiratory condition – presence of permanent shortness of breath with light activity due to pulmonary disease, or on home ventilation
- renal condition – receiving chronic renal replacement therapy (haemodialysis, haemofiltration and peritoneal dialysis)
- immunological condition – receiving chemotherapy, radiotherapy or daily high-dose steroid treatment (≥ 0.3 mg/kg, prednisolone or equivalent) for 6 months, or diagnosis of human immunodeficiency virus (HIV)/acquired immunodefiency syndrome (AIDS), lymphoma, acute or chronic myelogenous/lymphocytic leukaemia, multiple myeloma and active metastatic disease.

Sequential Organ Failure Assessment

The SOFA score consists of weightings for six organ systems to give a total score ranging from 0 to 24, with higher scores indicating a greater degree of organ failure.[30] Organ dysfunction is defined as follows:

- respiratory dysfunction, defined as $PaO_2/FiO_2 < 400$ mmHg
- cardiovascular dysfunction, defined as mean arterial pressure < 70 mmHg (irrespective of vasopressor use)
- renal dysfunction, defined as creatinine of ≥ 1.2 mg/dl (110 µmol/l)
- neurological dysfunction, defined as GCS score of ≤ 14
- hepatic dysfunction, defined as bilirubin of ≥ 1.2 mg/dl (20 µmol/l)
- coagulation dysfunction, defined as platelets $< 150 \times 10^9$/l.

Mortality in Emergency Department Sepsis

The MEDS score is derived from nine variables to give a total score ranging from 0 to 33, with higher scores indicating a greater risk of death.[34] The nine variables are as follows:

- terminal illness, defined as presence of metastatic disease [distant (not regional lymph node) metastases documented by surgery, imaging or biopsy]
- respiratory difficulties, defined as tachypnea (respiratory rate of > 20 breaths per minute) or hypoxia ($SpO_2 < 90\%$ or $FiO_2 \geq 0.4$)
- septic shock, defined as severe sepsis plus hypotension (systolic blood pressure < 90 mmHg) that persists after initial fluid challenge of 20–30 ml/kg body weight of intravenous crystalloid
- low platelet count, defined as $< 150 \times 10^9$/l
- bandemia, defined as baseline immature neutrophils (band forms) < 5%
- age > 65 years
- suspected lower respiratory tract infection
- nursing home residence
- altered mental status, defined as a recent change in sensorium (confusion, disorientation, drowsiness, obtundation, stupor or coma) by history or physical examination or GCS score of ≤ 14.

Appendix 5 Critical Care Minimum Data Set criteria

Definitions

Duration of organ support in the critical care unit was defined as the number of days alive and free from support of each of the following organ systems, as defined by the UK Department of Health Critical Care Minimum Data Set,[31] during the first 28 days following randomisation. Patients that died within the first 28 days were assigned 0 days alive and free from organ support. Organ support definitions were as follows:

- advanced respiratory – indicated by one or more of invasive mechanical ventilatory support through a translaryngeal tube or tracheostomy; bilevel positive airway pressure through a trans-laryngeal tube or tracheostomy; continuous positive airway pressure through a trans-laryngeal tube; or extracorporeal respiratory support
- advanced cardiovascular – indicated by one or more of receipt of multiple intravenous and/or rhythm controlling drugs (of which at least one must be vasoactive) when used simultaneously to support or control arterial pressure, cardiac output or organ/tissue perfusion; continuous observation of cardiac output and derived indices; an intra-aortic balloon pump or other assist device; or a temporary cardiac pacemaker
- renal – indicated by receipt of acute renal replacement therapy (e.g. haemodialysis, haemofiltration, etc.) or receipt of renal replacement therapy for chronic renal failure where other acute organ support is received.

Appendix 6 Patient follow-up cover letter

ProMISe

[redacted]

<TITLE FIRSTNAME SURNAME>
<ADDRESS 1>
<ADDRESS 2>
<ADDRESS 3>
<CITY>
<POSTCODE>

DATE

Dear <TITLE> <SURNAME>

Re: ProMISe: Protocolised Management in Sepsis

When you were treated at <NAME OF HOSPITAL> in <MONTH, YEAR>, you may remember that you agreed to take part in a research study called ProMISe, which is comparing different treatments for patients admitted to hospital with a severe infection. A Patient Newsletter is enclosed which contains further information about ProMISe.

As part of the study, we are contacting patients <THREE MONTHS/ONE YEAR> after they were admitted to hospital to find out about their general health and well-being. We would be very grateful if you would complete the enclosed questionnaire – this should only take about 10 minutes of your time. A stamped, self-addressed envelope is provided for ease of return.

If you are the carer for the person to whom this letter is addressed and they are unable to read it, we would be very grateful if you could take the time to read this letter and the Patient Information Sheet on their behalf. If you feel that they would like to participate, please complete the questionnaire either with them or on their behalf. By better understanding the recovery of the person you care for, we hope to improve the care of future patients admitted to hospital with a severe infection.

The ProMISe Study, coordinated by the Intensive Care National Audit & Research Centre (ICNARC), is being conducted in 48 NHS hospitals and general information about the trial is available at the following website: www.icnarc.org. If you have any questions, or would like help completing the questionnaire, please contact the ProMISe Team at ICNARC (contact details above).

Thank you very much for your time. If you do not wish to fill in the questionnaire, please tick the relevant box on the questionnaire and return to us in the stamped self-addressed envelope provided.

Yours sincerely

[redacted]

Encs:

Version 2.1, 21/10/2013 **Patient Trial number:**

www.icnarc.org

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Appendix 7 Patient follow-up questionnaire

ProMISe

Trial Number: <Patient Trial ID No>

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

HEALTH QUESTIONNAIRE

We would be grateful if you would complete this questionnaire. The ProMISe trial aims to improve the care of patients with severe infection.

A pen is provided and a stamped self-addressed 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 tick the box and return the unanswered questionnaire in the stamped self-addressed envelope provided.

I do not wish to complete this questionnaire ☐

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

Health Questionnaire, Version 2.0, 21/11/11

YOUR HEALTH

We would be grateful if you could complete the following questions. We would like to understand how your health is since you left the hospital.

There are no right or wrong answers. We have found that the best way to answer the questions is to go with your first instinct, whatever **you** think is the correct response for you. Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

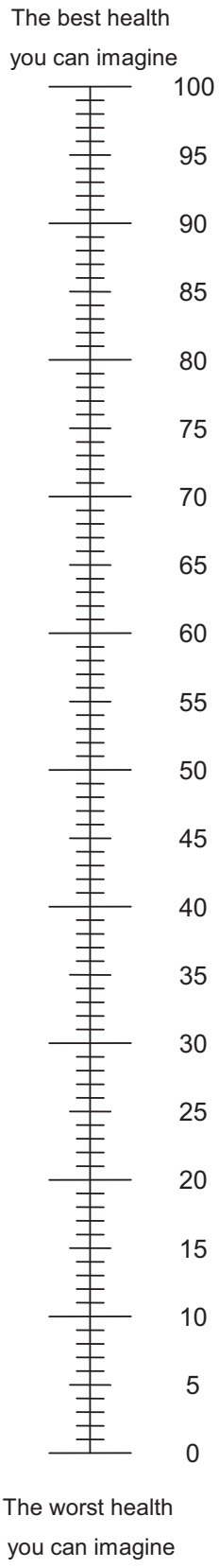
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



HEALTH SERVICES

We would be grateful if you could complete the following questions. It will help us understand the care you needed after leaving the hospital.

The questions refer to ALL health services that you have used since leaving the hospital on <Discharge date>, and before <Three months/one year>.

Part 1. Hospital Stay

A Since you left hospital on <Discharge 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 <Discharge 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 <Discharge 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 <Discharge 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 <Discharge 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…	☐	☐	☐
Psychologist	☐	_____	or…	☐	☐	☐
Speech and Language therapist	☐	_____	or…	☐	☐	☐
Physiotherapist	☐	_____	or…	☐	☐	☐
Dietician	☐	_____	or…	☐	☐	☐

Part 6. Other services not listed so far

A Since you left the hospital on <Discharge 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:

ProMISe Team
[redacted]
[redacted]

EME
HS&DR
HTA
PGfAR
PHR

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