Supplementary Appendix to Trial of Early, Goal-Directed Resuscitation for Septic Shock

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The North West London Research Ethics Committee approved the study. Research Ethics Committee Reference number: 10/H0722/42

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Supplementary Methods

Sites Inclusion Criteria

Criteria for participation were:

- Identification and sign-up of local investigators ("champions") from, at least, emergency medicine and critical care medicine;
- Not already providing early, goal-directed therapy (EGDT) as part of standard resuscitation practice;
- Identification of a ProMISe research nurse;
- Agreement to incorporate ProMISe into routine emergency department (ED) activity particularly highlighting the importance of screening at ED presentation;
- Agreement to adhere to randomization and to ensure adherence to study protocol;
- Agreement, where possible, to recruit all eligible patients and to maintain a ProMISe Screening Log to include reasons why eligible patients were screened and not recruited.

A Principal Investigator (PI), who was responsible for the conduct of the trial locally, was identified at each participating site.

Systemic Inflammatory Response Syndrome (SIRS) Criteria

Patients were required to have two or more SIRS criteria:[1]

a) core temperature of 36°C (98.8°F) or less or of 38°C (100.4°F) or more;
b) heart rate of 90 beats/min or more;
c) respiratory rate of 20 breaths/min or more (or hyperventilation indicated by either a $PaCO_2$ less than 4.3 kPa (32 mmHg) or mechanical ventilation for an acute process); or
d) white blood cell count of 4×10^9/L or less or of 12×10^9/L or greater (or the presence of greater than 10% immature neutrophils (band forms)).

Patient Exclusion Criteria

- Age less than 18 years
- Known pregnancy
- Primary diagnosis of:
  - acute cerebral vascular event
  - acute coronary syndrome
  - acute pulmonary edema
  - status asthmaticus
  - major cardiac arrhythmia (as part of primary diagnosis)

    - seizure
    - drug overdose
    - injury from burn or trauma
- Hemodynamic instability due to active gastrointestinal hemorrhage
- Requirement for immediate surgery
- Known history of AIDS
- Do-Not-Attempt-Resuscitation (DNAR) order
- Advanced directives restricting implementation of the resuscitation protocol
- Contraindication to central venous catheterization
- Contraindication to blood transfusion
- Attending clinician deems aggressive resuscitation unsuitable
- Transferred from another in-hospital setting
- Not able to commence resuscitation protocol within one hour of randomization or complete six hours of protocol treatment from commencement

Informed Consent

Once eligibility had been confirmed, if possible, informed consent was obtained from the patient before randomization. If the patient lacked mental capacity to provide informed consent, then, in accordance with the UK Mental Capacity Act (2005), a Personal Consultee (PeC), who could be a relative or close friend, was identified with whom to discuss the patient's participation in the study. If the PeC agreed to the patient's participation in the study, they were asked to sign the Consultee Agreement Form. If a PeC was only available via the telephone, verbal agreement was taken. If there was no PeC available, then the patient was provided with a Professional Consultee (PrC) – an Independent Mental Capacity Advocate appointed by the NHS Hospital Trust – to discuss the patient's participation in the study. If the PrC agreed to the patient's participation in the study, they were asked to sign the Consultee Agreement Form. If there was neither a PeC nor PrC immediately available, then an independent senior doctor or senior nurse was consulted in person or via telephone for emergency consent. If they agreed to the patient's participation in the study, the doctor or nurse completed the Emergency Consent Form. Once the patient had regained mental capacity to be able to provide informed consent, the patient was asked for their consent retrospectively to continue participation in the trial. Patients with pre-existing mental capacity issues, which meant they would never have capacity to give informed consent retrospectively even if they fully recovered from their sepsis, were excluded on advice from the Research Ethics Committee (REC).

Randomization

Following informed consent, agreement from a PeC or PrC, or emergency consent, patients were enrolled into the study. Eligible patients were randomly assigned in a 1:1 ratio to either six hours of EGDT or to usual resuscitation (usual care – standard UK resuscitation practice). We assigned patients to one of the two study groups by randomized permuted blocks (with variable block lengths of 4, 6 and 8) stratified by recruiting site, with the use of a centralized, 24-hour, seven days per week, telephone randomization service.

Details of Early, Goal-Directed Therapy

For patients randomized to EGDT, the clinical protocol commenced as soon as possible following randomization and within "one hour" (defined as up to the end of the following hour e.g. if the patient was randomized at 9:24 am then EGDT had to start by 11:00 am). Simple protocol guides were provided.

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

Central venous catheter

A central venous catheter (CVC) capable of continuous optical hemoglobin oxygen saturation ($ScvO_2$) monitoring (PreSep catheter connected to Vigileo monitor, Edwards Lifesciences, UK) was inserted either into a subclavian or internal jugular vein using standard techniques for central venous access and calibrated against a sample aspirated from the catheter and analyzed by co-oximetry. All CVCs were inserted and managed according to the guidelines of the CVC Care Bundle.[2]

Arterial catheter

An arterial catheter was recommended, but not mandated.

Fluid resuscitation

Fluid boluses in half-liter, or equivalent, increments were to be given every 30 minutes until a minimum central venous pressure (CVP) of 8 mmHg was reached. The type of fluid used was at the discretion of the treating clinician(s). The rate could be adjusted, based upon individual patient requirements, at the discretion of the treating clinician(s). Additionally, if the treating clinician(s) discerned a risk to patient safety, a lower CVP target could be used.

Blood pressure management

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

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

$ScvO_2$ management

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

If the $ScvO_2$ was less than 70% and the post-fluid resuscitation hemoglobin was less than 10g/dL, then red cells were to be transfused. If the $ScvO_2$ was still less than 70% and the hemoglobin was 10g/dL or above, then inotropic support was to be initiated with dobutamine. Dobutamine dosing was 2.5 µg/kg/min, over thirty minutes initially, then increased by 2.5 µg/kg/min every thirty minutes until the $ScvO_2$ was 70% or greater. Dobutamine was reduced/discontinued, at the discretion of the treating clinician(s), if there was concern about a likely, drug-induced tachycardia, arrhythmia, or if a maximum dose of 20 µg/kg/min was attained.

If the $ScvO_2$ remained low, then the patient was to be intubated, sedated and paralyzed, if not already done, to decrease oxygen consumption.

Post-goal monitoring

Once all goals were met, the patient was monitored continuously for the remainder of the intervention period (a total of six hours). If an end-point subsequently fell below its goal, then the resuscitation protocol recommenced. At the end of six hours, the patient returned to standard care and continuous $ScvO_2$ monitoring was no longer mandated.

Definitions of Baseline Variables

Age was calculated in whole years at the point of randomization. Sex was the genotypical sex of the patient. Severe comorbidities were defined according to the Acute Physiology And

Chronic Health Evaluation version II (APACHE II).[3] These comorbidities must have been present and documented in the past medical history within the six months prior to presentation at ED and were defined as follows:

- Patients with a severe liver condition in the past medical history were those with portal hypertension, biopsy proven cirrhosis or hepatic encephalopathy.
- Patients with a severe cardiovascular condition in the past medical history were those with fatigue, claudication, dyspnea or angina at rest (New York Heart Association Functional Class IV).
- Patients with a severe respiratory condition in the past medical history were those with permanent shortness of breath with light activity due to pulmonary disease, or on home ventilation.
- Patient with a renal condition in the past medical history were those who received chronic renal replacement therapy (hemodialysis, hemofiltration and peritoneal dialysis).
- Patients with an immunological condition in the past medical history were those who received chemotherapy, radiotherapy or daily high-dose steroid treatment (0.3 mg/kg, or greater, prednisolone or equivalent) for six months prior to presentation at ED, or those with HIV/AIDS, lymphoma, acute or chronic myelogenous/lymphocytic leukemia, multiple myeloma and active metastatic disease.

APACHE II severity of illness scores were calculated from raw data using standardized computer algorithms. Severity of illness scores were calculated using the last recorded physiology data prior to randomization. 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. The APACHE II Score comprises the Acute Physiology Score plus additional weightings for age and severe conditions in the past medical history (as defined above) to give a total score ranging from 0 to 71.[3]

Organ dysfunction was defined according to the Sequential Organ Failure Assessment (SOFA)[4] score as follows:

- Respiratory dysfunction was defined as PaO_2/FiO_2 less than 400 mmHg
- Cardiovascular dysfunction was defined as MAP less than 70 mmHg (irrespective of vasopressor use)
- Renal dysfunction was defined as creatinine of 1.2 mg/dL (110 µmol/L) or more
- Neurological dysfunction was defined as Glasgow Coma Score (GCS) of 14 or less
- Hepatic dysfunction was defined as bilirubin of 1.2 mg/dL (20 µmol/L) or more
- Coagulation dysfunction was defined as platelets less than 150×10^9/L

The SOFA score[4] was calculated from raw physiology and treatment data collected prior to randomization. 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.

The Mortality in Emergency Department Sepsis (MEDS) score[5] was calculated from raw data at baseline. The MEDS score is derived from nine variables (terminal illness, respiratory difficulties, septic shock, platelets less than 150×10^9/L, baseline immature neutrophils (band forms) less than 5%, age greater than 65 years, suspected lower respiratory tract infection, nursing home resident and altered mental status) to give a total score ranging from 0 to 33.

MEDS terminal illness was defined as presence of metastatic disease (distant (not regional lymph node) metastases documented by surgery, imaging or biopsy).

MEDS respiratory difficulties was defined as tachypnea (respiratory rate of greater than 20 breaths per minute) or hypoxia (SpO_2 less than 90% or FiO_2 of 0.4 or more).

MEDS septic shock was defined as severe sepsis plus hypotension (systolic blood pressure less than 90 mmHg) that persisted after fluid challenge of 20-30 mL/kg body weight of intravenous crystalloid.

MEDS altered mental status was defined as a recent change in sensorium (confusion, disorientation, drowsiness, obtundation, stupor or coma) by history or physical examination or GCS of 14 or less.

Resource Use Categories

Intervention

- Equipment and consumables - the type of vascular catheter (CVC capable of $ScvO_2$ monitoring, standard CVC and/or arterial catheter) used was recorded for each patient. Unit costs of the CVC capable of $ScvO_2$ monitoring and monitor were obtained from the manufacturer. It was assumed that to provide the EGDT protocol in routine practice each site would require two monitors, which would have a lifespan of, on average, five years. The monitor costs per patient were calculated by dividing the total costs of the monitors by the expected number of eligible patients over five years. The annual number of eligible patients was calculated by taking the average number of potentially eligible patients per site per year from the trial screening log data. The costs of consumables including the CVC capable of $ScvO_2$ monitoring and pressure transducers to measure intravascular pressures were also included (Table S11). Other additional consumables (saline infusion, cleaning packs, sterile gloves) associated with each type of vascular line insertion were also considered (Table

S11). Consumable costs anticipated to be similar across the two groups were excluded.

- Blood products and dobutamine – the use of transfused blood products and dobutamine was recorded for each patient. Other items such as other blood products, albumin, crystalloid and vasoactive drugs were not anticipated to differ across groups, and were included in the cost per day in critical care.

Staff time

Delivery of the EGDT protocol required additional staff time whether it was delivered in the ED or in the critical care unit. Staff time included:

- Time for vascular catheter insertion (doctor's time) and setting-up the monitor (nurse's time) was estimated based on expert opinion (Table S11).
- Delivery of the EGDT protocol – if the EGDT protocol was delivered in the ED, it was assumed that staff training and additional nurse time for monitoring patients was required. Whereas, if delivered in critical care, it was assumed that staff training and additional nurse time for monitoring patients was not required. It was assumed that in the ED at least one trained nurse was available for the duration of delivery of the EGDT protocol. Hence the base case analysis used information recorded in the case report forms (CRFs) on the number of hours that each patient received EGDT in each setting (ED versus critical care) to recognize that the training and monitoring costs of delivering the EGDT protocol were lower in critical care than in the ED.

The base case analysis assumed that, when delivered in the ED, each patient in EGDT group required an additional 10 minutes of nurses' monitoring time per hour of the EGDT protocol. Additional formal or informal training beyond the existing hospital education program was considered necessary to implement EGDT into clinical practice. Staff at each site were trained to deliver the EGDT protocol. A training time of 20 minutes per ED clinical staff member in delivery of the EGDT protocol was assumed. The total cost of training time for introducing the EGDT protocol into the ED was calculated for each site assuming an average staff mix, over the assumed five-year life cycle of the protocol, of seven (attending) consultants, 23 junior doctors and 75 nurses.[6] The training costs per patient were calculated from total training costs per site divided by total eligible patients per site over five years.

Hospital stay

Hospital stay during the primary admission, included time spent in the ED and days spent in the critical care unit and/or general medical/surgical wards. For each day in the critical care unit, the number of organs supported was also recorded, from which a Healthcare Resource Group (HRG) for the critical care episode was assigned according to maximum number of organs supported during the episode.[7]

Re-admissions to critical care

Re-admission costs included the costs of critical care and time on a general medical/surgical ward. The base case included the costs of those re-admissions recorded in the ICNARC Case Mix Programme (CMP) database[8].

In hospital re-admissions, hospital outpatient visits and community service use

In the base case in hospital re-admissions that did not require critical care, hospital outpatient visits and community service use for reasons both related and unrelated to septic shock reported from responses to the Health Services Questionnaire administered as part of the 90-day follow-up were included. Other hospital outpatient visits and community service use (e.g. visits to the family doctor, nurse, health visitor, occupational therapist, physiotherapist, psychologist) were taken from responses to a Health Services Questionnaire administered to surviving patients at 90 days post-randomization.

Unit Costs

The unit cost of the monitor was obtained from the manufacturer (Table S12). The cost of the CVC capable of $ScvO_2$ monitoring was obtained from the manufacturer and the procurement department of the participating hospital. The costs per critical care bed day by HRG and general medical bed day were taken from the 'Payment by Results' database.[9] Unit costs for hospital outpatient visits and community service use were obtained from a recommended published source for Health and Social Care costs.[10] Unit costs for blood products and other drugs were taken respectively from NHS Blood & Transplant,[11] and British National Formulary.[12]

Linkage with Routine Data Sources

ProMISe data were linked with death registrations using the Data Linkage and Extract Service of the Health and Social Care Information Centre to follow-up mortality following discharge from hospital.

Definitions of Outcome Measures

The primary outcome of 90-day mortality was defined as death from any cause within 90 days following the date of randomization.

Advanced respiratory support, advanced cardiovascular support and renal support in the critical care unit were defined by the UK Department of Health Critical Care Minimum Dataset (CCMDS),[7] during the first 28 days following randomization, as follows:

- Advanced respiratory support was indicated by one or more of: invasive mechanical ventilatory support via a trans-laryngeal tube or tracheostomy; bilevel positive airway

pressure via a trans-laryngeal tube or tracheostomy; continuous positive airway pressure via a trans-laryngeal tube; or extracorporeal respiratory support.

- Advanced cardiovascular support was 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 temporary cardiac pacemaker.
- Renal support was indicated by: receipt of acute renal replacement therapy (e.g. hemodialysis, hemofiltration etc.); or receipt of renal replacement therapy for chronic renal failure where other acute organ support is received.

Patients that died within the first 28 days were assigned zero days alive and free from organ support.

The length of stay in the ED was calculated as the sum of the duration, in hours, from the date and time of randomization to the date and time of the first change in location of care or death in the ED.

The length of stay in critical care was calculated as the sum of the durations in days and fractions of days (from the date and time of randomization for the first stay or date and time of admission for subsequent stays to the date and time of discharge from the critical care unit or death) of all critical care unit stays between randomization and discharge from acute hospital. The length of stay in acute hospital was calculated as the duration in days from the date of randomization to the date of discharge from acute hospital or death.

Mortality at discharge from the critical care unit, at discharge from acute hospital, at 90 days and at one year from randomization were defined as deaths from any cause within these timeframes.

Health-related quality-of-life (QOL) was measured using a generic measure, the EQ-5D (http://www.euroqol.org/), which requires patients to describe their health on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D instrument chosen was the ED-5D with 5 levels (EQ-5D-5L) which for each dimension requires patients to state whether they have ‘no problems’, ‘slight problems’, ‘moderate problems’, ‘severe problems’ or ‘extreme problems’. Each patient’s described health at each time point was valued according to health state preferences from the general population to calculate EQ-5D utility scores, which are anchored on a scale from 0 (death) to 1 (perfect health).[13] Quality-Adjusted Life years (QALYs) were calculated by valuing each patient’s survival time by their health-related QOL at 90 days according to the ‘area under the curve’

approach.[14] For 90-day survivors, QALYs were calculated using the EQ-5D scores at 90 days, assuming an EQ-5D score of zero at randomization, and a linear interpolation between randomisation and 90 days. For decedents between randomization and 90 days, we assumed zero QALYs.

Adverse Event Reporting

Patients were monitored for adverse events occurring between randomization and 30 days following randomization. Specified adverse events were defined as follows:

- Pneumothorax was defined as any new pneumothorax requiring insertion of a chest drain (intercostal catheter) that occurred between randomization and 30 days following randomization.
- Hemo-pneumothorax was defined as any new hemo-pneumothorax requiring insertion of a chest drain that occurred between randomization and 30 days following randomization.
- Bleeding was defined as any new, overt blood loss requiring transfusion of one or more units of blood that occurred between randomization and 30 days following randomization.
- Thrombosis was defined as any new clinical and radiographic evidence of a deep vein thrombosis that occurred between randomization and 30 days following randomization.
- Pulmonary emboli was defined as any new evidence from computed tomography (CT) pulmonary angiogram with appropriate clinical history that occurred between randomization and 30 days following randomization.
- Vascular catheter infection was defined as any new vascular catheter related infection that occurred between randomization and 30 days following randomization where a vascular catheter, such as a CVC, was identified as the primary source of infection and associated with signs and symptoms of infection requiring antimicrobials.
- Pulmonary edema was defined as any new radiographic evidence consistent with pulmonary edema that occurred between randomization and 30 days following randomization.
- Blood transfusion reaction was defined as any allergic reaction to blood transfusion, hemolysis related to incompatible blood type, or alteration of immune system related to blood transfusion that occurred between randomization and 30 days following randomization.
- Myocardial ischemia was defined as any new acute electrocardiogram (ECG) changes with appropriate clinical findings and changes in cardiac troponins or non-ST

segment elevation myocardial infarction (NSTEMI) with appropriate increases in cardiac troponins but without ECG changes that occurred between randomization and 30 days following randomization.

- Peripheral ischemia was defined as any new sustained depression or loss of arterial pulse (as determined by palpation or Doppler ultrasonography) resulting in symptoms consistent with ischemia or obvious gangrene that occurred between randomization and 30 days following randomization.

Unspecified adverse events were defined as an unfavorable symptom or disease temporally associated with the use of the study treatment, whether or not it was related to the study 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 that were assessed to be serious (i.e. prolonging hospitalization or resulting in persistent or significant disability/incapacity), life-threatening or fatal (collectively termed 'serious adverse events') were reported to the ICNARC Clinical Trials Unit and reviewed by a clinical member of the Trial Management Group. Serious adverse events that were unspecified and considered to be possibly, probably or definitely related to the study treatment were reported to the REC.

Statistical Analysis

Clinical effectiveness

A single, planned, interim analysis was performed, and reviewed by the independent Data and Safety Monitoring Committee, at the point that 90-day outcomes for the first 500 patients were available. A Haybittle-Peto stopping rule ($P<0.001$) was used to guide recommendations for early termination.

The adjusted analysis used multilevel logistic regression, adjusted for the components of MEDS score and a site-level random effect. Missing baseline data were imputed in adjusted analyses using multivariate imputation by chained equations (MICE).[15]

A sensitivity approach was taken when the primary outcome was missing by assuming all patients with missing outcomes survived in the EGDT group and died in the usual resuscitation group and repeating with the opposite assumptions.

A site-level learning curve for patients in the EGDT group 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.[16]

The primary analysis was repeated adjusting for adherence using a structural mean model[17] with an instrumental variable of assigned group, assuming a linear relationship between the

degree of adherence (proportion of the intervention period assigned elements of the protocol delivered as intended) and treatment effect to estimate the efficacy of EGDT compared with usual resuscitation.[18]

For secondary outcomes, differences in mean SOFA score were analyzed using analysis of covariance (ANCOVA), number of patients receiving advanced cardiovascular, advanced respiratory and renal support using Fisher's exact test, mean number of days alive and free from receiving advanced cardiovascular, advanced respiratory and renal support up to 28 days using t-tests (with bootstrapping to account for anticipated non-normality in the distributions)[19] and lengths of stay, stratified according to survival, using Wilcoxon rank-sum tests. All mortality outcomes were tested with Fisher's exact test and reported as unadjusted Relative Risks and adjusted Odds Ratios. Kaplan-Meier survival curves to 90 days were plotted and compared using the log rank test. An adjusted analysis of duration of survival using a Cox proportional-hazards model was also conducted and reported as an adjusted hazard ratio.

We undertook subgroup analyses using the likelihood-ratio test to assess interactions between treatment group and the pre-specified subgroups in adjusted multilevel logistic regression models. Degree of protocolized care for the usual resuscitation group was assessed based on established guidelines[20-22] as the proportion of patients assigned to the usual resuscitation group that had lactate measured at baseline and, if ≥ 4 mmol/L at baseline, re-measured within six hours. Sites were categorized as having a higher degree of protocolized care if the proportion of patients in the usual resuscitation group that met this condition was greater than 50%. Sites with fewer than three patients assigned to the usual resuscitation group were excluded from this subgroup analysis. The remaining subgroups (age, MEDS score, SOFA score and time from ED presentation to randomization) were analyzed in quartiles.

Cost-effectiveness

Missing data in baseline covariates, resource use and health-related QOL variables were handled with MICE.[15] Under this approach each variable was imputed conditional on fully observed baseline variables such as age, gender, past medical history, site of sepsis, SOFA score, MEDS score, admitted from nursing home, length of stay in critical care and general medical ward up to 90 days, and all other imputed variables. Table S13 reports all the variables considered for multiple imputation, and for each variable, the number of missing values, and the imputation model chosen.

Patients who failed to return the EQ-5D questionnaire administered at 90 days, had their EQ-5D scores imputed from other survivors.

Total costs at 90 days were calculated by combining the resource use with unit costs at 2012 prices in GB pounds (£), and then converted to US dollars ($) [£1: $1.4215].[23] In the base case, incremental costs were reported as unadjusted mean differences between the study groups, together with 95% confidence intervals. We also reported unadjusted differences in health-related QOL and QALYs between the EGDT and usual resuscitation groups. The differences in average costs and QALYs between the randomized groups were used to calculate the incremental net benefits (INB). We valued the incremental QALY according to the threshold willingness to pay for a QALY gain recommended by the National Institute for Health and Care Excellence (NICE) (£20,000 [$28,430] per QALY),[24] and subtracted from this the incremental cost. INBs were reported overall, and for the same pre-specified subgroups as for the clinical endpoints.

The uncertainty around the differences in average costs and QALYs between the groups was illustrated on the cost-effectiveness plane. We estimated the incremental costs and QALYs with a seemingly unrelated regression model. To express the uncertainty in the estimation of the incremental costs and QALYs, we used the estimates of the means, variances and the covariance from the regression model, to generate 500 estimates of incremental costs and QALYs from the joint distribution of these endpoints, assuming Asymptotic Normality. We then plotted these incremental costs and QALYs on the cost-effectiveness plane. We also reported cost-effectiveness acceptability curves, by calculating the probability that, compared to usual resuscitation, EGDT is cost-effective given the data, at alternative levels of willingness to pay for a QALY gain.[24]

The main assumptions made in the base case scenario, and how each was relaxed in sensitivity analyses are detailed below and summarized in Table S16.

- Equipment costs for the intervention – in the base case, unit costs for the monitor and CVC capable of $ScvO_2$ monitoring were taken from manufacturer's discounted costs. These unit costs entail over 50% discounts on list prices. In the sensitivity analysis full list prices for monitor and catheters were applied.
- Staff monitoring time (during delivery of the EGDT resuscitation protocol) – the intervention involves intensive monitoring of patients during six hours post randomization for the delivery of the resuscitation protocol. In the base case we assumed 10 minutes of nurse's time per hour of the resuscitation protocol. In the sensitivity analysis we varied the nurse's time over 5-15 minutes per hour that the protocol was delivered for.
- Staff training time (for delivery of the EGDT resuscitation protocol) – staff training for the protocol was required in the trial and staff in each site were trained. For the implementation of this protocol in routine ED practice, the base case assumes that for

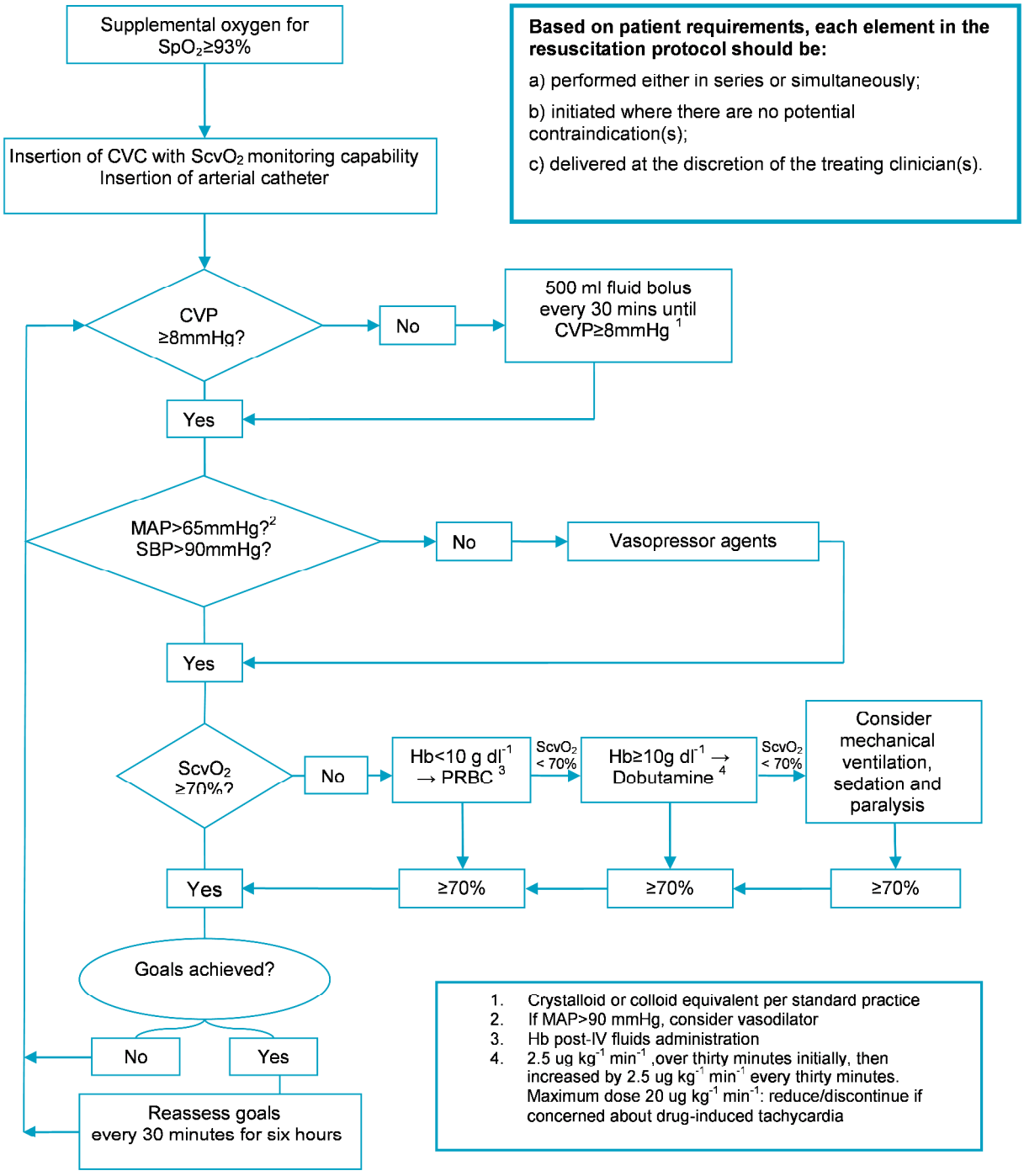
each member of staff 20 minutes is required with re-training required every five years. In the sensitivity analysis training time was varied between 15-30 minutes.

- Delivery of the EGDT resuscitation protocol (costs of delivering exclusively in the ED versus exclusively in the critical care unit – the base case analysis incorporated the relative time that each patient in the EGDT group received the protocol in the ED versus in a critical care unit. In practice EGDT may be exclusively delivered in either setting, the sensitivity analysis allowed the costs of monitoring and training to reflect either extreme i.e. EGDT delivered solely in the ED and EGDT delivered solely in critical care.
- Re-admissions (from Health Services Questionnaire) – the base case analysis included re-admissions recorded on the CMP database but also those recorded from responses to the Health Services Questionnaire. To consider the possible impact of double-counting, this sensitivity analysis only included re-admissions from the CMP database.
- Baseline covariates – the base case reported unadjusted mean differences of both incremental costs and QALYs without any covariate adjustment, assuming randomization had ensured no imbalances in key prognostic factors such as components of MEDS score.[5] In the sensitivity analysis, we adjusted for any chance imbalances in MEDS score using seemingly unrelated regression.
- Distributional assumptions (for costs and QALY) – the base case assumed that costs and QALYs were normally distributed when reporting the 95% confidence intervals around incremental costs and QALYs. In sensitivity analyses we assessed the robustness of the cost-effectiveness results to alternative distributional assumptions about both outcomes. 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 model assuming gamma distribution for each endpoint (i.e. ignoring possible correlation between the endpoints).

The results of the sensitivity analysis are reported as mean INBs with corresponding 95% confidence intervals (CI) (Figure S9).

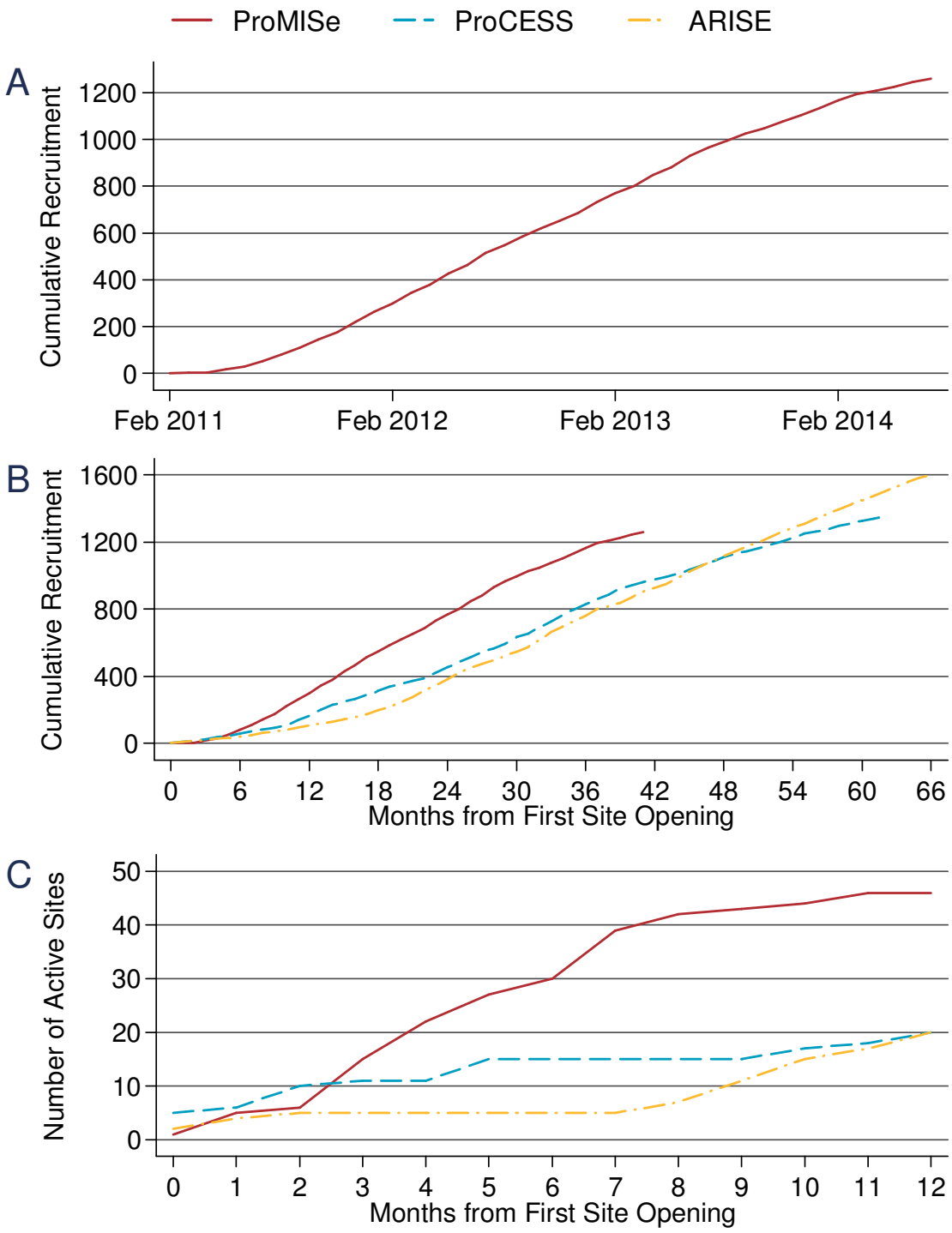
Supplementary Figures

Figure S1. Early, Goal-Directed Therapy Resuscitation Protocol.



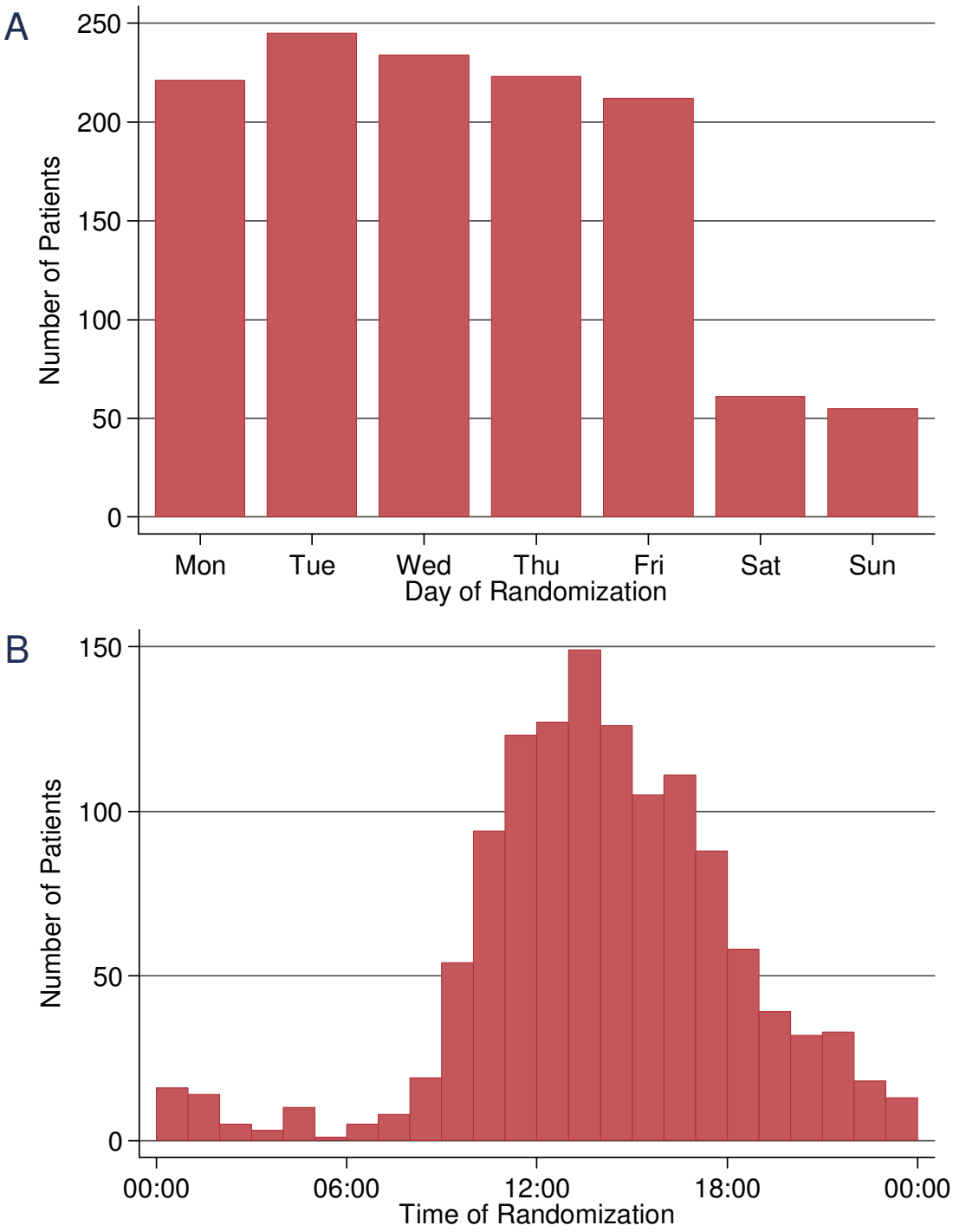
Adaptation from original EGDT algorithm[25] as follows: arterial catheter recommended, not mandated; option to use SBP as a blood pressure goal, rather than solely MAP; minimum goals set for CVP and MAP, rather than a range.

Figure S2. Patient Recruitment and Site Opening.



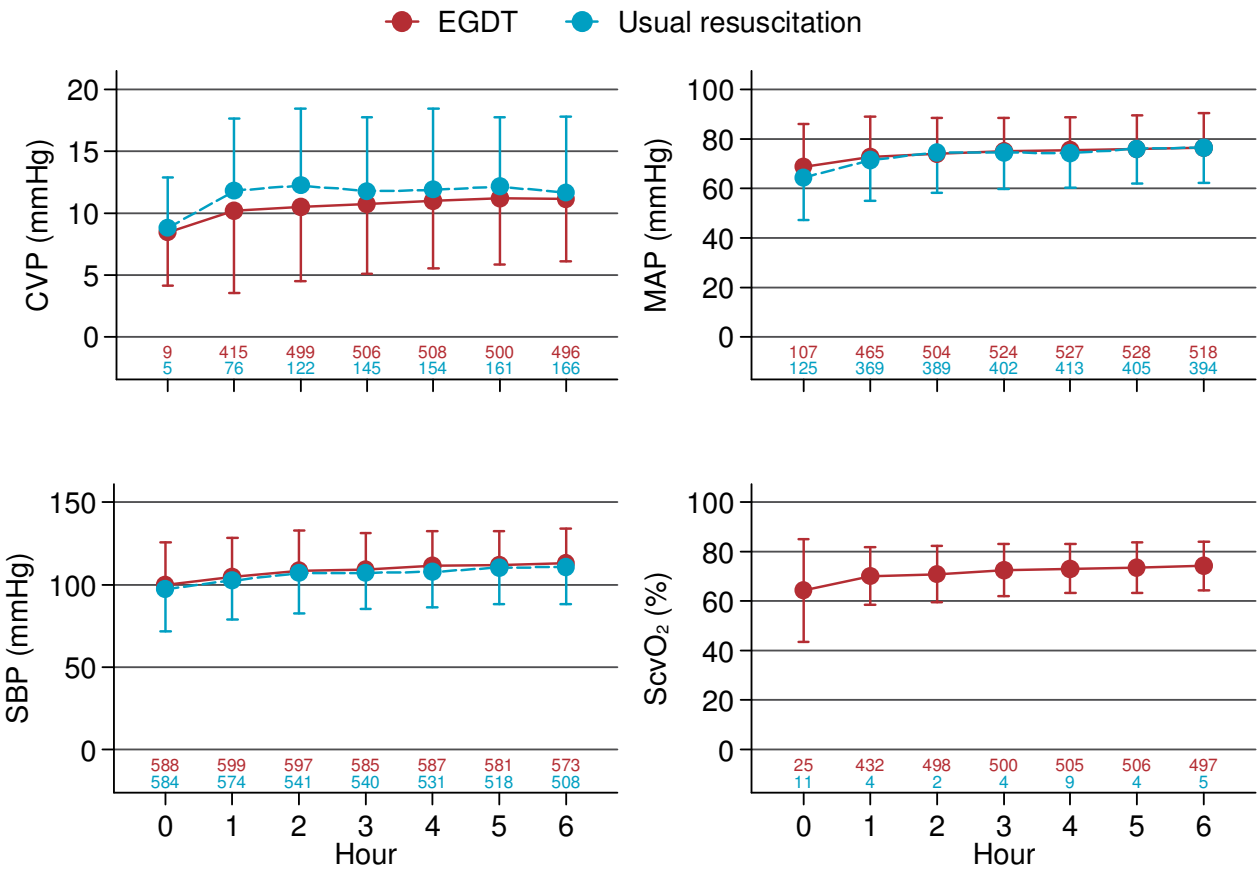
Cumulative recruitment of patients into the ProMISe trial, (A) for ProMISe alone and (B) for ProMISe compared with ProCESS and ARISE. (C) Number of sites open and recruiting to ProMISe compared with ProCESS and ARISE during the first 12 months of recruitment (note: ARISE included a six-month pilot phase).

Figure S3. Randomization by Day of Week and Time of Day.



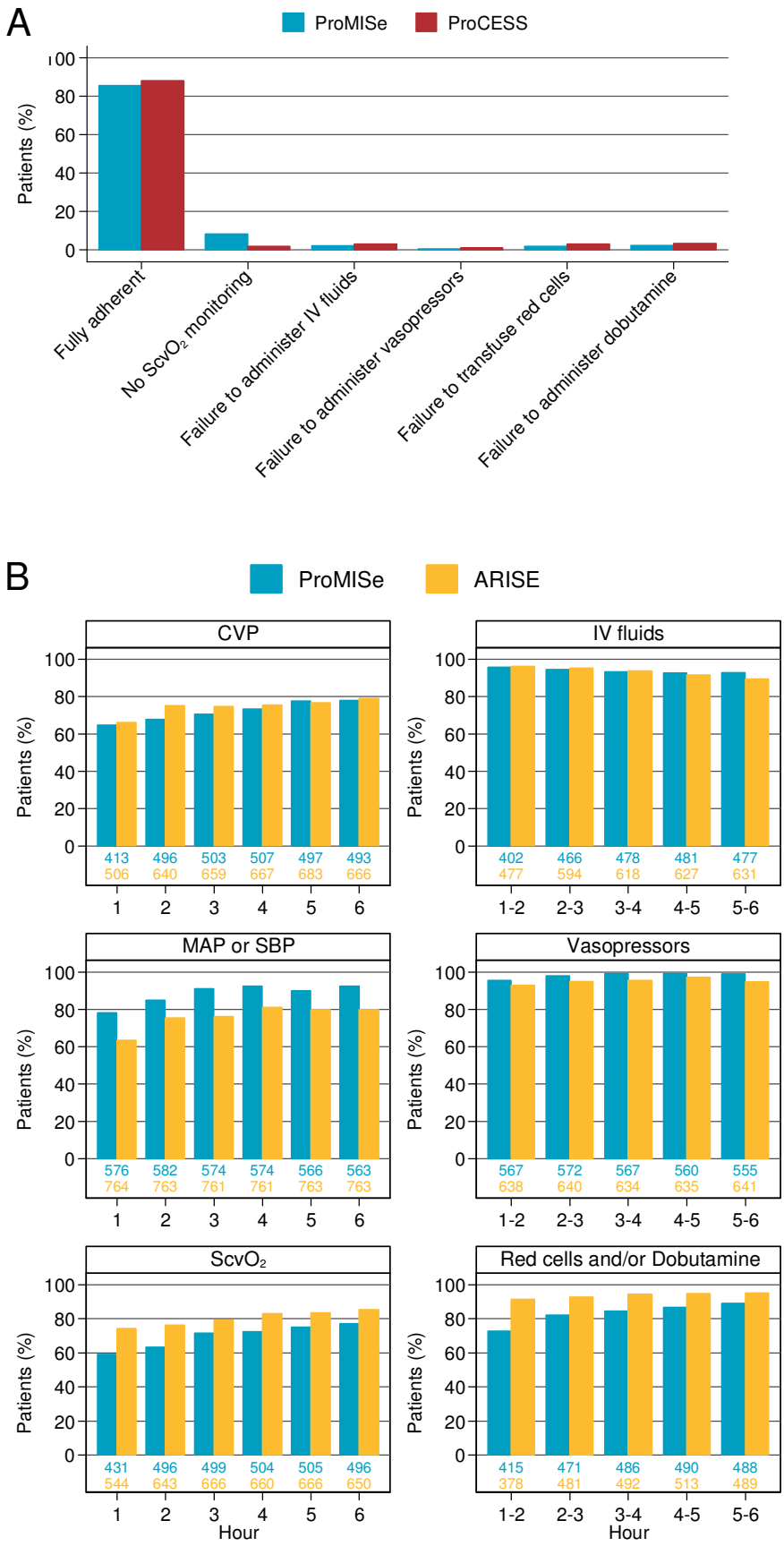
Timing of randomization by (A) day of the week and (B) time of the day.

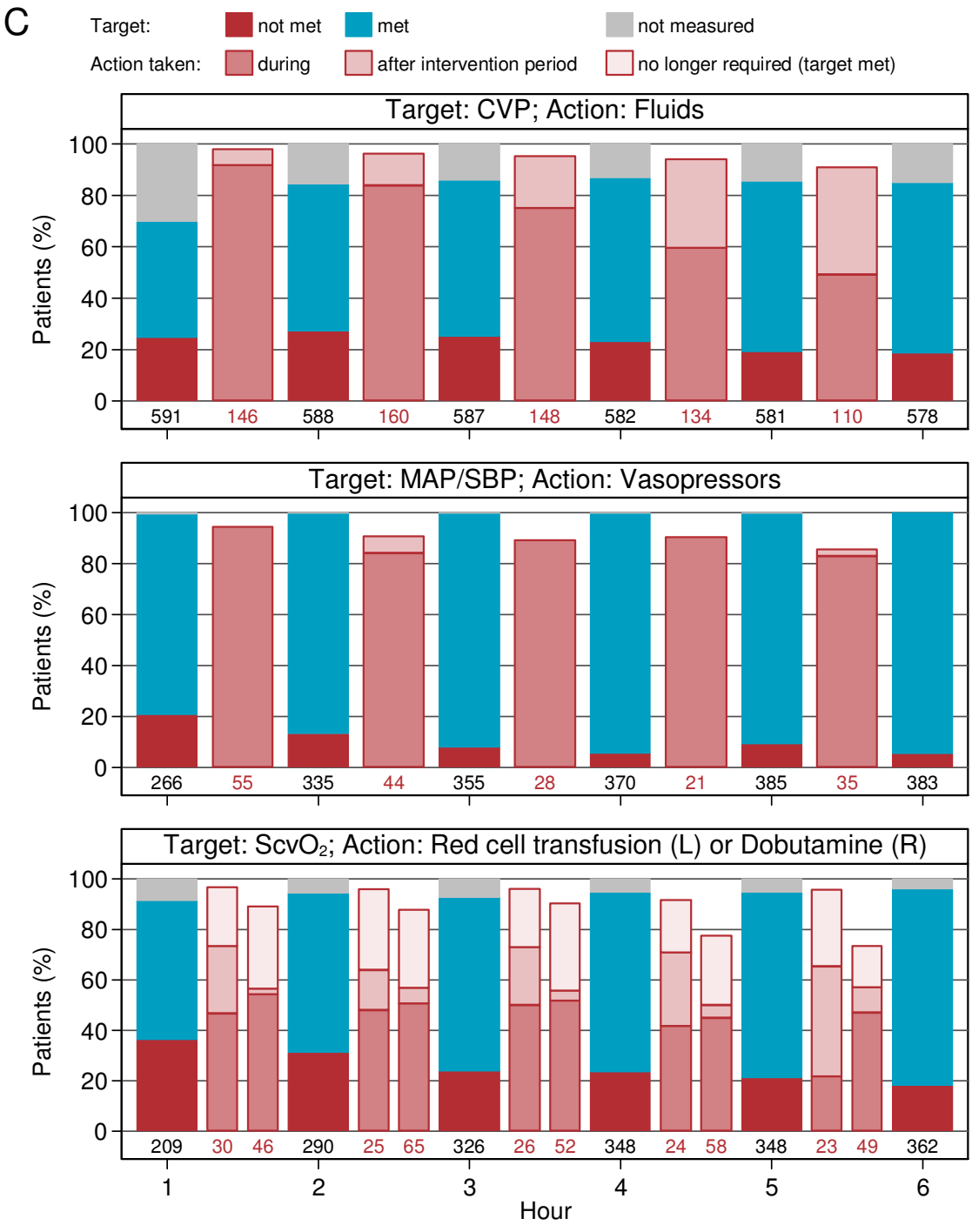
Figure S4. Physiology during the Intervention Period.



Values reported are the mean plus/minus standard deviation for values recorded within 15 minutes either side of the specified time points. For the EGDT group, first recorded values after insertion of the CVC with continuous $ScvO_2$ monitoring capability is at Hour one. Numbers at the foot of each point represent the denominator for the means in that point. $ScvO_2$ measurements are not reported for the usual resuscitation group due to very small numbers of patients for which these were recorded.

Figure S5. Adherence to the EGDT Protocol.

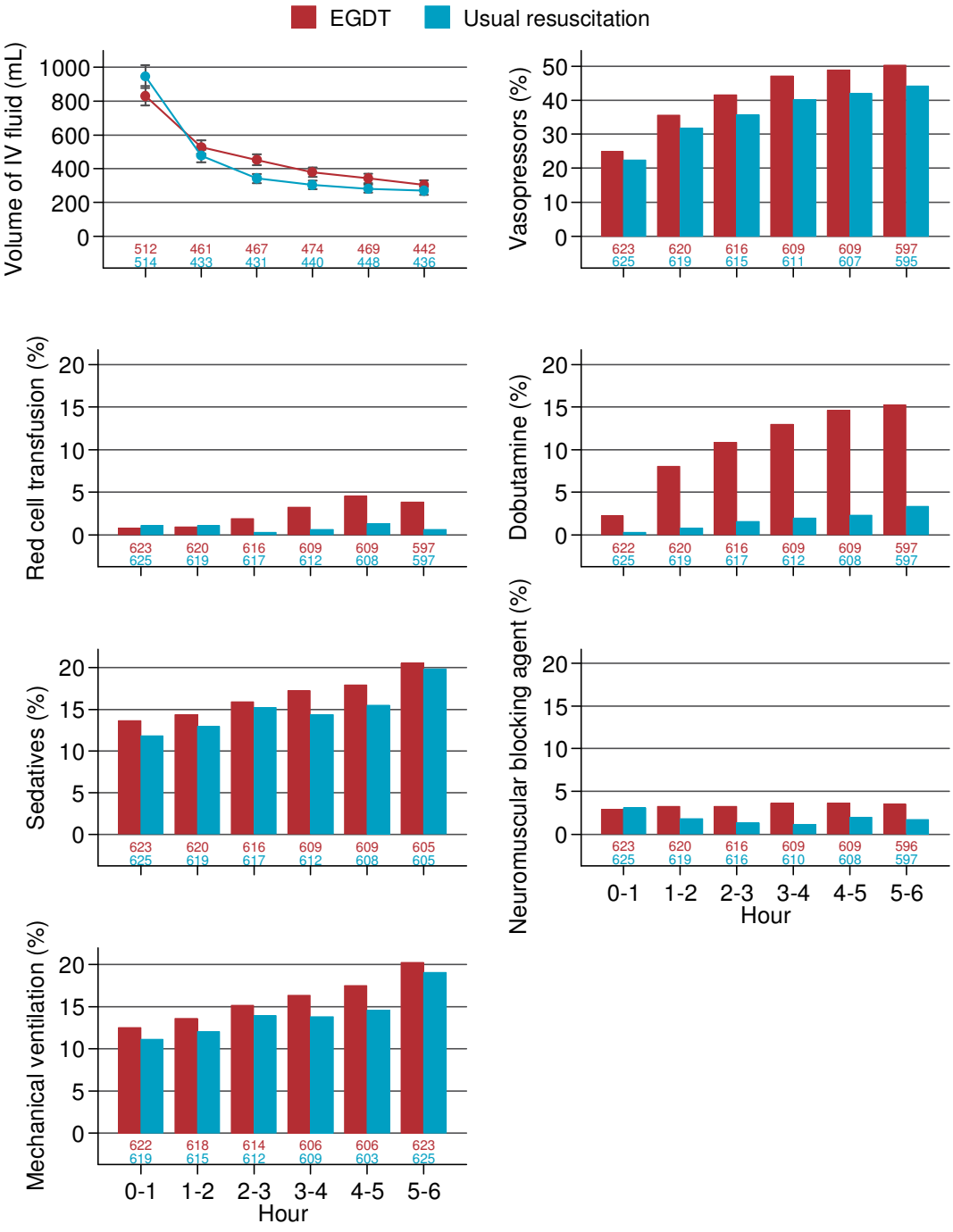




Adherence to the protocol for patients assigned to the EGDT group, (A) for ProMISe compared with ProCESS according to the ProCESS adherence algorithm (as presented in supplementary appendix, figure S3 and table S3[26]), (B) for ProMISe compared with ARISE according to the ARISE adherence algorithm (as presented in supplementary appendix, figure S4[27]) and (C) according to the ProMISe adherence algorithm. Panel C reports, for each hour during the intervention period, the percentages of patients meeting each

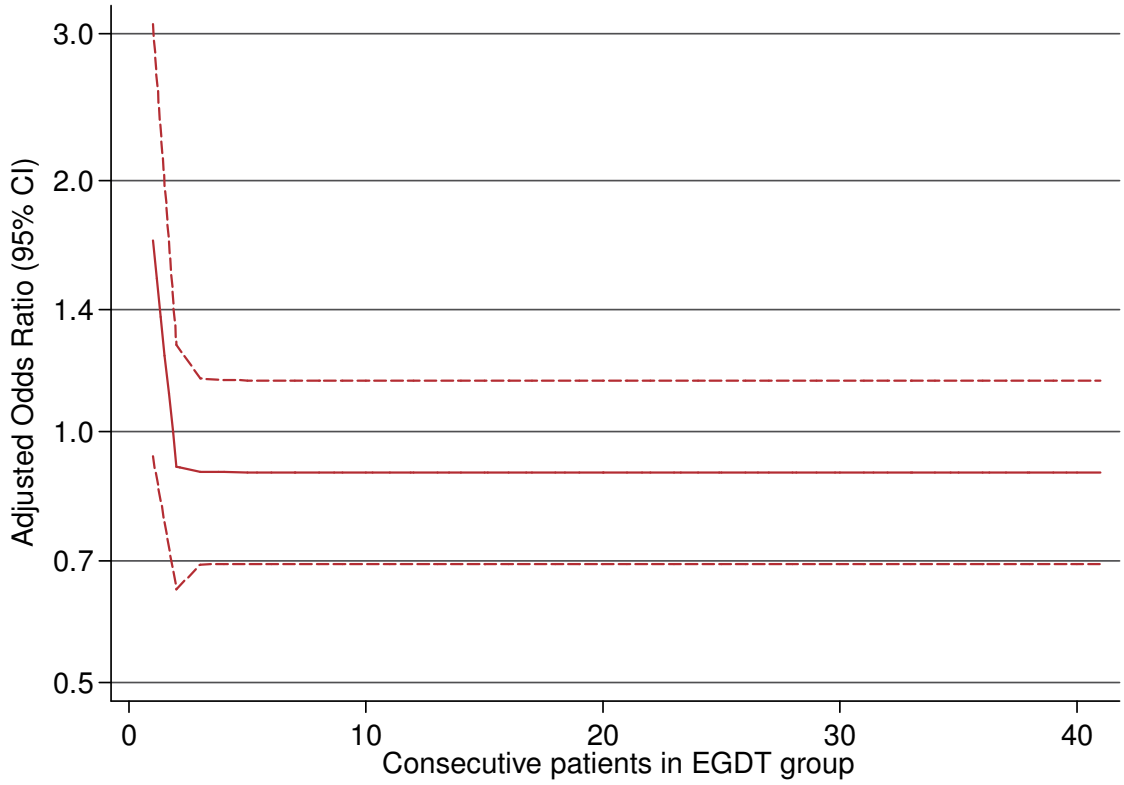
physiological target and receiving the associated action. The bars plotted on each hour are the percentage of patients (of those meeting the previous targets) not meeting (red), meeting (blue) and not measured for (grey) each physiological target in the EGDT group (based on values recorded within 15 minutes either side of the specified time point). The bars plotted between each hour are the percentage of patients (of those that did not meet the target at the previous hour) that received the associated action during the intervention period (darkest shading), after the intervention period (mid shading) or no longer required the action as the target was subsequently met (lightest shading). Numbers at the foot of each bar represent the denominator for the percentages in that bar. Each target is considered sequentially (i.e. the blue shaded portion for CVP becomes the denominator for MAP/SBP and the blue shaded portion for MAP/SBP becomes 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 that no longer met eligibility criteria or declined the intervention were excluded from the evaluation of adherence.

Figure S6. Interventions Delivered during the Intervention Period.



Values reported are the mean and 95% confidence interval (volume of intravenous fluid) or percentage of patients receiving the intervention (all other panels) during each hour of the intervention period. Numbers at the foot of each bar represent the denominators for the means/percentages in that bar.

Figure S7. Learning Curve for Delivery of Early, Goal-Directed Therapy.



Reports the results of the learning curve analysis as the adjusted odds ratio for EGDT compared with usual resuscitation according to the number of patients (within each site) assigned to the EGDT group. The Y (vertical) axis is presented on a log scale.

Figure S8. Uncertainty in the Mean Cost in GB Pounds (£) and QALY Differences and their Joint Distribution for EGDT versus Usual Resuscitation.

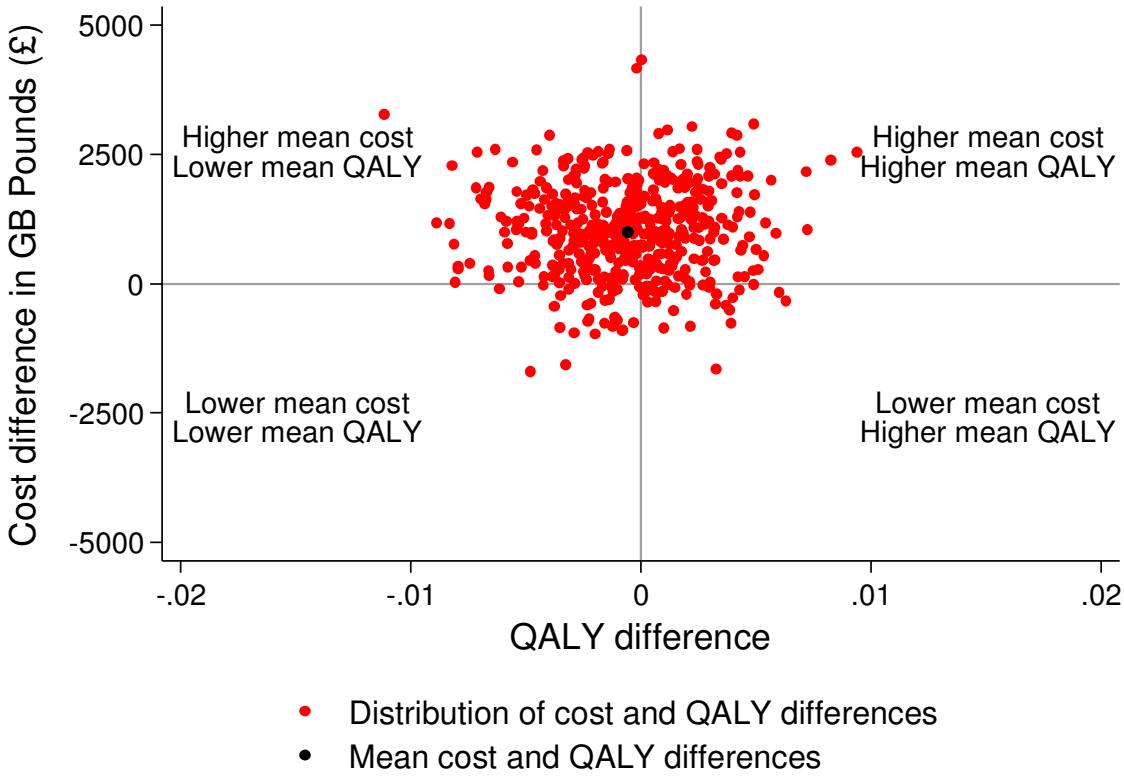
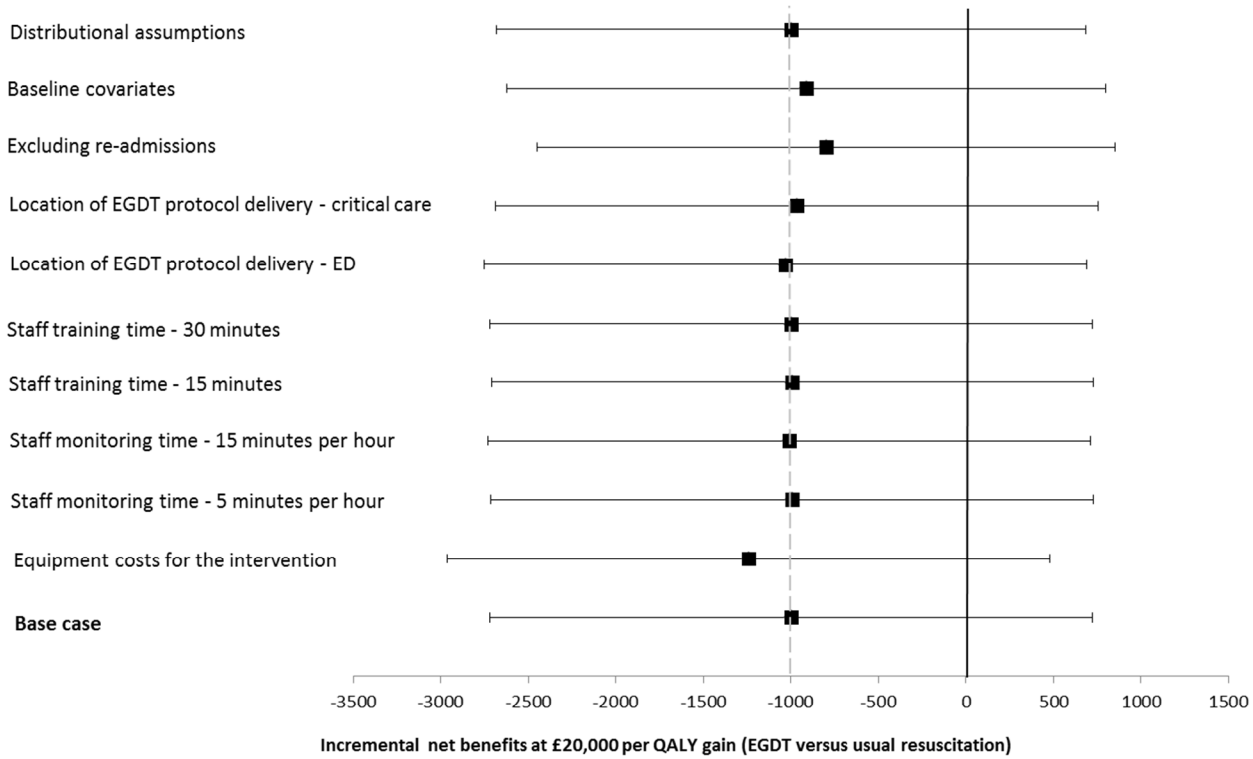
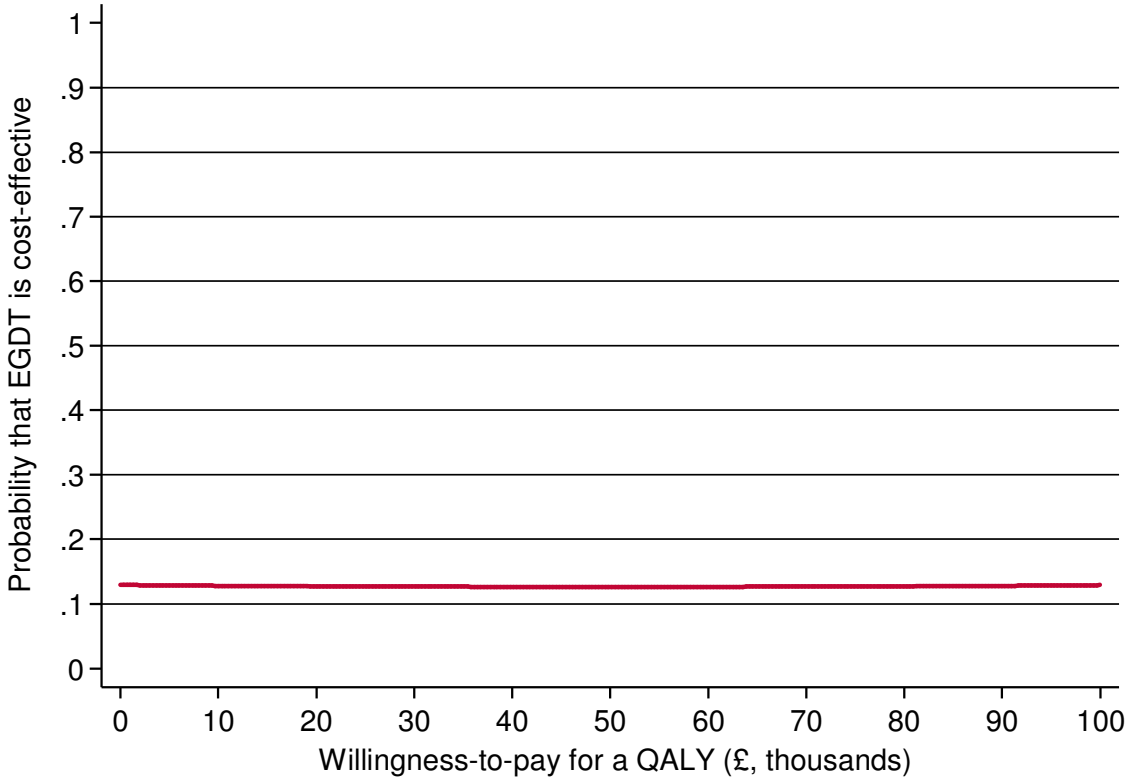


Figure S9. Sensitivity Analyses for the Cost-effectiveness Analysis.



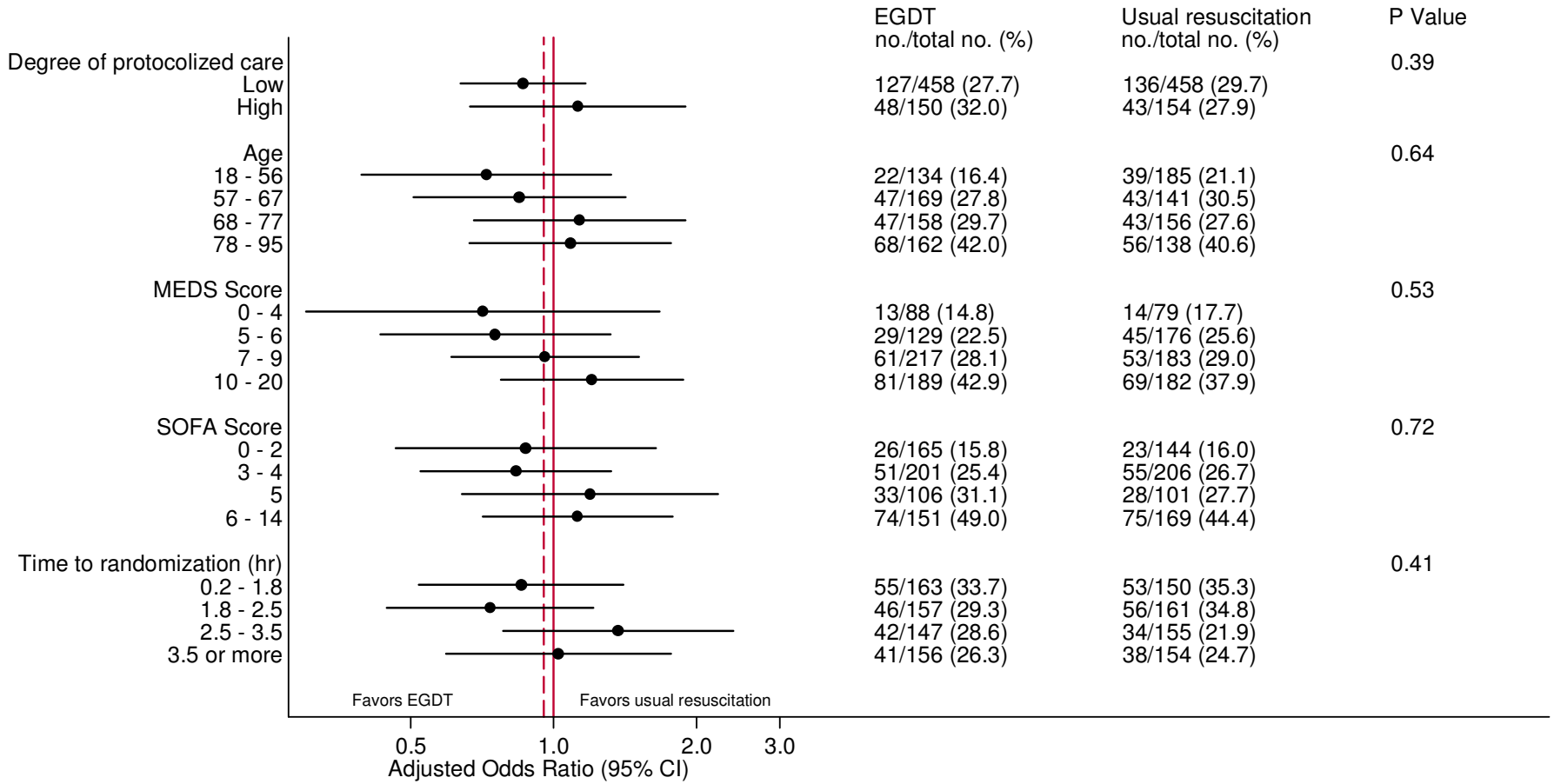
Reports the mean with 95% confidence interval of the incremental net benefit (at £20,000 per QALY) according to alternative assumptions, compared with the base case. The dashed vertical line indicates the incremental net benefit in the base case. The solid vertical line indicates no difference in net monetary benefits between the treatment groups.

Figure S10. Cost-effectiveness Acceptability Curve.



Reports the probability that the EGDT is cost-effective at alternative levels of willingness to pay for a QALY gain.

Figure S11. Subgroup Analyses of Primary Outcome.



Adjusted odds ratio with 95% confidence interval across pre-specified subgroups for the primary outcome of 90-day mortality. P values are reported from tests of interaction. The X (horizontal) axis is presented on a log scale.

Supplementary Tables

Table S1. Description of Sites.

Site	Teaching status*	Recruitment period	Number of hospital beds	Number of annual ED presentations	Total patients randomized	Patients randomized to EGDT	Location(s) of EGDT delivery†	Reviewed by Consultant (Attending) - no. (%)	Specialty of most senior doctor‡
Addenbrooke's Hospital	Teaching	November 2011 - October 2012 & April 2013 - July 2014	950	100000	30	15	ED (14)/CCU (14)	8 (53.3)	EM (6)/CCM (6)/AM (2)/other (1)
Arrowe Park Hospital	Non-teaching	June 2011 - July 2014	750	93000	31	15	ED (5)/CCU (12)/Ward (1)	13 (86.7)	EM (1)/CCM (13)/AM (1)
Barnsley Hospital	Non-teaching	September 2011 - January 2014 & April 2014 - July 2014	450	80000	28	14	ED (12)/CCU (9)/Ward (2)	13 (92.9)	EM (14)
Bedford Hospital	Non-teaching	November 2011 - October 2013	380	70000	11	5	ED (1)/CCU (5)	4 (80.0)	EM (2)/CCM (3)
Birmingham Heartlands Hospital	Non-teaching	May 2011 - October 2013	730	112171	14	6	ED (5)/CCU (4)/Ward (1)	4 (66.7)	CCM (5)/AM (1)
Blackpool Victoria Hospital	Non-teaching	November 2012 - July 2014	769	92000	9	5	ED (3)/CCU (5)	5 (100.0)	CCM (5)
Bristol Royal Infirmary	Teaching	September 2011 - December 2012	450	65000	6	4	CCU (4)	4 (100.0)	CCM (3)/AM (1)
Broomfield Hospital	Non-teaching	May 2011 - April 2014	521	81513	15	7	ED (5)/CCU (7)	7 (100.0)	EM (2)/CCM (5)
Chelsea and Westminster Hospital	Non-teaching	May 2011 - July 2014	430	114695	16	8	ED (6)/CCU (7)	7 (87.5)	CCM (8)
Derriford Hospital	Teaching	April 2011 - November 2013	900-1000	87000	12	6	ED (3)/CCU (5)/Ward (1)	6 (100.0)	CCM (5)/AM (1)

Dorset County Hospital	Non-teaching	October 2011 - April 2014	292	40000	17	7	ED (3)/CCU (7)	7 (100.0)	CCM (7)
Frenchay Hospital	Non-teaching	April 2012 - July 2014	526	88000	25	14	ED (12)/CCU (4)/Ward (6)	11 (78.6)	EM (6)/CCM (4)/AM (4)
Hinchingbrooke Hospital	Non-teaching	May 2011 - April 2014	247	44962	19	10	ED (5)/CCU (8)/Ward (1)	9 (90.0)	EM (1)/CCM (8)/other (1)
Hull Royal Infirmary	Teaching	May 2011 - July 2014	709	122000	30	14	ED (2)/CCU (14)	12 (85.7)	EM (2)/CCM (12)
John Radcliffe Hospital	Teaching	July 2011 - January 2013 & June 2013 - October 2013	832	137766	8	4	ED (3)/CCU (3)/Ward (1)	3 (75.0)	CCM (4)
Kettering General Hospital	Non-teaching	February 2011 - October 2013	580	88000	15	8	ED (3)/CCU (8)	8 (100.0)	CCM (8)
King's College Hospital	Teaching	July 2012 - July 2014	1000	140000	33	15	ED (11)/CCU (15)	12 (80.0)	EM (3)/CCM (12)
Leicester Royal Infirmary	Teaching	December 2011 - July 2014	1000	150000	41	22	ED (3)/CCU (21)	21 (95.5)	EM (1)/CCM (21)
Leighton Hospital	Non-teaching	June 2011 - October 2013	460	82000	12	6	ED (1)/CCU (6)	6 (100.0)	CCM (4)/AM (2)
Manchester Royal Infirmary	Teaching	July 2011 - July 2014	650	100000	41	21	ED (20)/CCU (5)/Ward (1)	18 (85.7)	EM (15)/CCM (2)/other (4)
Medway Maritime Hospital	Non-teaching	June 2011 - April 2014	550	90000	27	13	ED (8)/CCU (12)	9 (69.2)	CCM (6)/AM (5)/other (1)
Musgrove Park Hospital	Non-teaching	August 2011 - July 2014	700	56000	29	15	ED (1)/CCU (15)	13 (86.7)	CCM (15)
New Cross Hospital	Non-teaching	September 2011 - October 2013	700	111000	8	4	ED (1)/CCU (4)	4 (100.0)	CCM (4)

Newham University Hospital	Non-teaching	September 2012 - July 2013	234	125000	10	4	ED (4)/CCU (1)/Ward (2)	3 (75.0)	EM (1)/AM (1)/other (2)
North Devon District Hospital	Non-teaching	September 2012 - July 2014	281	40000	20	10	ED (5)/CCU (9)/Ward (1)	10 (100.0)	EM (3)/CCM (7)
North Tyneside General Hospital	Non-teaching	September 2011 - April 2012	450	60000	1	1	CCU (1)	1 (100.0)	CCM (1)
Peterborough City Hospital	Non-teaching	March 2013 - July 2014	611	90475	24	12	ED (1)/CCU (12)/Ward (1)	9 (75.0)	CCM (12)
Poole Hospital	Non-teaching	May 2011 - June 2013	623	67000	42	21	ED (3)/CCU (20)	21 (100.0)	EM (7)/CCM (13)/AM (1)
Queen Elizabeth Hospital Birmingham	Teaching	July 2011 - March 2012 & October 2013 - July 2014	1313	102000	21	10	ED (6)/CCU (6)/Ward (4)	6 (60.0)	EM (2)/CCM (6)/AM (2)
Queen Elizabeth Hospital Gateshead	Non-teaching	September 2011 - July 2014	600	87000	30	15	ED (1)/CCU (15)	13 (86.7)	CCM (15)
Queen's Medical Centre	Teaching	January 2013 - July 2014	1300	185000	25	13	ED (9)/CCU (10)/Ward (1)	12 (92.3)	EM (4)/CCM (7)/AM (2)
Royal Berkshire Hospital	Non-teaching	August 2011 - July 2014	660	100000	55	27	ED (22)/CCU (26)/Ward (1)	26 (96.3)	EM (15)/CCM (11)/AM (1)
Royal Bournemouth Hospital	Non-teaching	July 2011 - June 2014	607	71316	23	11	ED (1)/CCU (11)	11 (100.0)	EM (5)/CCM (6)
Royal Lancaster Infirmary	Non-teaching	May 2011 - July 2014	428	56000	21	11	ED (9)/CCU (3)/Ward (8)	7 (63.6)	EM (7)/CCM (2)/AM (2)
Royal Preston Hospital	Non-teaching	June 2011 - July 2014	708	74852	22	10	ED (4)/CCU (8)/Ward (1)	9 (90.0)	EM (1)/CCM (7)/AM (1)/other (1)

Royal Surrey County Hospital	Non-teaching	March 2011 - October 2013	550	71175	15	7	ED (3)/CCU (7)	7 (100.0)	CCM (7)
Royal Sussex County Hospital	Teaching	September 2011 - July 2014	850	110000	29	14	ED (9)/CCU (14)	13 (92.9)	EM (1)/CCM (11)/AM (2)
Royal Victoria Infirmary	Teaching	May 2011 - August 2011 & June 2012 - August 2013	1000	130756	2	1	CCU (1)	1 (100.0)	CCM (1)
Salford Royal Hospital	Non-teaching	January 2012 - July 2014	661	88000	53	27	ED (22)/CCU (19)/Ward (4)	17 (63.0)	EM (17)/CCM (3)/AM (4)/other (3)
South Tyneside District Hospital	Non-teaching	June 2011 - August 2012	400	74000	4	2	CCU (2)	2 (100.0)	CCM (2)
Southend University Hospital	Non-teaching	July 2011 - November 2011	700	89965	1	1	CCU (1)	1 (100.0)	CCM (1)
Stafford Hospital	Non-teaching	June 2011 - May 2013	299	46761	15	7	CCU (6)Ward (1)	7 (100.0)	CCM (7)
The Great Western Hospital	Non-teaching	October 2011 - October 2012 & April 2013 - November 2013	400	70000	15	6	ED (1)/CCU (6)	5 (83.3)	CCM (4)/other (2)
The Ipswich Hospital	Non-teaching	June 2011 - April 2014	500	80000	18	10	ED (4)/CCU (10)	9 (90.0)	CCM (10)
The James Cook University Hospital	Non-teaching	January 2012 - July 2014	1000	104000	28	14	ED (7)/CCU (14)/Ward (1)	8 (57.1)	CCM (14)
The Queen Elizabeth Hospital, King's Lynn	Non-teaching	May 2011 - July 2014	489	55000	71	35	ED (1)/CCU (34)/Ward (1)	29 (82.9)	CCM (35)
The Royal Blackburn Hospital	Non-teaching	October 2012 - March 2014	693	177901	8	4	ED (3)/CCU (3)/Ward (1)	3 (75.0)	CCM (3)/AM (1)

The Royal London Hospital	Teaching	September 2011 - July 2014	680	150000	49	24	ED (23)/CCU (15)/Ward (7)	19 (79.2)	EM (16)/CCM (7)/AM (1)
Torbay Hospital	Non-teaching	February 2013 - March 2014	400	117896	3	2	ED (2)/CCU (2)	2 (100.0)	CCM (2)
University College Hospital	Teaching	March 2011 - July 2014	665	129000	33	16	ED (8)/CCU (14)/Ward (1)	13 (81.3)	EM (1)/CCM (15)
University Hospital of North Staffordshire	Teaching	March 2011 - July 2014	1180	128000	21	10	ED (8)/CCU (5)	9 (90.0)	EM (5)/CCM (4)/AM (1)
Wansbeck General Hospital	Non-teaching	September 2011 - April 2012	350	60000	1	0	N/A	N/A	N/A
Whipps Cross University Hospital	Non-teaching	January 2013 - July 2014	450	110000	8	4	ED (4)/CCU (2)	3 (75.0)	EM (2)/CCM (2)
Whiston Hospital	Non-teaching	March 2011 - July 2014	646	100895	83	41	ED (40)/CCU (29)	25 (61.0)	EM (40)/CCM (1)
Worthing Hospital	Non-teaching	August 2011 - October 2013	500	58000	17	9	ED (7)/CCU (6)/Ward (1)	7 (77.8)	EM (1)/CCM (5)/AM (3)
York Hospital	Teaching	October 2011 - July 2014	700	85000	15	8	ED (3)/CCU (8)	8 (100.0)	CCM (7)/other (1)

* Teaching hospitals are defined as the main hospital(s) linked with each university medical school.

† ED denotes emergency department, CCU denotes critical care unit. Each patient may have had the protocol delivered in multiple locations.

‡ EM denotes emergency medicine, CCM denotes critical care medicine, AM denotes acute medicine.

Table S2. Summary of Sites in ProMISe compared with all Emergency Departments in England.*

Teaching status†	Sites in ProMISe	Emergency Departments in England
Teaching	16 (29%)	36 (20%)
Non-teaching	40 (71%)	145 (80%)

* Values are number and percentage.

† Teaching hospitals are defined as the main hospital(s) linked with each university medical school.

Table S3. Informed Consent and Withdrawals.*

Type of consent/agreement	Patients	Requested removal of all data†	Ineligible - excluded from analysis	Withdrew before 90 days
Informed consent from patient prior to randomization	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

* Values are number and percentage. All consent processes were in accordance with the UK Mental Capacity Act (2005). EGDT denotes early goal-directed therapy.

† Patient/Consultee requested removal of all data from the analysis.

Table S4. Additional Baseline Characteristics.*

	EGDT (N = 625)	Usual resuscitation (N= 626)
Intravenous fluids pre hospital† - no. (%)	119 (19.3)	128 (20.7)
Median intravenous fluids pre hospital (IQR) - mL	500 (250, 500)	500 (255, 500)
Intravenous fluids ED presentation to randomization‡ - no. (%)	607 (97.1)	599 (95.8)
Median intravenous fluids ED presentation to randomization (IQR) - mL	1600 (1000, 2500)	1790 (1000, 2500)
Blood products ED presentation to randomization§ - no. (%)	4 (0.7)	10 (1.6)
Median blood products ED presentation to randomization (IQR) - mL	922 (559, 1000)	919 (500, 1000)
Time from ED presentation to inclusion criteria met - hr	1.6±1.3	1.7±1.4
Median time from ED presentation to inclusion criteria met (IQR) - hr	1.3 (0.5, 2.3)	1.3 (0.6, 2.4)
Time from ED presentation to randomization - hr	2.7±1.3	2.8±1.4
Median age (IQR) - yr	68 (58, 78)	67 (54, 76)
Median APACHE II Score¶ (IQR)	18 (13, 23)	17 (13, 22)
Median MEDS Score‖ (IQR)	8 (6, 10)	8 (6, 10)
MEDS terminal illness** - no. (%)	11 (1.8)	14 (2.2)
MEDS respiratory difficulties†† - no. (%)	510 (82.3)	499 (80.7)
MEDS septic shock‡‡ - no. (%)	277 (44.4)	305 (49.0)
MEDS platelets < 150 x109/L§§ - no. (%)	144 (24.6)	144 (24.6)
MEDS bandforms > 5%¶¶ - no. (%)	52 (96.3)	64 (91.4)
MEDS lower respiratory infection - no. (%)	220 (35.2)	196 (31.3)
MEDS nursing home resident‖‖ - no. (%)	18 (2.9)	14 (2.2)
MEDS altered mental status*** - no. (%)	206 (33.9)	208 (34.6)
MEDS age > 65 - no. (%)	363 (58.1)	329 (52.6)
Median SOFA score††† (IQR)	4 (2, 5)	4 (3, 6)
SOFA respiratory dysfunction - no. (%)	323 (51.7)	357 (57.0)
SOFA neurological dysfunction - no. (%)	196 (31.4)	200 (31.9)
SOFA cardiovascular dysfunction - no. (%)	410 (65.6)	433 (69.2)
SOFA coagulation dysfunction - no. (%)	144 (23.0)	144 (23.0)
SOFA hepatic dysfunction - no. (%)	211 (33.8)	199 (31.8)
SOFA renal dysfunction††† - no. (%)	426 (68.2)	406 (64.9)
Severe liver disease‡‡‡ - no. (%)	11 (1.8)	11 (1.8)
Severe renal disease‡‡‡ - no. (%)	4 (0.6)	3 (0.5)
Immunocompromized‡‡‡ - no. (%)	84 (13.5)	70 (11.2)
Severe respiratory disease‡‡‡ - no. (%)	93 (15.0)	81 (12.9)
Severe cardiovascular disease‡‡‡ - no. (%)	22 (3.5)	17 (2.7)
Organism causing infection - no. (%)		

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§§§	4 (0.6)	3 (0.5)
Unknown (not reported or no growth)	275 (44.0)	269 (43.0)

* Plus-minus values are means ±SD. EGDT denotes early goal-directed therapy.

† Includes intravenous crystalloid and colloid administration > 20mL. Intravenous fluids pre hospital was not recorded for 18 patients (9 EGDT, 9 usual resuscitation).

‡ Includes intravenous crystalloid and colloid administration > 20mL. Intravenous fluids ED presentation to randomization was not recorded for 1 patient (1 usual resuscitation).

§ Blood products were not recorded for 21 patients (11 EGDT, 10 usual resuscitation).

¶ Scores on the Acute Physiology And Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater severity of illness. The APACHE II Score was calculated using the last recorded physiology data prior to randomization and is not based on data over a 24 hour time period.

‖ Mortality in Emergency Department Sepsis (MEDS) scores range from 0 to 27, with higher scores indicating greater severity of illness. The MEDS score was calculated using the last recorded physiology data prior to randomization.

** Variables for calculation of MEDS terminal illness were not recorded for 3 patients (3 EGDT).

†† Variables for calculation of MEDS respiratory difficulties were not recorded for 13 patients (5 EGDT, 8 usual resuscitation).

‡‡ Variables for calculation of MEDS septic shock were not recorded for 5 patients (1 EGDT, 4 usual resuscitation).

§§ Variables for calculation of MEDS platelets were not recorded for 81 patients (40 EGDT, 41 usual resuscitation).

¶¶ Variables for calculation of MEDS bandforms were not recorded for 1127 patients (571 EGDT, 556 usual resuscitation).

‖‖ Variables for calculation of MEDS nursing home resident were not recorded for 3 patients (3 EGDT).

*** Variables for calculation of MEDS altered mental status were not recorded for 41 patients (17 EGDT, 24 usual resuscitation).

††† Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. The SOFA score was calculated using the last recorded physiology data prior to randomization. The SOFA renal score was based on plasma creatinine concentration only (i.e. did not include urine output).

‡‡‡ Severe conditions in the past medical history defined according to APACHE II. Comorbidities were not recorded for 3 patients (3 EGDT).

§§§ Confirmed following randomization.

Table S5. Interventions Delivered during the Intervention Period.*

	EGDT (N = 625)	Usual resuscitation (N = 626)
Supplemental O_2 - no./total no. (%)	558/623 (89.6)	557/625 (89.1)
Arterial catheter insertion - no./total no. (%)	462/623 (74.2)	389/625 (62.2)
Time from randomization to insertion - hr	1.3±1.6	1.2±1.7
Median time from randomization to insertion (IQR) - hr	1.1 (0.4, 1.9)	1.0 (0.2, 1.9)
Any CVC insertion - no./total no. (%)	575/624 (92.1)	318/625 (50.9)
Time from randomization to insertion - hr	1.2±0.9	1.8±1.7
Median time from randomization to insertion (IQR) - hr	1.1 (0.8, 1.5)	1.4 (0.6, 2.9)
CVC line insertion with $ScvO_2$ monitoring capability - no./total no. (%)	545/624 (87.3)	2/625 (0.3)
Timing of insertion - no. (%)		
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 intravenous fluid† - no./total no. (%)	609/623 (97.8)	604/625 (96.6)
Any intravenous fluid – mL	2226±1443	2022±1271
Median any intravenous fluid (IQR) - mL	2000 (1150, 3000)	1784 (1075, 2775)
Intravenous colloid† - no./total no. (%)	197/623 (31.6)	180/625 (28.8)
Intravenous colloid - mL	1062±801	913±627
Median intravenous colloid (IQR) - mL	1000 (500, 1500)	750 (500, 1000)
Intravenous crystalloid† - no./total no. (%)	584/623 (93.7)	597/625 (95.5)
Intravenous crystalloid - mL	1963±1357	1767±1178
Median intravenous crystalloid (IQR) - mL	1750 (999, 2750)	1500 (900, 2380)
Vasopressors - no./total no. (%)	332/623 (53.3)	291/625 (46.6)
Red cell transfusion - no/total no. (%)	55/623 (8.8)	24/625 (3.8)
Red cell transfusion - mL	426±209	540±294
Median red cell transfusion (IQR) - mL	309 (285, 577)	535 (305, 607)
Dobutamine - no./total no. (%)	113/623 (18.1)	24/625 (3.8)
Mechanical ventilation - no./total no. (%)	126/623 (20.2)	119/625 (19.0)
Sedatives - no./total no. (%)	138/623 (22.2)	130/625 (20.8)
Neuromuscular blocking agent - no./total no. (%)	53/623 (8.5)	40/625 (6.4)
Critical care admission - no./total no. (%)	551/625 (88.2)	467/626 (74.6)
Time from randomization to critical care admission - hr	2.0±2.3	2.5±5.7
Median time from randomization to critical care admission (IQR) - hr	1.2 (0.4, 2.8)	1.2 (0.3, 2.8)

Location of protocol delivery - no. (%)		
Emergency department (ED)	64 (10.2)	---
Critical care	276 (44.2)	---
Ward	10 (1.6)	---
ED and critical care	235 (37.6)	---
ED and ward	37 (5.9)	---
Critical care and ward	2 (0.3)	---
ED, critical care and ward	1 (0.2)	---
Review by Consultant (Attending) - no./total no. (%)	520/624 (83.3)	494/625 (79.0)
Specialty of most senior doctor to review the patient - no. (%)		
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)

* Plus-minus values are means ±SD. EGDT denotes early goal-directed therapy.

† Includes intravenous fluid administration > 20 mL.

Table S6. Physiology Measurements at the End of the Intervention Period.*

	EGDT (N = 625)	Usual resuscitation (N= 626)
CVP - mmHg	11.2±5.1 [496]	11.7±6.1 [166]
MAP - mmHg	76.5±13.9 [518]	76.5±14.3 [394]
SBP - mmHg	113.1±21.0 [573]	110.7±22.4 [508]
$ScvO_2$ - %	74.2±9.8 [497]	---
Hemoglobin - g/dL	11.0±2.0 [384]	11.3±2.3 [163]

* Plus-minus values are means ±SD. EGDT denotes early goal-directed therapy. Numbers in square brackets denote the number of patients with this variable recorded.

Table S7. Ancillary Interventions Delivered.*

	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)**
Total intravenous fluid† - no./total no. (%)	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)
Total intravenous fluid - mL	1890±1105	1965±1149	2226±1443	2022±1271	4215±3068	4366±3114	5946±3740	5844±3651
Median total intravenous fluid (IQR) - mL	1950 (1000, 2500)	2000 (1000, 2500)	2000 (1150, 3000)	1784 (1075, 2775)	3623 (1800, 6060)	3981 (1895, 6291)	5587 (2915, 8150)	5410 (3000, 7970)
Intravenous colloid‡ - no./total no. (%)	---	---	197/623 (31.6)	180/625 (28.8)	171/603 (28.4)	150/603 (24.9)	260/623 (41.7)	240/625 (38.4)
Intravenous colloid - mL	---	---	1062±801	913±627	1207±1042	1093±1012	1598±1391	1369±1150
Median intravenous colloid (IQR) - mL	---	---	1000 (500, 1500)	750 (500, 1000)	750 (500, 1750)	750 (500, 1500)	1000 (575, 2000)	1000 (500, 1750)
Intravenous crystalloid‡ - no./total no. (%)	---	---	584/623 (93.7)	597/625 (95.5)	537/603 (89.1)	543/603 (90.0)	609/623 (97.8)	617/625 (98.7)
Intravenous crystalloid - mL	---	---	1963±1357	1767±1178	3909±2869	4136±2914	5323±3518	5317±3435
Median intravenous crystalloid (IQR) - mL	---	---	1750 (999, 2750)	1500 (900, 2380)	3403 (1576, 5647)	3694 (1832, 5911)	4864 (2520, 7241)	4900 (2700, 7408)
Vasopressors - no./total no. (%)	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)
Red cell transfusion - no./total no. (%)	---	---	55/623 (8.8)	24/625 (3.8)	76/603 (12.6)	51/603 (8.5)	107/623 (17.2)	65/625 (10.4)
Red cells transfusion- mL	---	---	426±209	540±294	487±335	606±403	565±393	674±506
Median red cell transfusion (IQR) - mL	---	---	309 (285, 577)	535 (305, 607)	351 (291, 579)	552 (317, 620)	529 (298, 602)	562 (317, 660)
Dobutamine - no./total no. (%)	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)

Mechanical ventilation - no./total no. (%)	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 - no./total no. (%)	---	---	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 - no./total no. (%)	---	---	53/623 (8.5)	40/625 (6.4)	39/603 (6.5)	34/603 (5.6)	74/623 (11.9)	60/625 (9.6)
Supplemental O_2§ - no./total no. (%)	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)
Platelets - no./total no. (%)	---	---	11/623 (1.8)	10/625 (1.6)	23/603 (3.8)	25/603 (4.1)	31/623 (5.0)	30/625 (4.8)
Platelets - mL	---	---	286±72	242±131	314±167	278±162	325±194	315±207
Median platelets (IQR) - mL	---	---	315 (200, 340)	180 (163, 342)	274 (182, 366)	187 (172, 357)	290 (191, 366)	250 (173, 418)
Fresh frozen plasma - no./total no. (%)	---	---	15/623 (2.4)	14/625 (2.2)	28/603 (4.6)	30/603 (5.0)	41/623 (6.6)	39/625 (6.2)
Fresh frozen plasma - mL	---	---	847±383	769±285	836±721	869±507	881±658	945±533
Median fresh frozen plasma (IQR) - mL	---	---	1007 (539, 1095)	793 (526, 1085)	587 (483, 1000)	846 (528, 1057)	791 (516, 1095)	1025 (528, 1140)
Co-interventions for the source of sepsis								
Surgery - no./total no. (%)	0/625 (0.0)	0/626 (0.0)	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 - no./total no. (%)	---	---	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 - no./total no. (%)	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)
Antimicrobial (change since ED) - no./total no. (%)	---	---	---	---	---	---	359/615 (58.4)	342/617 (55.4)

* Plus-minus values are means ±SD. EGDT denotes early goal-directed therapy.

† Includes intravenous crystalloid and colloid administration > 20mL and all blood product administration at baseline. Includes intravenous fluid administration > 20mL at all other time points.

‡ Includes intravenous fluid administration > 20mL.

§ At baseline supplemental O_2 is based on FiO_2.

Table S8. Ancillary Physiology Measurements.*

	Baseline		*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	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	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]
Hemoglobin† - g/dL	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† - mmol/L	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 P/F ratio - mmHg	244.6±195.8 [383]	254.8±219.0 [416]	227.7±189.4 [464]	232.0±154.9 [432]	230.4±152.4 [436]	228.7±125.6 [393]	232.4±163.2 [255]	213.6±108.6 [225]
Highest creatinine - µmol/L	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	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 platelets - $x10^9$/L	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	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 - no. (%)	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 - no. (%)	196 (31.4)	200 (31.9)	226 (36.2)	186 (29.7)	169 (27.8)	144 (23.7)	126 (23.3)	93 (17.6)
SOFA cardiovascular dysfunction - no. (%)	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 - no. (%)	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 - no. (%)	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‡ - no. (%)	426 (68.2)	406 (64.9)	430 (68.8)	415 (66.3)	347 (57.1)	332 (54.7)	199 (36.8)	196 (37.1)
Median SOFA Score‡ (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)

* Plus-minus values are means ±SD. EGDT denotes early goal-directed therapy. Numbers in square brackets denotes the number of patients with this variable recorded. Baseline physiology values were based on the last recorded value prior to randomization.

† Hemoglobin and blood lactate concentration were recorded at the end of the time period.

‡ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. At baseline the SOFA score was calculated using the last recorded physiology data prior to randomization. The SOFA renal score was based on plasma creatinine concentration only (i.e. did not include urine output). Patients in whom the variables for SOFA renal and SOFA coagulation scores were not recorded during hour 0 to hour 6 had these values carried forward from baseline, if recorded at baseline. Patients in whom the variables for SOFA renal and SOFA coagulation scores were not recorded during hour 6 to hour 24 had these values carried forward from hour 0 to hour 6, if recorded.

Table S9. Subgroup and Secondary Analyses of Primary Outcome.*

Analysis	EGDT (N = 625)	Usual resuscitation (N= 626)	Incremental Effect (95% CI)	P value
Sensitivity analyses for missing primary outcome:				
EGDT survive, usual resuscitation die	184/625 (29.4)	187/626 (29.9)	0.99 (0.83 to 1.17)†	0.90
EGDT die, usual resuscitation survive	186/625 (29.8)	181/626 (28.9)	1.03 (0.87 to 1.22)†	0.76
Adherence-adjusted analysis			1.02 (0.78 to 1.32)†	0.90
Learning curve analysis:				0.56‡
Asymptote to adjusted odds ratio			0.89 (0.69 to 1.15)§	0.34
Subgroup analyses:				
Degree of protocolized care in usual resuscitation				0.39¶
Low	127/458 (27.7)	136/458 (29.7)	0.86 (0.64 to 1.17)§	
High	48/150 (32.0)	43/154 (27.9)	1.31 (0.71 to 2.38)§	
Age				0.64¶
18 - 56	22/134 (16.4)	39/185 (21.1)	0.72 (0.39 to 1.32)§	
57 - 67	47/169 (27.8)	43/141 (30.5)	1.17 (0.52 to 2.60)§	
68 - 77	47/158 (29.7)	43/156 (27.5)	1.57 (0.71 to 3.48)§	
78 - 95	68/162 (42.0)	56/138 (40.6)	1.50 (0.69 to 3.27)§	
MEDS Score				0.53¶
0 - 4	13/88 (14.8)	14/79 (17.7)	0.72 (0.30 to 1.67)§	
5 - 6	29/129 (22.5)	45/176 (25.6)	1.06 (0.38 to 2.95)§	
7 - 9	61/217 (28.1)	53/183 (29.0)	1.35 (0.51 to 3.57)§	
10 - 20	81/189 (42.9)	69/182 (37.9)	1.70 (0.65 to 4.46)§	
SOFA Score				0.72¶
0 - 2	26/165 (15.8)	23/144 (16.0)	0.87 (0.47 to 1.64)§	
3 - 4	51/201 (25.4)	55/206 (26.7)	0.95 (0.44 to 2.08)§	

5	33/106 (31.1)	28/101 (27.7)	1.37 (0.56 to 3.31)§	
6 - 14	74/151 (49.0)	75/169 (44.4)	1.29 (0.59 to 2.81)§	
Time to randomization - hr				0.41¶
0.2 - 1.8	55/163 (33.7)	53/150 (35.3)	0.86 (0.52 to 1.41)§	
1.8 - 2.5	46/157 (29.3)	56/161 (34.8)	0.86 (0.42 to 1.74)§	
2.5 - 3.5	42/147 (28.6)	34/155 (21.9)	1.60 (0.76 to 3.39)§	
3.5 or more	41/156 (26.3)	38/154 (24.7)	1.20 (0.57 to 2.50)§	

* Values are number/total number and percentage. EGDT denotes early goal-directed therapy.
† Relative risk.
‡ Test of nonlinearity.
§ Adjusted odds ratio.
¶ Test of interaction.

Table S10. Additional Outcomes.*

Outcome	EGDT (N = 625)	Usual resuscitation (N= 626)	P value†
Median time in ED for survivors (IQR) - hr	1.4 (0.4, 3.1)	1.3 (0.3, 2.9)	0.38
Median time in ED for non-survivors (IQR) - hr	3.7 (2.4, 4.1)	2.4 (1.2, 5.9)	0.25
Median time in critical care for survivors (IQR) - days	2.9 (1.1, 6.1)	2.8 (0.0, 5.9)	0.008
Median time in critical care for non-survivors (IQR) - days	1.6 (0.6, 3.1)	1.2 (0.5, 4.3)	0.83
Median time in acute hospital for survivors (IQR) - days	11 (7, 25)	11 (7, 22)	0.42
Median time in acute hospital for non-survivors (IQR) - days	2 (1, 8)	2 (1, 7)	0.44

* EGDT denotes early goal-directed therapy.
† Wilcoxon rank-sum test.

Table S11. Quality-Of-Life (EQ-5D-5L) Health State Profiles.*

EQ-5D-5L component	EGDT (N = 339†)	Usual resuscitation (N = 332†)
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)

* Values are number and percentage. EGDT denotes early goal-directed therapy.

† Reported for those randomized patients who were alive and fully completed the EQ-5D-5L questionnaire at 90 days post-randomization. 215 patients did not return a complete EQ-5D-5L questionnaire (102 EGDT, 113 usual resuscitation). Results are presented for the samples with complete information.

Table S12. Equipment, Consumables and Staff Time for Catheter Insertion and Monitor Set-Up.

Catheter	Equipment*	Doctor time (catheter insertion)	Nurse time (set-up catheter/monitor)	Consumables
CVC with $ScvO_2$ monitoring capability	Monitor	30 minutes	20 minutes† + 30 minutes‡	Transducer†, saline, CVC, consumables pack for insertion
Standard CVC	---	30 minutes	20 minutes†	Transducer†, saline, CVC, consumables pack for insertion
Arterial catheter	---	20 minutes	20 minutes†	Transducer†, saline, skin cleaning device and dressing

* The costs of standard central venous pressure and blood pressure monitoring were included in the HRG bed day costs, and so are not included as separate items.

† It is assumed that one transducer pack and same amount of nurse time is required whether single or multiple catheters are inserted.

‡ Additional nurse time for setting up the monitor.

Table S13. Unit Costs in GB pounds (£).*

Items	Unit costs (£)	Source
Equipment and consumables		
Monitor†	70	Manufacturer's price
CVC with $ScvO_2$ monitoring capability	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‡	22	Local NHS finance department
Cleaning device for arterial catheter‡	5	Local NHS finance department
Blood products		
Red cell transfusion (280 mL)	122	NHSBT
Platelets (200 mL)	208	NHSBT
Frozen fresh plasma (250 mL)	28	NHSBT
Drug and other related		
Dobutamine (250 mg) §	9	BNF
Staff time		
Doctor - Consultant (per hour)	139	PSSRU
Doctor - Registrar level (per hour)	59	PSSRU
Nurse - Grade 6 (per hour)	49	PSSRU
Staff training costs (per patient) ¶	11	ProMISe data & assumption
Hospital costs (bed day)		
Critical care bed day – 0 organ supported	619	NHS Reference Costs
Critical care bed day – 1 organ supported	852	NHS Reference Costs
Critical care bed day – 2 organs supported	1236	NHS Reference Costs
Critical care bed day – 3 organs supported	1422	NHS Reference Costs
Critical care bed day – 4 organs supported	1573	NHS Reference Costs
Critical care bed day – 5 organs supported	1697	NHS Reference Costs
Critical care bed day – 6+ organs supported	1867	NHS Reference Costs
General ward bed day	265	NHS Reference Costs
Emergency room (per hour)	27	Dixon et al 2009[28]
Outpatient and community health services		
Hospital outpatient (per visit)	135	PSSRU
GP practice visit (per visit)	45	PSSRU
GP home visit (per visit)	114	PSSRU
GP practice nurse‖	10	PSSRU
Hospital staff nurse‖	12	PSSRU
Health visitor‖	13	PSSRU

	Occupational therapist‖	9	PSSRU
	Psychologist‖	15	PSSRU
	Speech and language therapist‖	9	PSSRU
	Physiotherapist‖	9	PSSRU
	Dietician‖	9	PSSRU

* NHS denotes National Health Service, NHSBT denotes National Health Service Blood and Transport, BNF denotes British National Formulary and PSSRU denotes Personal Social Services Research Unit.

† Two monitors per site over average life span of five years were costed. The monitor costs per patient were calculated by dividing the total costs of the monitors (£4,000 each) by the expected number of eligible patients (23 patients per year) over five years.

‡ Cost of saline included.

§ Cost of syringe, giving set and saline included.

¶ 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 five years.

‖ 15 minutes of consultation time.

Table S14. Variables Considered for Multiple Imputation and Form of Imputation Model.*

Variable	Missing values†	Imputation model
Baseline variables		
Randomized group	0 (0)	None required
Age	0 (0)	None required
Sex	0 (0)	None required
Past medical history	3 (0.2)	None required‡
Site of sepsis	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‡
Shortness of breath with light activity	3 (0.2)	None required‡
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 IV fluid ED presentation to randomization	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 hemoglobin	31 (2.5)	Predictive mean matching
Baseline white blood cell	49 (3.9)	Predictive mean matching
Resource use variables		
Days in critical care	0 (0)	None required
Days in general medical	0 (0)	None required
Outpatient visits at 90 days	242 (27.3)	Predictive mean matching
Quality-of-life (QOL) variables		
EQ-5D at 90 days	215 (24.3)	Predictive mean matching

* Values are number and percentage.

† For baseline variables, the overall sample size was all randomized patients (n=1251). For other resource use and QOL variables, the relevant sample sizes were those patients eligible for the 90 days follow-up (n=878).

‡ No past medical history assumed when missing past medical history.

Table S15. Resource Use Up To 90 Days.*

	EGDT (N = 625)	Usual resuscitation (N = 626)
Intervention		
CVC capable of $ScvO_2$ monitoring – no. (%)	545 (87.2)	2 (0.3)
Standard CVC – no. (%)	48 (7.7)	316 (50.5)
Arterial catheter – no. (%)	462 (73.9)	389 (62.1)
Blood products		
Red cell transfusion - mL	97±267	70±262
Platelets – mL	16±82	15±79
Fresh frozen plasma - mL	58±275	59±264
Dobutamine dose infused - mg	183±592	88±489
Duration of protocol delivered in ED – hr	2.0±1.9	-
Additional staff time		
Line insertion and set-up – hr	1.2±0.3	0.5±0.4
Monitoring – hr	0.3±0.3	-
Training – hr	0.3±0	-
Hospital length of stay		
Index admission		
ED - hr	2.3±3.2	1.9±2.1
Critical care unit - days	4.9±7.8	4.7±8.9
General medical bed - days	10.5±15.0	9.6±13.5
Re-admissions		
Re-admissions - no. (%)	27 (4.3)	30 (4.8)
Days in critical care	0.3±2.5	0.4±3.2
General medical bed days	0.7±4.2	0.7±4.5
Total length of stay up to 90 days	16.7±19.2	15.5±17.8

* Plus-minus values are means ±SD. EGDT denotes early goal-directed therapy.

Table S16. Costs in GB pounds (£) Up To 90 Days.*

	EGDT (N = 625)	Usual resuscitation (N = 626)
Intervention		
Monitor and consumables	175±58	33±26
Blood products	83±208	66±207
Drug (Dobutamine)	8±24	4±19
Additional staff time costs		
Line insertion and set-up	64±18	29±21
Monitoring	16±16	-
Training	17±0	-
Hospital costs		
Index admission†		
ED	62±85	53±56
Critical care unit	7,255±12,045	6,852±13,529
General medical bed	2786±3980	2532±3586
Re-admission costs‡		
Critical care unit	467±3,577	626±4500
General medical	196±1,132	178±1178
In-hospital, outpatient and community costs§	1,252±2,848	1071±2681
Total costs up to 90 days†‡§¶	12,414±14,970	11,424±15,727

* Plus-minus values are means ±SD. EGDT denotes early goal-directed therapy.
† Source: ProMISe database.
‡ Source: CMP Database.
§ Source: Health Services Questionnaire.
¶ Multiply imputed data.

Table S17. Alternative Assumptions for Sensitivity Analyses.

	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 implementation	Protocol implemented in both ED and critical care	Protocol implemented exclusively either in ED or in critical care
Re-admissions 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

Table S18. Subgroup and Secondary Analyses of Cost-effectiveness Outcomes.

Subgroup	Incremental cost (95% CI)	Incremental QALY (95% CI)	Incremental net benefit* (95% CI)
Degree of protocolized care in usual resuscitaion			
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 - yr			
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 (-2037 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 (-2786 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 (-2004 to 627)
Time from ED presentation to randomization - hr			
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 or more	-1453 (-4882 to 1976)	-0.001 (-0.012 to 0.010)	1426 (-4613 to 4860)
Adherence adjusted			
	1423 (-1042 to 3888)	-0.001 (-0.009 to 0.007)	-1438 (-3909 to 1033)

* The incremental net benefit is calculated according to NICE methods guidance, by multiplying the mean QALY gain (or loss) by £20,000 ($28,430), and subtracting from this the incremental cost. The currency conversion factor used was £1:$1.4215.

Table S19. Serious Adverse Events.*

	EGDT (N = 625)	Usual resuscitation (N= 626)
Specified serious adverse events		
Pneumothorax	0 (0.0)	4 (0.6)
Hemo-pneumothorax	0 (0.0)	0 (0.0)
Bleeding	2 (0.3)	2 (0.3)
Thrombosis	2 (0.3)	0 (0.0)
Pulmonary emboli	4 (0.6)	2 (0.3)
Vascular catheter infection	0 (0.0)	0 (0.0)
Pulmonary edema	4 (0.6)	7 (1.1)
Blood transfusion reaction	0 (0.0)	1 (0.2)
Myocardial ischemia	7 (1.1)	4 (0.6)
Peripheral ischemia	0 (0.0)	1 (0.2)
Unspecified serious adverse events		
Cardiac arrest	5 (0.8)	4 (0.6)
Cerebrovascular event	4 (0.6)	1 (0.2)
Arrhythmia	1 (0.2)	2 (0.3)
Other†	5 (0.8)	5 (0.8)

* Values are number and percentage. Numbers do not add up as some patients experienced more than one serious adverse event. Serious adverse events are recorded between randomization and 30 days.

† Other serious adverse events (one patient each) were: bronchopleural fistula; encephalitis; fresh blood in endotracheal tube; hospital-acquired pneumonia; hypernatremia; myocardial infarction; perforation of ischemic ileum; requirement for emergency splenectomy; respiratory failure; worsening lactate; and deranged liver function tests.

Table S20. Usual Resuscitation Groups – Rivers and ProMISe.*

	Rivers	ProMISe
Timing		
ED presentation to randomization – hr	1.5±1.7	2.8±1.4
Baseline characteristics		
Age - yr	64.4±17.1	64.3±15.5
Male - %	50.4	58.6
SBP - mmHg	109±34	97.0±25.5
MAP - mmHg	76±24	64.7±17.2
Blood lactate concentration - mmol/L	6.9±4.5	5.1±3.5
APACHE II score	20.4±7.4	18.0±7.1
Interventions hour 0 to hour 6		
Total fluids - mL	3499±2438	2022±1271
Vasopressors - %	30.3	46.6
Red cell transfusion - %	18.5	3.8
Dobutamine - %	0.8	3.8
Mechanical ventilation - %	53.8	19.0
Outcomes		
Hospital mortality - %	46.5	24.6

* Plus-minus values are means ±SD.

Table S21. Usual Resuscitation Groups – ProCESS, ARISE and ProMISe.*

	ProCESS	ARISE	ProMISe
Timing			
ED presentation to randomization - hr	3.0±1.6	---	2.8±1.4
Median ED presentation to randomization (IQR) - hr	---	2.7 (2.0-3.9)	2.5 (1.8-3.5)
Median ED length of stay (IQR) - hr	---	2.0 (1.0-3.8)	1.3 (0.4-2.9)
Baseline characteristics			
Age - yr	62.0±16.0	63.1±16.5	64.3±15.5
Male - %	57.9	59.3	58.6
SBP - mmHg	99.9±29.5	---	97.0±25.5
MAP - mmHg	64.7±15.6	70.5±16.0	64.7±17.2
Blood lactate concentration - mmol/L	4.9±3.1	4.2±2.8	5.1±3.5
Refractory hypotension only - %	39.3	53.5	36.3
Hyperlactatemia only - %	46.7	30.2	44.4
Both refractory hypotension and hyperlactatemia - %	14.0	16.3	19.3
APACHE II score	20.7±7.5	15.8±6.5	18.0±7.1
Interventions hour 0 to hour 6			
Pre-randomization fluids† - L	2.1±1.4	2.6±1.3	2.0±1.1
Any fluids‡ - mL	2279±1881	1713±1401	2022±1271
Vasopressors§ - %	44.1	57.8	46.6
Red cell transfusion - %	7.5	7	3.8
Dobutamine - %	0.9	2.6	3.8
Mechanical ventilation¶ - %	21.7	22.4	19.0
CVC insertion‖ - %	57.9	61.9	50.9
Outcomes			
Hospital mortality - %		15.7	24.6
Discharge home** %	51.5	79.6	82.2
28-day mortality - %		15.9	24.5
90-day mortality - %	33.7	18.8	29.2

* Plus-minus values are means ±SD.

† ProMISe includes intravenous crystalloid and colloid administration > 20mLs and all blood product administration; ProCESS includes intravenous crystalloid, colloid and blood product administration.

‡ ProMISe and ARISE include intravenous crystalloid and colloid administration > 20mLs.

§ ARISE includes vasopressor infusion at any dose for ≥ 30 minutes.

¶ ProCESS includes mechanical ventilation from ED presentation.

‖ ProCESS and ARISE include CVC insertion from ED presentation.

** ProCESS discharge home is at 60 days.

Table S22. Mortality for Admissions to English ICUs with Severe Sepsis and Refractory Hypotension and/or Hyperlactatemia.*

	Number of admissions	Acute hospital mortality
Refractory hypotension only	2186 (18.2)	687 (31.4)
Hyperlactatemia only	5339 (44.5)	1397 (26.2)
Both refractory hypotension and hyperlactatemia	4479 (37.3)	2485 (55.5)

* Values are number and percentage. Based on 12,004 admissions from ED to ICU with infection, two or more SIRS criteria and with either refractory hypotension (lowest SBP < 90 mmHg) or hyperlactatemia (highest blood lactate concentration ≥ 4 mmol/L) in 183 adult, general ICUs in England (Feb 2011 to Jun 2014).

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