ORIGINAL ARTICLE

# Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*


## ABSTRACT

### BACKGROUND

After a single-center trial and observational studies suggesting that early, goal-directed therapy (EGDT) reduced mortality from septic shock, three multicenter trials (ProCESS, ARISE, and ProMISe) showed no benefit. This meta-analysis of individual patient data from the three recent trials was designed prospectively to improve statistical power and explore heterogeneity of treatment effect of EGDT.

### METHODS

We harmonized entry criteria, intervention protocols, outcomes, resource-use measures, and data collection across the trials and specified all analyses before unblinding. After completion of the trials, we pooled data, excluding the protocol-based standard-therapy group from the ProCESS trial, and resolved residual differences. The primary outcome was 90-day mortality. Secondary outcomes included 1-year survival, organ support, and hospitalization costs. We tested for treatment-by-subgroup interactions for 16 patient characteristics and 6 care-delivery characteristics.

### RESULTS

We studied 3723 patients at 138 hospitals in seven countries. Mortality at 90 days was similar for EGDT (462 of 1852 patients [24.9%]) and usual care (475 of 1871 patients [25.4%]); the adjusted odds ratio was 0.97 (95% confidence interval, 0.82 to 1.14; P=0.68). EGDT was associated with greater mean (±SD) use of intensive care (5.3±7.1 vs. 4.9±7.0 days, P=0.04) and cardiovascular support (1.9±3.7 vs. 1.6±2.9 days, P=0.01) than was usual care; other outcomes did not differ significantly, although average costs were higher with EGDT. Subgroup analyses showed no benefit from EGDT for patients with worse shock (higher serum lactate level, combined hypotension and hyperlactatemia, or higher predicted risk of death) or for hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation.

### CONCLUSIONS

In this meta-analysis of individual patient data, EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics. (Funded by the National Institute of General Medical Sciences and others; PRISM ClinicalTrials.gov number, NCT02030158.)


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*The Protocolized Resuscitation in Sepsis Meta-Analysis (PRISM) study is a collaboration of the Protocolized Care for Early Septic Shock (ProCESS) Investigators, based in the United States; the Australasian Resuscitation in Sepsis Evaluation (ARISE) Investigators, based in Australia and New Zealand; the Protocolised Management in Sepsis (ProMISe) Investigators, based in the United Kingdom; and the International Forum for Acute Care Trialists. A complete list of the investigator groups is provided in the Supplementary Appendix, available at NEJM.org.

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In 2001, Rivers and colleagues reported on a 263-patient, single-center, randomized, controlled trial of early, goal-directed therapy (EGDT) versus usual care in patients presenting with septic shock to an urban emergency department in the United States.[1] EGDT is a 6-hour resuscitation protocol for the administration of intravenous fluids, vasopressors, inotropes, and red-cell transfusion to achieve prespecified targets for arterial blood pressure, central venous pressure, central venous oxygen saturation, and hemoglobin level. EGDT reduced hospital mortality from 46.5% to 30.5%,[1] prompting many institutions worldwide to adopt EGDT.[2] Three subsequent, government-funded, multicenter, randomized, controlled trials from the United States (Protocolized Care for Early Septic Shock [ProCESS]),[3] Australasia (Australasian Resuscitation in Sepsis Evaluation [ARISE]),[4] and the United Kingdom (Protocolised Management in Sepsis [ProMISe])[5] failed to show lower mortality with EGDT than with usual care.

A meta-analysis combining the average results of the trials also indicated no overall benefit from EGDT.[6] There is considerable heterogeneity, however, in patients in whom septic shock develops and in usual care across hospitals; consequently, important treatment effects in patient subgroups or particular settings may have been missed.[7]

A prospective meta-analysis of individual patient data would provide greater statistical power to identify subgroup effects. The ProCESS, ARISE, and ProMISe investigators therefore planned this prospective meta-analysis of individual patient data (called the Protocolized Resuscitation in Sepsis Meta-Analysis [PRISM] study) before enrollment of the first patient into the first trial and harmonized entry criteria, intervention protocols, outcomes, major resource-use measures, and data collection across the three trials.[8] The goals of the current study were to use pooled data from the three trials to determine the effect of EGDT versus usual care on 90-day mortality and secondary clinical and economic outcomes and to compare the effects of EGDT across prespecified patient and care-delivery subgroups.

## METHODS

### STUDY DESIGN

All three trials evaluated the EGDT protocol, as described in the article by Rivers et al.[1] Core aspects of best care, including early recognition of sepsis and prompt delivery of intravenous fluids and antimicrobial agents, were promoted in the EGDT groups and the usual-care groups and reinforced through trial eligibility criteria.

We published the statistical analysis plan and a priori hypotheses for the current study before unblinding of any results from the three trials (ClinicalTrials.gov number, NCT02030158); the protocol is also available with the full text of this article at NEJM.org. Each trial supplied individual patient data after publication[3-5] and after the trial-level meta-analysis.[6] Before pooling data, we compared trial protocols, case-report forms, and data dictionaries to identify any recoding needed. We then provided a detailed data-set specification to each trial team to prepare the data file for pooling. After receipt of the data, we checked for missing or duplicate values and for consistency and plausibility, resolving data queries through direct consultation with each trial team before analysis. We did not reassess risk of bias because that had been performed for the trial-level meta-analysis.[6]

The final data-set specification is shown in Table S1 in the Supplementary Appendix, available at NEJM.org. The primary outcome measure was all-cause mortality at 90 days. Secondary outcome measures were in-hospital and 28-day mortality; duration of survival to 1 year; duration of stay in the emergency department, intensive care unit, and hospital; receipt and duration of invasive mechanical ventilation, vasopressors, and renal-replacement therapy; and costs and cost-effectiveness at 90 days.

Prespecified subgroups according to baseline patient characteristics were age, sex, severe coexisting conditions (liver, respiratory, cardiovascular, and renal conditions and immunocompromised state, all defined according to Acute Physiology and Chronic Health Evaluation [APACHE] II criteria), site of infection, and severity of illness. Severity of illness was operationalized in eight ways, according to eligibility criteria met (refractory hypotension, hyperlactatemia, or both), serum lactate level, illness-severity score (APACHE II Acute Physiology Score [range, 0 to 60, with higher scores indicating greater severity of illness] and APACHE II score [range, 0 to 71, with higher scores indicating greater severity of illness]), organ dysfunction (Sequential Organ Failure Assessment score), treatment (invasive mechanical ventilation [yes or no] and vasopressors [yes or no]), and

risk of death (derived from a customized model; see the Supplementary Appendix). Prespecified subgroups according to care-delivery characteristics were time from emergency department presentation to randomization, time of randomization (weekday or weekend and day or night), time from emergency department presentation to first administration of intravenous antimicrobial agents (available for the ProCESS and ARISE trials), and underlying intensity of care (derived from propensity models for the use of vasopressors or fluids during usual care; see the Supplementary Appendix).

The funders had no role in the design or conduct of the study, in the collection, analysis, or interpretation of the data, or in the writing of the manuscript or the decision to submit it for publication.

### STATISTICAL ANALYSIS

The individual trials each had 80 to 90% power to detect an absolute difference in mortality of 6.5 to 8.0 percentage points between the EGDT group and the usual-care group, under the assumption of a baseline mortality of 24 to 40%, depending on the trial. Because this was a prospective meta-analysis of individual patient data, the sample-size calculation was undertaken before the results of the individual trials were available. On the basis of a control event rate of 25 to 35%, a statistical power of 80%, and a two-sided P value of 0.05 (with no allowance for heterogeneity of treatment effect or clustering of outcomes across trials), this study could detect an absolute between-group difference in 90-day mortality of 4 to 5 percentage points and an interaction effect (odds ratio) of approximately 1.5 or 1.6 for a subgroup representing one half or one quarter of the total sample, respectively.

We conducted all analyses on an intention-to-treat basis. We used one-stage, hierarchical regression modeling (patients nested in sites nested in trials), with site as a random effect and trial as a fixed effect. We determined heterogeneity among trials by fitting a fixed interaction between treatment and trial. We analyzed binomial outcomes using hierarchical logistic regression, reported as odds ratios and 95% confidence intervals; survival time (censored at 1 year) using hierarchical (shared frailty) Cox proportional-hazards regression, reported as hazard ratios and 95% confidence intervals; and continuous outcomes using hierarchical linear regression, reported as differences in means and 95% confidence intervals. We presented survival to 1 year using a Kaplan–Meier survival curve.

We performed a secondary analysis of the primary outcome using the same hierarchical regression structure with adjustment for prespecified baseline covariates of age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), APACHE II score, and invasive mechanical ventilation at randomization (yes or no). Analyses of binomial secondary outcomes were adjusted for the same covariates. To determine heterogeneity between prespecified subgroups, we added fixed interaction terms between treatment and subgroup to the adjusted model for the primary outcome. To ascertain whether any variation in treatment effect across subgroups was consistent among the trials, we fitted three-way fixed interactions among trial, treatment, and subgroup. We analyzed continuous subgroup variables by dividing the cohort into thirds.

Our cost-effectiveness analysis compared the outcomes and costs, from the health-services perspective, up to 90 days after randomization. We used the combined mortality but reported cost and cost-effectiveness estimates separately for each trial because the interpretation of pooled cost-effectiveness estimates is unclear when drawn from health care systems with different cost structures.[9] The resource use for each patient was combined with trial-specific unit costs to report the incremental costs of EGDT versus usual care. We calculated quality-adjusted life-years (QALYs) up to 90 days by combining survival time with quality-of-life scores from the EuroQol questionnaire (EQ-5D-5L) administered at 90 days in the ProMISe trial, using the area-under-the-curve approach.[10] We estimated incremental costs and QALYs of EGDT versus usual care with a seemingly unrelated regression model,[11] with trial as a fixed effect for costs. We report results for each trial overall and for the same prespecified subgroups as for the clinical outcomes. We report incremental net monetary benefits by valuing QALYs at recommended thresholds for a QALY gain and performed sensitivity analyses to test the robustness of our results to alternative assumptions (see the Supplementary Appendix).

All analyses were performed with the use of SAS software, version 9.4 (SAS Institute), or Stata

**Table 1. Patient and Care-Delivery Characteristics at Baseline.***

| Characteristic | EGDT (N=1857) | Usual Care (N=1880) |
|---|---|---|
| **Patient characteristics** | | |
| Age — yr† | | |
| Median | 65 | 65 |
| IQR | 53–75 | 53–76 |
| Male sex — no. (%) | 1065 (57.4) | 1104 (58.7) |
| ≥1 Severe coexisting condition — no./total no. (%)‡ | 546/1854 (29.4) | 526/1880 (28.0) |
| Site of infection — no. (%) | | |
| Lungs | 657 (35.4) | 620 (33.0) |
| Abdomen | 172 (9.3) | 163 (8.7) |
| Blood | 172 (9.3) | 172 (9.1) |
| Central nervous system | 28 (1.5) | 19 (1.0) |
| Soft tissue | 154 (8.3) | 153 (8.1) |
| Urinary tract | 356 (19.2) | 371 (19.7) |
| Other | 113 (6.1) | 149 (7.9) |
| Unknown | 196 (10.6) | 218 (11.6) |
| Determined ultimately to have no infection | 9 (0.5) | 15 (0.8) |
| Entry criterion met — no./total no. (%) | | |
| Refractory hypotension only | 821/1854 (44.3) | 833/1880 (44.3) |
| Hyperlactatemia only | 717/1854 (38.7) | 732/1880 (38.9) |
| Both refractory hypotension and hyperlactatemia | 316/1854 (17.0) | 315/1880 (16.8) |
| Last values before randomization | | |
| Systolic blood pressure — mm Hg | | |
| Median | 94 | 94 |
| IQR | 83–112 | 82–111 |
| Mean arterial pressure — mm Hg | | |
| Median | 67 | 67 |
| IQR | 59–78 | 59–78 |
| Serum lactate — mmol/liter | | |
| Median | 4.3 | 4.2 |
| IQR | 2.5–5.9 | 2.4–5.9 |
| APACHE II Acute Physiology Score — median (IQR)§ | 11 (7–15) | 11 (7–15) |
| APACHE II score — median (IQR)¶ | 16 (12–21) | 16 (12–21) |
| SOFA score — median (IQR)‖ | 4 (2–6) | 4 (2–6) |
| Customized risk of death — median (IQR) | 0.21 (0.11–0.37) | 0.22 (0.11–0.36) |
| **Care-delivery characteristics** | | |
| Time from ED presentation to inclusion criteria met — min | | |
| Median | 85 | 81 |
| IQR | 40–150 | 36–145 |
| Time from ED presentation to randomization — min | | |
| Median | 162 | 159 |
| IQR | 119–223 | 115–221 |

**Table 1. (Continued.)**

| Characteristic | EGDT (N=1857) | Usual Care (N=1880) |
|---|---|---|
| Receiving antimicrobial agents at randomization — no./total no. (%) | 1726/1856 (93.0) | 1742/1880 (92.7) |
| Time from ED presentation to first IV antimicrobial agents — min** | | |
| Median | 75 | 72 |
| IQR | 42–120 | 42–119 |
| IV fluids administered before hospital presentation until randomization — no./total no. (%) | 1801/1846 (97.6) | 1818/1871 (97.2) |
| Volume administered — ml | | |
| Median | 2000 | 2000 |
| IQR | 1250–3000 | 1200–3000 |
| Volume administered per kilogram of body weight — ml | | |
| Median | 27.5 | 27.7 |
| IQR | 16.5–42.3 | 16.2–41.7 |

* Data are from the Protocolized Care for Early Septic Shock (ProCESS) trial, the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial, and the Protocolised Management in Sepsis (ProMISe) trial. The numbers of patients with data available for analysis were as follows: age, 1857 in the group that received early, goal-directed therapy (EGDT) and 1879 in the group that received usual care; systolic blood pressure, 1809 and 1824; mean arterial pressure, 1318 and 1352; serum lactate, 1626 and 1645; customized risk of death, 1849 and 1878; time from emergency department (ED) presentation to inclusion criterion met, 1853 and 1878; time from ED presentation to first intravenous (IV) antimicrobial agents, 1091 and 1095; volume of IV fluids administered, 1846 and 1871; and volume of IV fluids administered per kilogram of body weight, 1723 and 1687. For details on data harmonization, see Table S1 in the Supplementary Appendix. IQR denotes interquartile range.

† Age was estimated for 7 patients in the ProMISe trial.

‡ Severe coexisting conditions were defined according to Acute Physiology and Chronic Health Evaluation [APACHE] II criteria.

§ APACHE II Acute Physiology Scores range from 0 to 60, with higher scores indicating greater severity of illness.

¶ APACHE II scores range from 0 to 71, with higher scores indicating greater severity of illness.

‖ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. Baseline urine output was not used in the calculation of the renal SOFA score in the ARISE and ProMISe trials.

** Shown are data for patients who received IV antimicrobial agents before randomization in the ProCESS and ARISE trials. All patients in the ProMISe trial received IV antimicrobial agents before randomization (time not recorded).

software, version 11.2 (StataCorp), and a two-sided alpha level of 0.05. Complete-case analysis was used for clinical outcomes because data were missing for less than 0.5% for all outcomes; multiple imputation was used for missing quality-of-life scores. We did not adjust for multiple comparisons; with 22 planned subgroup analyses, 1 or 2 significant interaction tests ($P<0.05$) would be expected on the basis of chance alone.[12]

## RESULTS

### STUDY PATIENTS

From March 2008 through July 2014, the three trials enrolled 4211 patients at 138 hospitals in the United States (ProCESS); Australia, New Zealand, Finland, Hong Kong, and the Republic of Ireland (ARISE); and England (ProMISe). The 448 patients randomly assigned to receive protocol-based standard therapy in the ProCESS trial were excluded from the current study, resulting in 3763 patients randomly assigned to either usual care (1892 patients) or EGDT (1871 patients). After the exclusion of patients who withdrew consent, underwent randomization in error, or were lost to follow-up at 90 days, 3723 patients (98.9%) were included in the primary analysis and 3511 (93.3%) were followed up to 1 year (Fig. S1 in the Supplementary Appendix). Patient and care-delivery characteristics were well balanced at baseline (Table 1, and Tables S2 and S3 in the Supplementary Appendix).

**Table 2. Outcomes.***

| Outcome | EGDT (N=1857) | Usual Care (N=1880) | Incremental Effect (95% CI) | P Value | |
|---|---|---|---|---|---|
| | | | | Overall Comparison | Comparison among Trials |
| Primary outcome: death at 90 days — no./total no. (%) | 462/1852 (24.9) | 475/1871 (25.4) | 0.97 (0.82 to 1.14)†‡ | 0.68 | 0.73 |
| Secondary outcomes: mortality | | | | | |
| Death at hospital discharge — no./total no. (%)§ | 370/1857 (19.9) | 365/1878 (19.4) | 1.02 (0.85 to 1.21)† | 0.86 | 0.42 |
| Death at 28 days — no./total no. (%) | 375/1854 (20.2) | 385/1873 (20.6) | 0.96 (0.81 to 1.15)† | 0.68 | 0.57 |
| Secondary outcomes: duration of stay from randomization | | | | | |
| In ED — hr | | | | | |
| Median | 1 | 1 | | | |
| IQR | 0 to 3 | 0 to 3 | | | |
| Mean | 2.1±3.3 | 2.2±3.0 | −0.1 (−0.3 to 0.1)¶ | 0.19 | <0.001‖ |
| In ICU | | | | | |
| Admitted to ICU — no. (%) | 1684 (90.7) | 1532 (81.5) | | | |
| First stay — days | | | | | |
| Median among patients admitted | 3 | 4 | | | |
| IQR | 2 to 6 | 2 to 6 | | | |
| Mean overall | 4.9±6.6 | 4.5±6.4 | 0.5 (0.1 to 0.9)¶ | 0.02 | 0.76 |
| Total stay, including readmissions — days | | | | | |
| Median among patients admitted | 4 | 4 | | | |
| IQR | 2 to 7 | 2 to 7 | | | |
| Mean overall | 5.3±7.1 | 4.9±7.0 | 0.5 (0.0 to 0.9)¶ | 0.04 | 0.78 |
| In hospital — days§ | | | | | |
| Median | 9 | 9 | | | |
| IQR | 5 to 17 | 5 to 17 | | | |
| Mean | 14.8±17.5 | 14.9±26.2 | −0.1 (−1.5 to 1.4)¶ | 0.92 | 0.39 |
| Secondary outcomes: receipt and duration of organ support in ICU | | | | | |
| Respiratory support: invasive mechanical ventilation in ICU | | | | | |
| Receipt — no./total no. (%) | 565/1852 (30.5) | 544/1874 (29.0) | 1.05 (0.89 to 1.24)† | 0.57 | 0.04** |
| Duration — days | | | | | |
| Median among patients receiving support | 4 | 4 | | | |
| IQR | 2 to 8 | 2 to 8 | | | |
| Mean overall | 2.1±5.5 | 1.9±5.2 | 0.2 (−0.2 to 0.5)¶ | 0.36 | 0.58 |

| | | | | | |
|---|---|---|---|---|---|
| Cardiovascular support: vasopressors or inotropes in ICU | | | | | |
| Receipt — no./total no. (%) | 1040/1854 (56.1) | 923/1873 (49.3) | 1.42 (1.23 to 1.64)† | <0.001 | 0.40 |
| Duration — days | | | | | |
| Median among patients receiving support | 2 | 2 | | | |
| IQR | 1 to 4 | 1 to 4 | | | |
| Mean overall | 1.9±3.7 | 1.6±2.9 | 0.3 (0.1 to 0.5)¶ | 0.01 | 0.52 |
| Renal support: renal-replacement therapy in ICU | | | | | |
| Receipt — no./total no. (%) | 204/1852 (11.0) | 198/1874 (10.6) | 1.02 (0.81 to 1.28)† | 0.88 | 0.91 |
| Duration — days | | | | | |
| Median among patients receiving support | 3 | 4 | | | |
| IQR | 2 to 7 | 2 to 7 | | | |
| Mean overall | 0.7±3.3 | 0.6±2.4 | 0.0 (–0.1 to 0.2)¶ | 0.68 | 0.99 |
| Cost-effectiveness analysis†† | | | | | |
| Total costs up to 90 days — $ | | | | | |
| ProCESS | 32,178±30,181 | 30,930±30,150 | 1276 (–1799 to 4352)¶ | 0.42 | |
| ARISE | 25,014±25,737 | 22,973±22,822 | 2042 (–264 to 4352)¶ | 0.08 | |
| ProMISe | 14,112±15,120 | 12,906±16,017 | 1183 (–1418 to 3783)¶ | 0.37 | |
| EQ-5D-5L score among survivors at 90 days‡‡ | 0.623±0.313 | 0.625±0.309 | –0.002 (–0.039 to 0.000)¶ | 0.91 | |
| QALYs among all patients to 90 days | 0.058±0.048 | 0.058±0.048 | 0.000 (–0.004 to 0.004)¶ | 0.96 | |
| Incremental net benefit at 90 days — $§§ | | | | | |
| ProCESS | | | –1266 (–4373 to 1841) | 0.43 | |
| ARISE | | | –2032 (–4378 to 314) | 0.09 | |
| ProMISe | | | –1172 (–3813 to 1469) | 0.39 | |

* Plus–minus values are means ±SD. For details on data harmonization, see Table S1 in the Supplementary Appendix. CI denotes confidence interval, ICU intensive care unit, and QALY quality-adjusted life-year.

† Shown is the adjusted odds ratio, with adjustment for age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), APACHE II score, and receipt of invasive mechanical ventilation (yes or no).

‡ The unadjusted odds ratio for the primary outcome was 0.98 (95% CI, 0.84 to 1.14; P=0.78).

§ Data were censored at 60 days after randomization in the ProCESS trial.

¶ Shown is the difference in means.

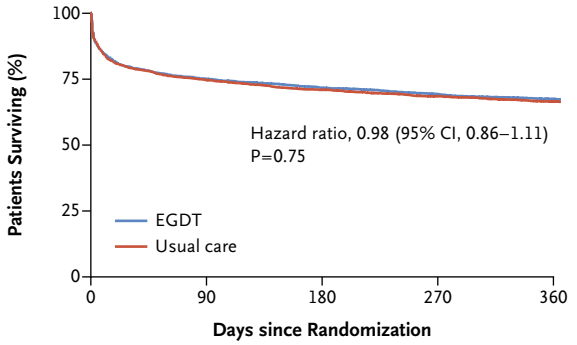
‖ The incremental effect (difference in means) according to trial was as follows: ProCESS, 0.3 (95% CI, –0.1 to 0.7); ARISE, –0.6 (95% CI, –0.9 to –0.3); and ProMISe, 0.2 (95% CI, 0.0 to 0.4).

** The incremental effect (adjusted odds ratio) according to trial was as follows: ProCESS, 1.51 (95% CI, 1.12 to 2.04); ARISE, 0.98 (95% CI, 0.78 to 1.23); and ProMISe, 0.98 (95% CI, 0.76 to 1.26).

†† Missing data were multiply imputed.

‡‡ Quality of life was assessed with the use of the EuroQol questionnaire (EQ-5D-5L; a score of 0 indicates death and 1 perfect quality of life), which was administered to eligible patients in the ProMISe trial at 90 days after randomization. For all patients in the ProCESS and ARISE trials and those in the ProMISe trial who did not complete an EQ-5D-5L questionnaire, we used all available covariate information to estimate each patient's quality-of-life score with multiple imputation.

§§ The incremental net benefit was calculated by multiplying the QALY gain (or loss) by $100,000 and subtracting from this the incremental cost.




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| EGDT | 1857 | 1391 | 1287 | 1209 | 1119 |
| Usual care | 1880 | 1395 | 1295 | 1206 | 1110 |

**Figure 1. Patient Survival over a Period of 1 Year.**
There was no significant difference in the duration of survival to 1 year between the group that received early, goal-directed therapy (EGDT) and the group that received usual care. Data with respect to survival were censored at the actual date that the patient was last known to be alive or at 365 days. CI denotes confidence interval.

**Figure 2 (facing page). 90-Day Mortality According to Patient Subgroup.**
For details on data harmonization, see Table S1 in the Supplementary Appendix. Odds ratios were adjusted for age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), Acute Physiology and Chronic Health Evaluation (APACHE) II score (range, 0 to 71, with higher scores indicating greater severity of illness), and receipt of invasive mechanical ventilation (yes or no). The size of the square corresponds to the number of patients in each subgroup. Age was estimated for seven patients in the Protocolised Management in Sepsis (ProMISe) trial. The odds ratios according to trial for immunocompromised state versus no immunocompromised state were as follows: Protocolized Care for Early Septic Shock (ProCESS), 1.26 (95% CI, 0.72 to 2.20) versus 0.82 (95% CI, 0.58 to 1.17); Australasian Resuscitation in Sepsis Evaluation (ARISE), 1.23 (95% CI, 0.60 to 2.50) versus 0.96 (95% CI, 0.73 to 1.26); and ProMISe, 0.66 (95% CI, 0.33 to 1.29) versus 1.08 (95% CI, 0.83 to 1.40). For site of infection, patients with other or unknown site include those with an infection in the central nervous system and those who were determined ultimately to have no infection. Three patients did not meet the eligibility criteria for refractory hypotension or hyperlactatemia. APACHE II Acute Physiology Scores range from 0 to 60, with higher scores indicating greater severity of illness. Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure.

### PRIMARY OUTCOME

Mortality at 90 days did not differ significantly between the two groups. Death occurred in 462 of 1852 patients (24.9%) in the EGDT group and in 475 of 1871 (25.4%) in the usual-care group (Table 2). The adjusted odds ratio was 0.97 (95% confidence interval [CI], 0.82 to 1.14; P=0.68). There was no interaction with respect to treatment effect among the trials.

### SECONDARY OUTCOMES

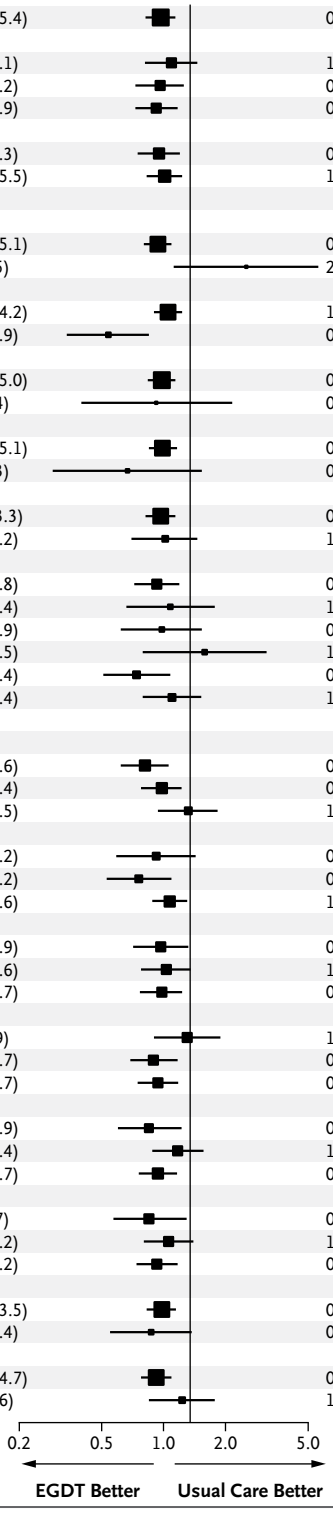
Duration of stay in the intensive care unit (first admission and total days) and receipt of cardiovascular support (both percentage of patients and duration) were greater in the EGDT group than the usual-care group (Table 2). No other secondary outcomes differed significantly. Duration of stay in the emergency department was shorter in the EGDT group than in the usual-care group in the ARISE trial but not in the ProCESS or ProMISe trials. There was no significant difference in the duration of survival to 1 year between the two groups (hazard ratio, 0.98; 95% CI, 0.86 to 1.11; P=0.75) (Fig. 1).

### SUBGROUP ANALYSES

Of the 16 a priori patient characteristics evaluated in subgroup analyses (Fig. 2), only 2 had significant interactions. In particular, there was no evidence of benefit associated with EGDT in the subgroups with the most severe septic shock, including those with a serum lactate level of 4.1 mmol per liter or more (1796 of 3258 patients [55.1%]; mean, 6.7 mmol per liter), those who presented with both hypotension and hyperlactatemia (628 of 3720 patients [16.9%]; mean systolic blood pressure, 89 mm Hg; mean serum lactate level, 6.7 mmol per liter), those in the upper third of APACHE II scores (1217 of 3723 patients [32.7%]; mean score, 24.6), and those in the upper third of predicted risk of death (1227 of 3715 patients [33.0%]; 90-day mortality, 46.2%). EGDT was associated with higher mortality among patients with severe chronic liver disease (117 of 3720 patients [3.1%]) than among those without such disease and lower mortality among those with severe chronic respiratory disease (370 of 3720 patients [9.9%]) than among those without such disease.

Among the six a priori care-delivery characteristics evaluated, we found no treatment-by-subgroup interactions (Fig. 3). In particular, analy-

| Subgroup | EGDT | Usual Care | Odds Ratio (95% CI) | P Value: Overall Comparison | P Value: Comparison among Trials |
|---|---|---|---|---|---|
| | *no. of deaths/total no. of patients (%)* | | | | |
| Overall | 462/1852 (24.9) | 475/1871 (25.4) | 0.97 (0.82–1.14) | 0.68 | 0.73 |
| Age | | | | 0.69 | 0.85 |
| <57 yr | 111/611 (18.2) | 112/655 (17.1) | 1.09 (0.81–1.46) | | |
| 57–71 yr | 145/619 (23.4) | 139/575 (24.2) | 0.96 (0.73–1.25) | | |
| ≥72 yr | 206/622 (33.1) | 224/641 (34.9) | 0.92 (0.73–1.17) | | |
| Sex | | | | 0.71 | 0.98 |
| Female | 192/790 (24.3) | 195/772 (25.3) | 0.95 (0.75–1.20) | | |
| Male | 270/1062 (25.4) | 280/1099 (25.5) | 1.01 (0.83–1.23) | | |
| Severe coexisting condition | | | | | |
| Liver | | | | 0.01 | 0.12 |
| No | 427/1790 (23.9) | 455/1813 (25.1) | 0.94 (0.80–1.09) | | |
| Yes | 34/59 (57.6) | 20/58 (34.5) | 2.51 (1.12–5.63) | | |
| Respiratory | | | | 0.01 | 0.18 |
| No | 415/1658 (25.0) | 409/1692 (24.2) | 1.05 (0.90–1.23) | | |
| Yes | 46/191 (24.1) | 66/179 (36.9) | 0.54 (0.34–0.85) | | |
| Cardiovascular | | | | 0.84 | 0.89 |
| No | 442/1800 (24.6) | 456/1824 (25.0) | 0.98 (0.84–1.14) | | |
| Yes | 19/49 (38.8) | 19/47 (40.4) | 0.92 (0.40–2.15) | | |
| Renal | | | | 0.36 | 0.69 |
| No | 446/1787 (25.0) | 454/1808 (25.1) | 0.99 (0.85–1.16) | | |
| Yes | 15/62 (24.2) | 21/63 (33.3) | 0.67 (0.29–1.53) | | |
| Immunocompromised state | | | | 0.92 | 0.01 |
| No | 357/1568 (22.8) | 375/1609 (23.3) | 0.97 (0.82–1.14) | | |
| Yes | 104/281 (37.0) | 100/262 (38.2) | 1.02 (0.70–1.46) | | |
| Site of infection | | | | 0.39 | 0.35 |
| Lungs | 171/656 (26.1) | 172/618 (27.8) | 0.93 (0.72–1.19) | | |
| Abdomen | 49/172 (28.5) | 43/163 (26.4) | 1.08 (0.66–1.77) | | |
| Blood | 59/171 (34.5) | 60/172 (34.9) | 0.98 (0.62–1.53) | | |
| Soft tissue | 24/154 (15.6) | 16/152 (10.5) | 1.58 (0.79–3.16) | | |
| Urinary tract | 61/354 (17.2) | 79/369 (21.4) | 0.74 (0.51–1.08) | | |
| Other or unknown | 98/345 (28.4) | 105/397 (26.4) | 1.10 (0.79–1.52) | | |
| Severity of illness | | | | | |
| Eligibility criterion met | | | | 0.09 | 0.53 |
| Refractory hypotension | 121/819 (14.8) | 146/831 (17.6) | 0.81 (0.62–1.06) | | |
| Hyperlactatemia | 213/715 (29.8) | 221/727 (30.4) | 0.98 (0.78–1.22) | | |
| Both | 128/315 (40.6) | 108/313 (34.5) | 1.32 (0.94–1.83) | | |
| Last lactate level before randomization | | | | 0.26 | 0.21 |
| <2.1 mmol/liter | 44/313 (14.1) | 52/342 (15.2) | 0.92 (0.59–1.43) | | |
| 2.1–4.0 mmol/liter | 64/397 (16.1) | 83/410 (20.2) | 0.76 (0.53–1.09) | | |
| ≥4.1 mmol/liter | 319/912 (35.0) | 297/884 (33.6) | 1.07 (0.88–1.30) | | |
| APACHE II Acute Physiology Score | | | | 0.95 | 0.65 |
| <9 | 96/677 (14.2) | 96/643 (14.9) | 0.97 (0.71–1.32) | | |
| 9–13 | 134/572 (23.4) | 135/598 (22.6) | 1.03 (0.78–1.35) | | |
| ≥14 | 232/603 (38.5) | 244/630 (38.7) | 0.98 (0.77–1.23) | | |
| APACHE II score | | | | 0.24 | 0.82 |
| <14 | 74/666 (11.1) | 58/650 (8.9) | 1.30 (0.90–1.88) | | |
| 14–19 | 137/576 (23.8) | 158/614 (25.7) | 0.89 (0.69–1.17) | | |
| ≥20 | 251/610 (41.1) | 259/607 (42.7) | 0.94 (0.75–1.18) | | |
| SOFA score | | | | 0.34 | 0.47 |
| <3 | 69/527 (13.1) | 75/503 (14.9) | 0.85 (0.60–1.22) | | |
| 3 or 4 | 127/547 (23.2) | 118/579 (20.4) | 1.17 (0.88–1.56) | | |
| ≥5 | 266/778 (34.2) | 282/789 (35.7) | 0.94 (0.76–1.16) | | |
| Customized risk of death | | | | 0.65 | 0.97 |
| <14% | 46/617 (7.5) | 55/634 (8.7) | 0.85 (0.57–1.29) | | |
| ≥14% and <30% | 135/609 (22.2) | 133/628 (21.2) | 1.06 (0.80–1.39) | | |
| ≥30% | 280/619 (45.2) | 287/608 (47.2) | 0.93 (0.74–1.17) | | |
| Invasive mechanical ventilation | | | | 0.55 | 0.62 |
| No | 386/1670 (23.1) | 401/1708 (23.5) | 0.98 (0.83–1.15) | | |
| Yes | 76/182 (41.8) | 74/163 (45.4) | 0.87 (0.55–1.37) | | |
| Vasopressor infusion | | | | 0.17 | 0.21 |
| No | 360/1559 (23.1) | 393/1592 (24.7) | 0.92 (0.78–1.09) | | |
| Yes | 101/291 (34.7) | 82/277 (29.6) | 1.23 (0.85–1.77) | | |



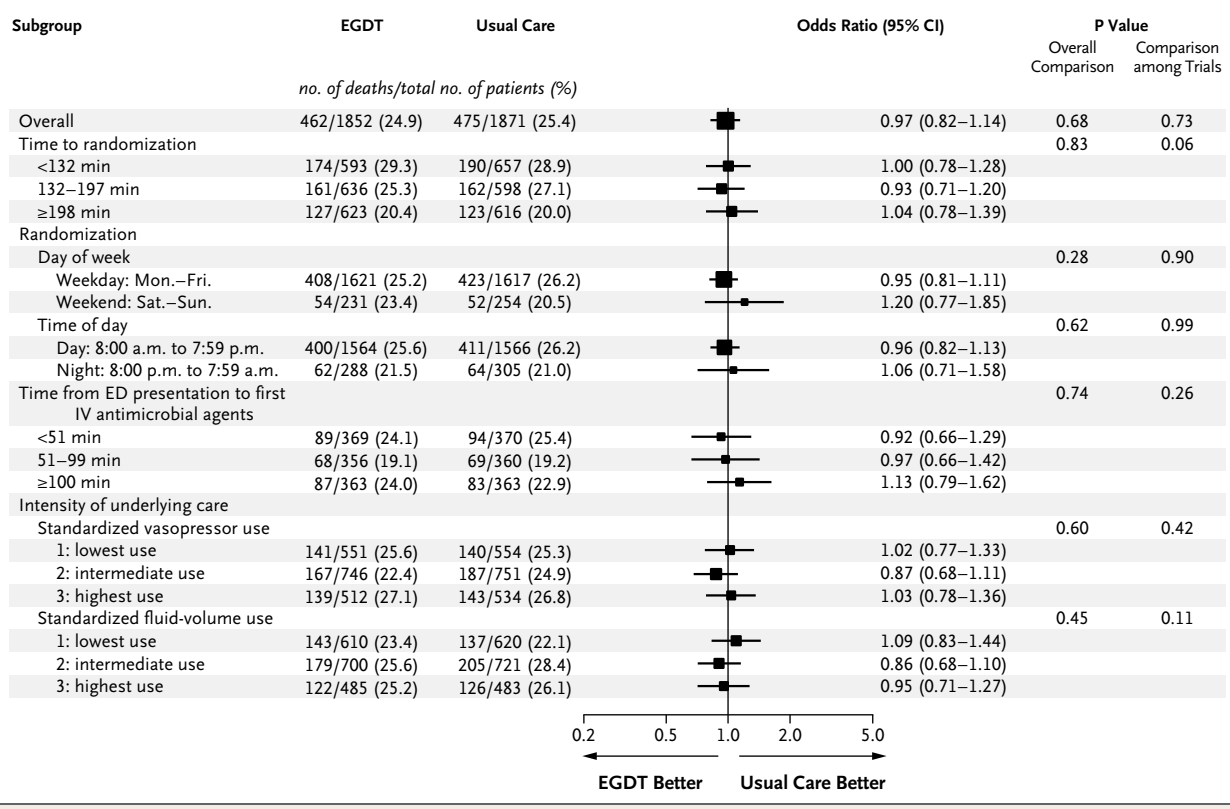



**Figure 3. 90-Day Mortality According to Care-Delivery Subgroup.**

For details on data harmonization, see Table S1 in the Supplementary Appendix. Odds ratio were adjusted for age, sex, last systolic blood pressure before randomization (<90 or ≥90 mm Hg), APACHE II score, and receipt of invasive mechanical ventilation (yes or no). The size of the square corresponds to the number of patients in each subgroup. Data for time from emergency department (ED) presentation to first intravenous (IV) antimicrobial agents are only for patients who received IV antimicrobial agents before randomization in the ProCESS and ARISE trials; all patients in the ProMISe trial received antimicrobial agents before randomization (time not recorded). Results for intensity of underlying care were reported for 115 (83%) of the 138 participating sites with at least three patients who received usual care.

ses of treatment effects according to differences in usual care showed no interaction and no evidence of benefit at sites providing less aggressive resuscitation, despite considerable variation among sites in the propensity to administer vasopressors (mean propensity according to third, 23.2%, 44.2%, and 65.3%) or intravenous fluids (mean volume according to third, 1.3, 2.0, and 3.4 liters) in the usual-care group.

In the total of 22 analyses, there were 2 significant interaction tests. This finding is consistent with the 1 or 2 such tests that would be expected by chance alone.

### COSTS AND COST-EFFECTIVENESS

In each of the three trials, the average cost up to 90 days was higher with EGDT than with usual care (Table 2, and Fig. S2 and Table S13 in the Supplementary Appendix). Average quality-of-life scores and QALYs were similar in the two groups; thus, for each trial, the average incremental net monetary benefit for EGDT versus usual care was negative, and the probability that EGDT is cost-effective was less than 0.25 across all realistic willingness-to-pay thresholds (Fig. S3 in the Supplementary Appendix). The sensitivity analysis showed that these base case results were robust to alternative assumptions (Fig. S4 in the Supplementary Appendix). Although the estimated incremental net benefit of EGDT was positive for a few of the prespecified subgroups, these results had wide 95% confidence intervals that included zero (Table S14 in the Supplementary Appendix).

## DISCUSSION

The results of our prospective meta-analysis of individual patient data provide a more granular and robust insight than the results of the individual trials and of our trial-level meta-analysis into the overall effectiveness of EGDT versus usual care in patients presenting to the emergency department with septic shock. We found no evidence that EGDT resulted in lower mortality than usual care, a finding that is consistent with the results of our trial-level meta-analysis.[6] We also found that, although the three trials occurred in geographically distinct health care systems, there was no evidence of any trial-specific effect.

Concerns exist that the divergent findings between the trial by Rivers et al.[1] and the three large, multicenter, randomized, controlled trials are because the patients included in the trial by Rivers et al. were sicker.[13] We found no evidence of treatment benefit with EGDT in patients with greater severity of illness, despite using several approaches to identify subgroups of very sick patients that were considerably larger than the entire population in the trial by Rivers et al. For example, the cohort in the upper third of predicted risk of death, which was more than four times as large as the entire population in the trial by Rivers et al., had similar mortality in the EGDT group and the usual-care group (approximately 45%); mortality was also similar to that in the control group in the trial by Rivers et al. We do not believe, therefore, that differences in severity explain the differences in findings. There were treatment interactions between EGDT and the presence of either severe preexisting respiratory or liver disease, but these effects were inconsistent and probably spurious, given the small number of patients with these coexisting conditions and the large number of subgroup analyses.

Another important concern raised about the recent trials was that usual care may have been superior to that reported in positive studies, explaining the failure to show a benefit with EGDT. Our subgroup analyses explored whether the effect of EGDT depended on the usual resuscitation practice in an emergency department; despite wide variation in practice, even in those emergency departments with the least aggressive practice, there was no evidence of benefit. As noted previously, all three trials are more recent than the trial by Rivers et al., and early recognition of sepsis and prompt delivery of intravenous fluids and antimicrobial agents were promoted in all treatment groups. It remains possible that general advances in the provision of care for sepsis and septic shock, to the benefit of all patients, explain part or all of the difference in findings between the trial by Rivers et al. and the more recent trials.

Unlike the results of observational studies,[14,15] which were proposed as evidence supporting the ongoing use of EGDT,[2,13] this prospectively defined analysis of individual patient data relies exclusively on random assignment, avoiding biases related to confounding by indication, regression to the mean, or secular trends in sepsis-related mortality.[16,17] This collaboration among trial groups also shows that key methodologic aspects of independently conducted research can be harmonized in advance, facilitating the generation of a richer evidence base to guide clinicians dealing with complex conditions such as septic shock. The return on investment for the patient, investigator, and funding agency is enhanced by our model of early collaboration among research groups, aligning key measurements and using a prespecified plan to perform a prospective meta-analysis of individual patient data to answer questions beyond the scope of each individual trial.

Nonetheless, there are important limitations to this analysis. Although the overall sample size is large, some clinically important subgroups are small, which limits statistical power. The analysis is also limited by the underlying internal and external validity of the three trials. None were blinded, which may introduce bias. Patients were enrolled in both academic and nonacademic metropolitan and rural hospitals across several regions of the world. However, the control groups may not be representative of usual care in all settings, especially those in low-income and middle-income countries.

Although our analysis confirms that EGDT as a packaged protocol of care is not superior to usual care, there are still unresolved questions regarding the most effective fluid and vasopressor regimens, the role of hemodynamic monitoring, and appropriate targets in the resuscitation of patients with sepsis and septic shock. Even though a policy that mandates routine measurement of central venous pressure and central venous oxygen saturation in all patients with sepsis did not improve outcomes, clinical judgment should always be applied because, in specific circum-

stances, there may be a role for these measurements. The future of sepsis therapy may yet lie with protocols that permit a more individualized approach that is based on a greater understanding of the complex interplay among host genetics, individual pathophysiological features, and the infective agent.[18-20]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

## APPENDIX

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# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The PRISM Investigators. Early, goal-directed therapy for septic shock — a patient-level meta-analysis. N Engl J Med. DOI: 10.1056/NEJMoa1701380

# Supplementary Appendix

# Early, Goal-Directed Therapy for Septic Shock: A Patient-Level Meta-Analysis

**Protocolized Resuscitation in Sepsis Meta-Analysis (PRISM) Writing Committee on behalf of the ProCESS, ARISE and ProMISe Investigators**

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# Supplementary Methods

## Statistical methods

### *Customized risk of death model*

We developed a customized risk of death model using a logistic regression model on 90-day mortality derived from usual care patients including predefined variables: age, sex, presence of any Acute Physiology and Chronic Health Evaluation (APACHE) II severe coexisting condition, nursing home resident, eligibility criteria, APACHE II Acute Physiology Score and site of infection. These variables were chosen *a priori* based on established relationships with outcome and not on the presence of baseline imbalance. No iterative selection of variables was performed. The resulting model is presented in Table S5.

### *Intensity of care measures*

We developed two surrogate measures of intensity of care at a site level by dividing all sites with three or more usual care patients into thirds based on the ratio of observed to expected vasopressor and fluid usage in usual care patients only. The expected proportion of patients receiving vasopressors within the first six hours was established using logistic regression controlling for age, sex, nursing home resident, presence of any APACHE II severe coexisting condition, site of infection, eligibility criteria, last APACHE II Acute Physiology Score before randomization, mechanical ventilation before randomization, receipt of vasopressors before randomization, day of week randomized, time of day randomized, total volumes of fluid received before randomization and during the first six hours after randomization and total volume of blood received during the first six hours after randomization. The expected total volume of fluid delivered in the first six hours was determined using linear regression controlling for age, sex, weight, nursing home resident, presence of any APACHE II severe coexisting condition, site of infection, eligibility criteria, last APACHE II Acute Physiology Score before randomization, mechanical ventilation before randomization, time from emergency department (ED) presentation to randomization, day of week randomized, time of day randomized, total volume of fluid received before randomization, total volume of blood received during the first six hours after randomization and the receipt of vasopressors before randomization and during the first six hours after randomization. The resulting models are presented in Tables S6 and S7.

### *Assessment of model fit*

Discrimination of the hierarchical logistic regression models was assessed with the area under the receiver operating characteristic curve (AUC) and calibration with the Hosmer-Lemeshow test. For the primary outcome of 90-day mortality, the unadjusted model (including treatment group, fixed effect of trial and random effect of site) had an AUC of 0.66 (95% confidence interval, 0.64 to 0.68). After adjustment for patient factors, this increased to 0.77 (0.75 to 0.78). There was no significant departure from perfect calibration for either the unadjusted or adjusted model (P=1.00 and P=0.49, respectively). The AUC for adjusted analyses of the binary secondary outcomes ranged from 0.78 to 0.84. The only significant departure from perfect calibration was for receipt of cardiovascular support (P<0.001).

Goodness of fit of the hierarchical linear regression models was assessed with proportion of explained variation (R-squared). The R-squared for analyses of the continuous secondary outcomes ranged from 4.9% to 29.4%. These models were not adjusted for patient characteristics.

## Economic evaluation

The aim of the economic evaluation was to compare the incremental cost-effectiveness of early, goal-directed therapy (EGDT) versus usual care at 90 days post-randomization, using individual patient data from three multinational randomized clinical trials.

### *Overview of cost-effectiveness analysis*

The cost-effectiveness analysis (CEA) assessed whether the intervention costs of EGDT were offset by any subsequent reduction in morbidity costs, for example from reduced use of the intensive care unit (ICU), and whether there were sufficient improvements in either mortality or health-related quality of life (QOL). We used trial-specific resource use and unit costs to report costs from a hospital perspective. We combined QOL scores collected at 90 days in the ProMISe trial with information on vital status for each patient, to report trial-wide measures of quality-adjusted life-years (QALYs) up to 90 days post-randomization. We reported the incremental QALYs of EGDT versus usual care as the difference in the overall mean 90-day QALYs between the randomization groups. We valued each QALY using recommended threshold of willingness to pay for a QALY gain (US$ 100,000), and for each trial subtracted the incremental costs of EDGT versus usual care, to report the incremental net monetary benefits (INB) of EGDT versus usual care. For each trial, we report the INB overall and for the same pre-specified subgroups explored in the evaluation of clinical effectiveness. For each trial we also calculated the probability that EGDT is cost-effective at alternative thresholds of willingness to pay for a QALY gain (0$ to $500,000), and reported cost-effectiveness acceptability curves (CEACs). We subjected the main assumptions of the CEA to sensitivity analyses (see: *Sensitivity analysis*).

### *Resource use measurement*

We measured resource use from randomization until 90 days post-randomization or death. We harmonized resource use measurement across the settings for the key resource use items including the intervention period, staff time and length of the initial hospitalization. The resource use items included were those items where differences between EGDT and usual care were anticipated to drive incremental costs. We excluded items that were already included in the hospital cost per bed-day, to avoid double counting. The categories of resource use measures included in the cost analysis are as follows:

*Equipment, consumables and use of blood products*

We recorded the type(s) of vascular catheter (PreSep$^{TM}$ central venous oximetry catheter, standard central venous catheter [CVC] and/or arterial catheter) used for each patient. For ARISE patients, CVC lines were inserted under ultrasound guidance, and so we included the accompanying costs of ultrasound imaging. Other consumables used in measuring intravascular pressures and with each type of vascular line insertion (e.g. saline infusion, cleaning packs, sterile gloves) were not anticipated to drive incremental costs and were not considered as separate items in the cost analysis. The harmonized data set included information on the total volume of blood products rather than each specific item (packed red blood cells [PRBC], platelets and frozen fresh plasma [FFP]).

*Staff time for delivering EGDT protocol*

The EGDT protocol required additional staff time for: CVC insertion (physicians' time); monitor set-up (nurses' time); monitoring patients in ED (nurses' time); and staff training (nurses' and physicians' time). The level of additional staff time for EGDT in the base case was estimated from each trial setting using expert opinion and

tested in sensitivity analyses. We 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 the EGDT protocol, when delivered in the ED, required an additional 10 minutes of nurses' monitoring time per hour (see Table S8).

To provide EGDT in the ED as part of routine practice required additional formal or informal training beyond the existing hospital education program. The base case analysis assumed that staff training is required for the cohort of ED staff once in every five years. We assumed the life cycle of ED staff in each setting to be five years. The level of staffing considered was as follows – ProCESS: 12 attending consultants, 30 junior doctors and 48 nurses[1]; ARISE: 8 consultants, 12 registrars, 19 junior medical staff and 65 nurses[2]; ProMISe: 7 attending consultants, 23 junior doctors and 75 nurses.[3]

*Use of hospital bed resources*

We calculated the duration and location of the acute hospital stay following randomization for up to 90 days for each individual patient in each trial. The total duration of the hospital stay included the duration of EGDT protocol delivery, the time spent in the ED, the days spent in ICU and days on the general floor/ ward.

- *Time for protocol delivery:* for each trial, the duration of protocol delivery in the ED and ICU from randomization for up to 7 hours was calculated from the location (ED, ICU, floor/ ward) at each exact hour since randomization.[a]
- *Time in ED:* the number of whole hours in the ED from randomization.[b]
- *Duration of stay in ICU (up to 90 days):* the number of whole days from ED discharge until the time of eventual discharge from ICU or death.
- *Duration of stay on floor/ ward (up to 90 days):* the number of whole days from ED or ICU discharge until the time of eventual discharge or death.
- *Duration of stay adjustment for ProCESS cases:* the ProCESS trial recorded duration of stay for up to 60 days post-randomization, unlike the other two trials which recorded duration of stay until hospital discharge. For patients in the ProCESS trial that were still in the hospital at 60 days, additional days in hospital were mean imputed using data from patients from the other two trials whose hospital stay was greater than 60 days. An additional concern in the ProCESS trial was discharge to long-term acute care hospitals (LTACHs). For these patients, we assumed that the mean stay in LTACH (up to 90 days post-randomization) was 30 days, which was the average for severe sepsis patients in the US discharged to LTACH in a previous study. [c]

### *Unit costs*

We accessed unit costs of resource use items from manufacturers' list and procurement prices, national unit cost databases, participating sites and published sources, as listed in Table S9. For ARISE, unit costs were taken

[a] This harmonized measure of protocol duration differed somewhat from the measure reported previously for the ARISE and ProMISe trials, where the duration of protocol delivery was calculated from exact protocol start and stop times.
[b] This approach differs to the original ARISE and ProMISe trial publications, where the time in the ED was calculated according to the number of hours from the date and time of randomization to the time of transfer from the ED or death.
[c] From personal communication with Jack Iwashyna and Hallie Prescott (Dec 12, 2017).

from national unit costs for Australia, which is the country which provided the majority of patients recruited to the study. We report all unit costs in 2012-13 prices (US dollars, $ PPP).[d]

*Equipment and consumables*

We assigned the fixed unit costs of the oxymetric monitor for eligible patients, assuming a five-year life cycle of the monitor. We calculated the expected number of eligible patients per year in each setting from each trial's screening log or observational study at the trial participating sites. Specifically, there were 12, 35 and 23 eligible patients per site per year in ProCESS, ARISE and ProMISe, respectively. The unit costs of the monitor, obtained via personal communication with manufacturer (Edwards Lifesciences), were $13,310 (ARISE) and $5,640 (ProMISe); we assumed unit costs of the monitor for ProCESS were the same as for ProMISe. In calculating the unit cost per patient, we assumed that to provide EGDT in routine practice each site would require two monitors, which would have an average lifespan of 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.

We took a similar approach to calculating the unit costs of ultrasound imaging for CVC placement at ARISE sites. We assumed that each site in ARISE would require four ultrasound machines, each costing $50,000.

*Blood products*

We took unit costs for blood components (PRBC, platelets, FFP) from national/local sources for each trial setting and calculated a weighted average unit cost for the overall use of blood product. We estimated these weights from the relative volume of each component of blood products delivered during the intervention period in each trial setting.

*Staff time*

We calculated the total additional training cost per site by valuing the time of the average mix of ED staff who required training to deliver the EGDT protocol. The unit costs of ED staff included the salaries and accompanying on-costs according to the midpoint of each relevant level of staff, which were: ED physician, resident/junior doctors and ED nurse for ProCESS; consultant/specialist (year 6), registrar (year 4) and registered nurse (level 2 year 6) for ARISE; and consultant, registrar and registered nurse (grade 6) for ProMISe. 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 five years, the assumed life cycle of the EGDT protocol.

*Hospital beds*

We took unit costs of ED hour and bed day in ICU and on the general floor/ ward from national database and published sources. We derived ED unit costs in each setting from published estimates on similar patient groups and inflated to 2012-13 price levels. We used average unit costs of an ICU bed day for ProCESS and ARISE. For

[d] Unit costs in GBP (ProMISe) and AUD (ARISE) were converted to USD using 2012 World Bank purchasing power parity (PPP) at exchange rates of £1 GBP=$1.41 USD and $1 AUD=$0.66 USD (http://data.worldbank.org/indicator/PA.NUS.PPP).

ProMISe, we calculated unit costs of an ICU bed day as a weighted average of ICU bed day costs across health resource groups.

The unit costs applied in each trial setting are reported in Table S9. It should be recognized that the approach taken to the unit costing was consistent with the overall study objective; that is, while we attempted to harmonize the key resource use items, we acknowledged that there would be differences in unit costs between the trial settings. Rather than attempt to adopt a unified costing methodology, we allowed for these local variations in unit costs, and rather than reporting trial wide incremental costs, we report incremental costs in each trial setting. This approach enables the incremental costs of EGDT versus usual care to be specific to the setting of policy-relevance.

### *Mortality and health-related quality of life*

We used data on the number of days from randomization to death to calculate the survival time up to 90 days for each randomized patient. ProMISe collected health-related QOL at 90 days post-randomization for all patients. ARISE collected QOL at 180 days and 365 days post-randomization for all patients. ProCESS collected QOL at 90 days post-randomization for only a small sub-sample of survivors. This current study required 90-day QOL data for all patients, we therefore applied QOL data from ProMISe to 90-day survivors in all three trials (see: *Cost-effectiveness analysis*). In sensitivity analysis, we tested the robustness of these findings by applying the available trial-specific QOL values (see: *Sensitivity analysis*).

ProCESS, ARISE and ProMISe all measured QOL using a generic measure, the EuroQol questionnaire (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. ProCESS and ProMISe used the 5-level (EQ-5D-5L) measure ('no problems', 'slight problems', 'moderate problems', 'severe problems' or 'extreme problems') and ARISE used the 3-level (EQ-5D-3L) measure. We mapped responses onto health state preferences (utilities) from the general population to calculate EQ-5D utility scores, anchored on a scale from 0 (death) to 1 (perfect health). The QOL Index score was calculated applying general population QOL weights for England.[4] For patients with missing health-related QOL data, we imputed values using Multiple Imputation with Chained Equations (MICE).[5] Under this approach, each variable is imputed conditional on fully observed baseline variables such as age, sex, presence of any APACHE II severe coexisting condition, site of infection, SOFA score, admitted from nursing home and length of stay in ICU and in hospital up to 90 days. Patients who did not return or fully complete the EQ-5D questionnaire administered at 90 days had their EQ-5D scores imputed using data from those survivors who did fully complete the questionnaire. Table S10 reports all the variables considered for multiple imputation, and for each variable, the number of missing values and the imputation model chosen.

We calculated QALYs at 90 days post-randomization by valuing each patient's survival time by their health-related QOL at 90 days according to the 'area under the curve' approach.[6] For 90-day survivors, we calculated QALYs using the EQ-5D scores at 90 days, assuming an EQ-5D score of zero at randomization and a linear interpolation between randomization and 90 days. For decedents between randomization and 90 days, we assumed zero QALYs.

### *Cost-effectiveness analysis*

The CEA followed the intention-to-treat principle and reported incremental costs, QOL scores, QALYs and cost-effectiveness up to 90 days, according to randomized group. Incremental costs and QALYs were estimated with a seemingly unrelated regression model.[7] We estimated incremental costs for each trial, by combining trial-specific resource use data with local unit costs. We estimated incremental QALYs at the aggregate level by pooling QALY estimates across trials. This approach drew on the additional power from pooled versus trial-specific mortality and QOL data and assumed that these outcomes were exchangeable across the trial settings. We calculated trial-specific measures of cost-effectiveness by combining trial-wide estimates of incremental QALYs with trial-specific incremental costs.

We reported unadjusted mean differences between the randomized groups in 90-day costs, QOL scores and QALYs together with 95% confidence intervals. We used the differences in average costs and QALYs between the randomized groups to calculate the INB of EGDT versus usual care. We valued each QALY with the threshold of willingness to pay for a QALY gain of US$ 100,000 in the base case,[8] and subtracted the incremental costs to report the INB of EGDT versus usual care, overall and for the same pre-specified subgroups as for the evaluation of clinical effectiveness. For the subgroup analyses, we repeated the base case analysis but including main effects and interaction terms for randomized group by the covariates defining each relevant subgroup.

We report the parameter uncertainty around the cost-effectiveness results by using 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 plot these incremental costs and QALYs on the cost-effectiveness plane. We also reported CEACs by calculating the probability that, compared to usual care, EGDT is cost-effective given the data, at alternative levels of willingness to pay for a QALY gain.

*Base case assumptions and subsequent sensitivity analyses*

We checked the robustness of results to assumptions made in the base case scenario in sensitivity analyses, summarized in Table S11.

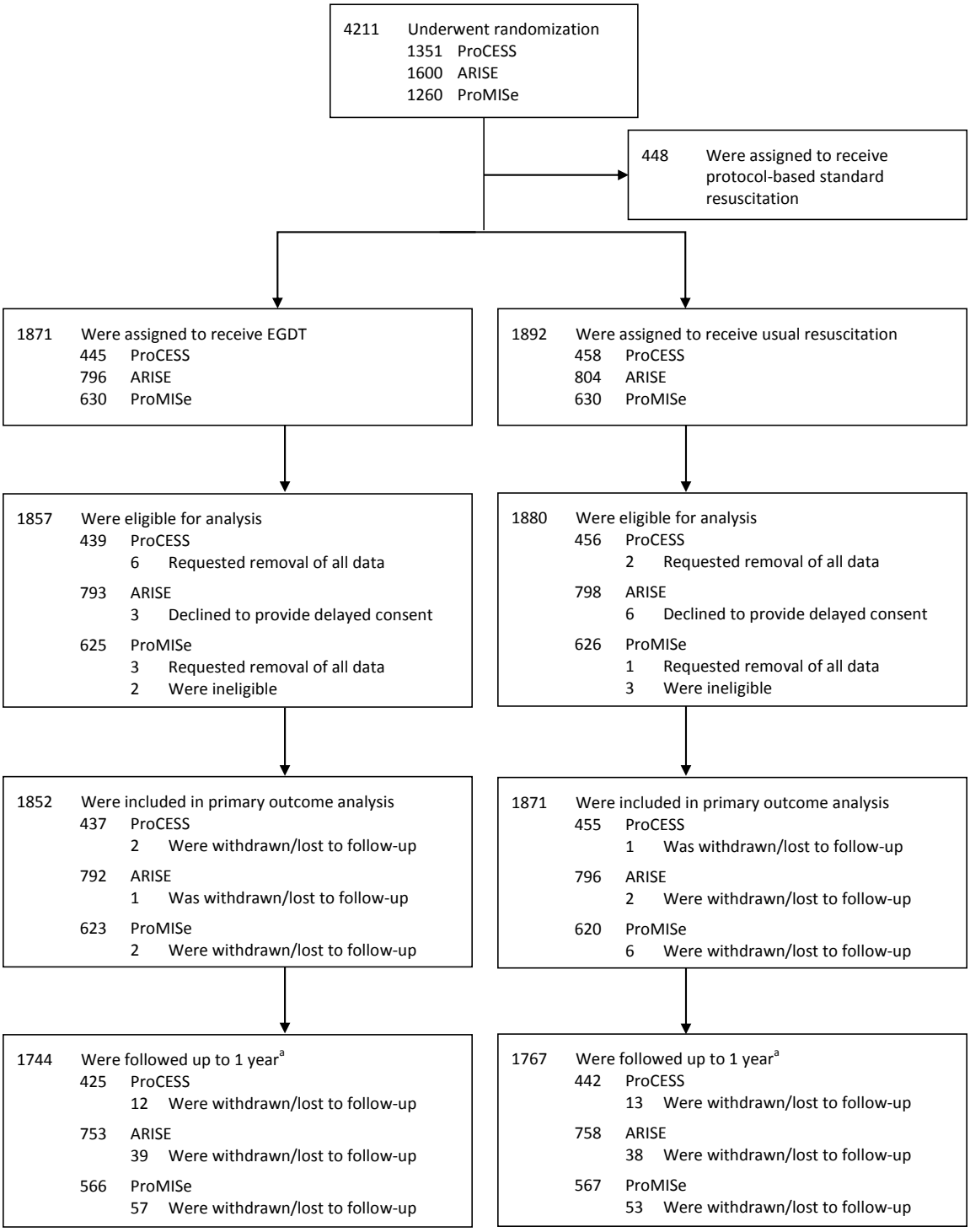
- *Staff time for line insertion and monitor set-up*: In the base case, we applied trial-specific staff time for line insertion and monitor set-up. In the sensitivity analysis, we allowed the duration of staff time to take alternative values according to expert, clinical opinion. For this sensitivity analysis, we defined the maximum (minimum) staff time as 20 (15) minutes physicians' time for arterial line insertion and for nurses' time as 50 (45) minutes for PreSep$^{TM}$ catheter, 30 (25) minutes for standard CVC and 25 (20) minutes for arterial line insertion.
- *Staff monitoring time during delivery of the EGDT resuscitation protocol*: The intervention requires intensive monitoring of patients for the duration of the delivery of the EGDT protocol (up to six hours). In the base case, we assumed that this monitoring would require an additional 10 minutes of nurses' time per hour. In the sensitivity analysis, we varied the additional nurses' time from 5-15 minutes per hour over the period that the protocol was delivered for.

- *Staff training time for delivery of the EGDT resuscitation protocol*: The base case assumed that when EGDT is provided in the ED, each member of staff would require 20 minutes of additional training. In the sensitivity analysis, training time was varied between 15 and 30 minutes.
- *Delivery of the EGDT resuscitation protocol exclusively in the ED versus ICU*: The base case analysis recognized the time that each patient in the EGDT arm received the protocol in the ED and/or in the ICU, according to the duration of time in each location recorded in the Case Report Forms for each patient in each trial. In practice, EGDT may be exclusively delivered in either the ED or the ICU. The sensitivity analysis allowed the costs of monitoring and training to reflect either extreme, i.e. EGDT delivered solely in the ED or EGDT delivered solely in the ICU.
- *Imputation of missing QOL scores*: The base case analysis imputed missing QOL scores across all three trials using the QOL values reported in the ProMISe trial, which were collected at 90 days using the EQ-5D-5L instrument. In the sensitivity analysis, the missing QOL data were imputed using trial-specific QOL data, which for ProCESS were EQ-5D-5L data from a subsample of randomized patients at 90-day follow-up and for ARISE were EQ-5D-3L data measured at six-month follow-up.
- *Baseline covariates*: The base case reported incremental costs and QALYs without any covariate adjustment, assuming randomization had ensured no imbalances in key prognostic factors such as age, sex, presence of any APACHE II severe coexisting condition, nursing home resident, eligibility criteria, APACHE II Acute Physiology Score and site of infection. In the sensitivity analysis, we adjusted for any chance imbalances in these baseline covariates.
- *Distributional assumptions for costs and QALY*: The base case analysis 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 models assuming a gamma distribution for each endpoint (i.e. ignoring possible correlation between the endpoints).

We report the results of the sensitivity analysis as mean INBs with corresponding 95% confidence intervals.

# Supplementary Figures

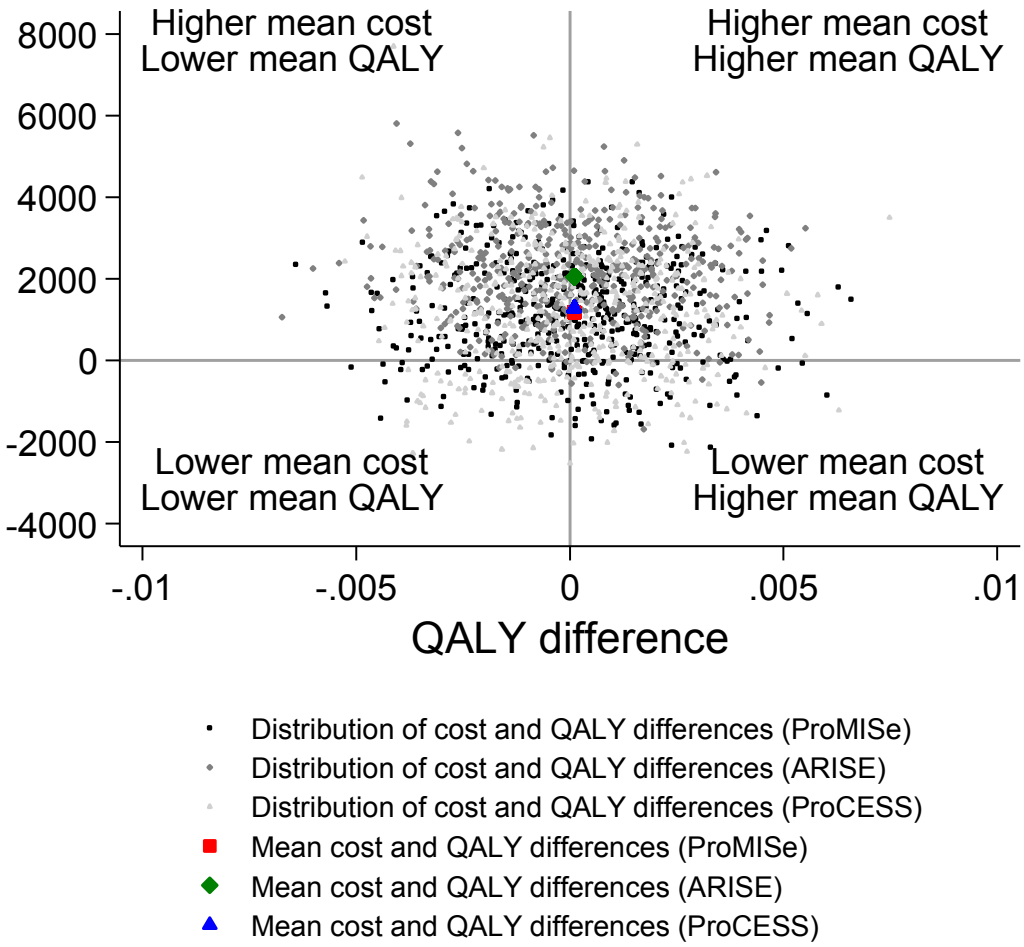
## Figure S1 Enrollment and follow-up




ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; EGDT – early, goal-directed therapy.

[a] Established to be alive in the 12th month (≥ 335 days)

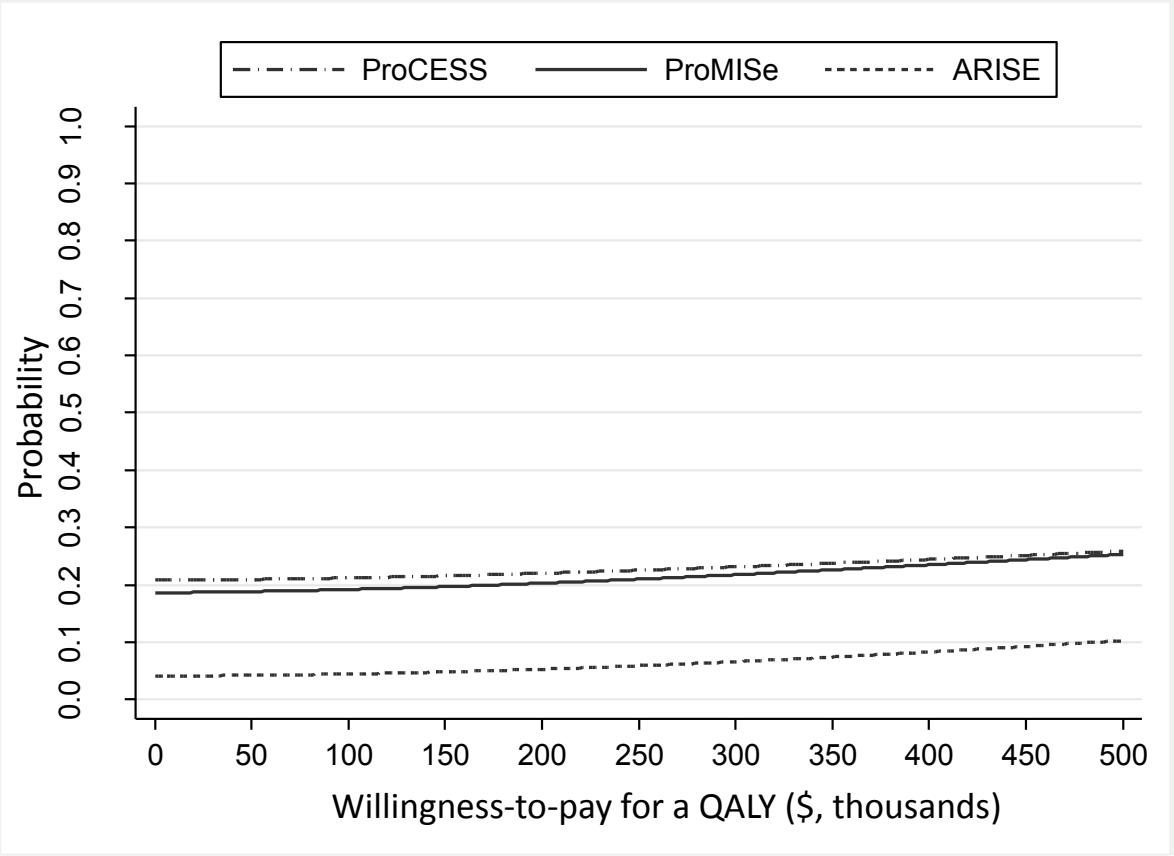
**Figure S2** **Mean costs (US $) and QALY differences and their distribution for EGDT versus usual care**




These results are for the time horizon of 90 days post-randomization

QALY – quality-adjusted life-year; EGDT – early, goal-directed therapy; ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis.

**Figure S3 Cost-effectiveness acceptability curves**



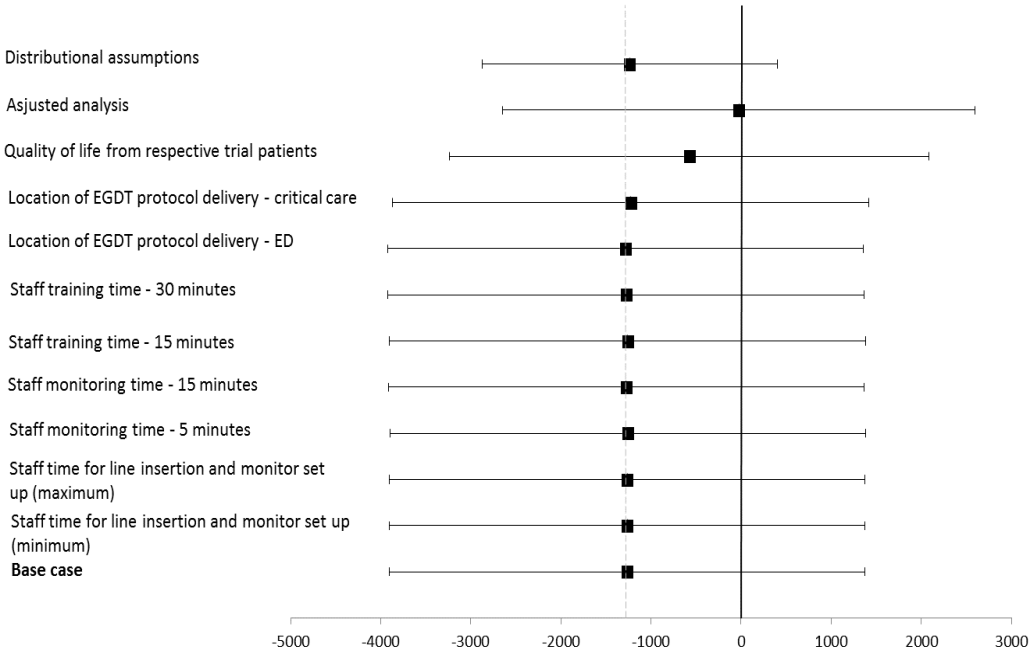

These results are for the time horizon of 90 days post-randomization. Curves report the probability that EGDT is cost-effective according to alternative thresholds of willingness to pay per QALY gain

EGDT – early, goal-directed therapy; QALY – quality-adjusted life-year; ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis.

The probability (y-axis) that EGDT would be deemed to have an acceptable cost-effectiveness ratio, defined as falling at or below the societal willingness-to-pay threshold (x-axis), as determined from each of the three trials

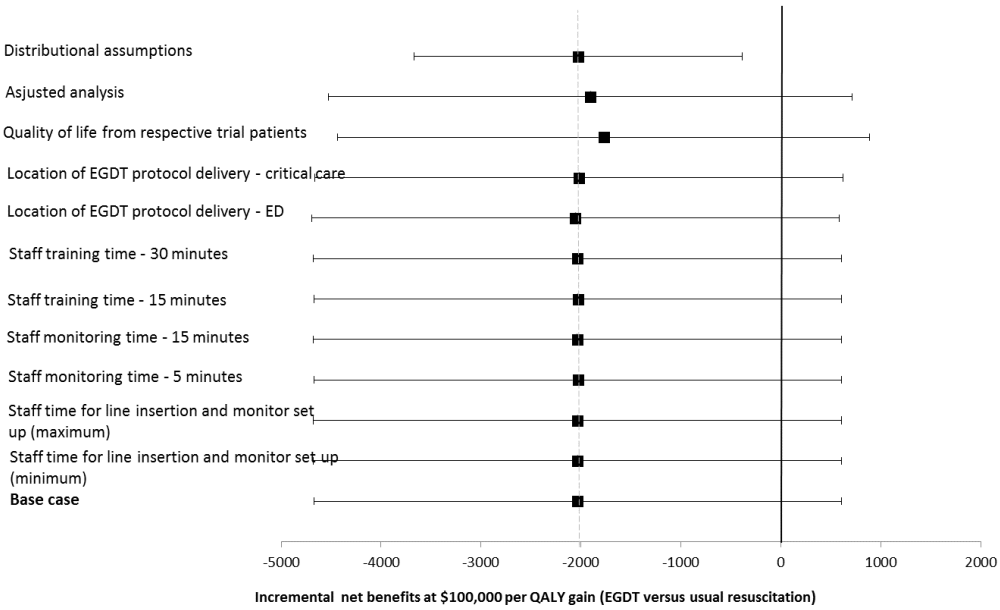
## Figure S4 Sensitivity analysis of incremental net benefit

### (S4a) ProCESS



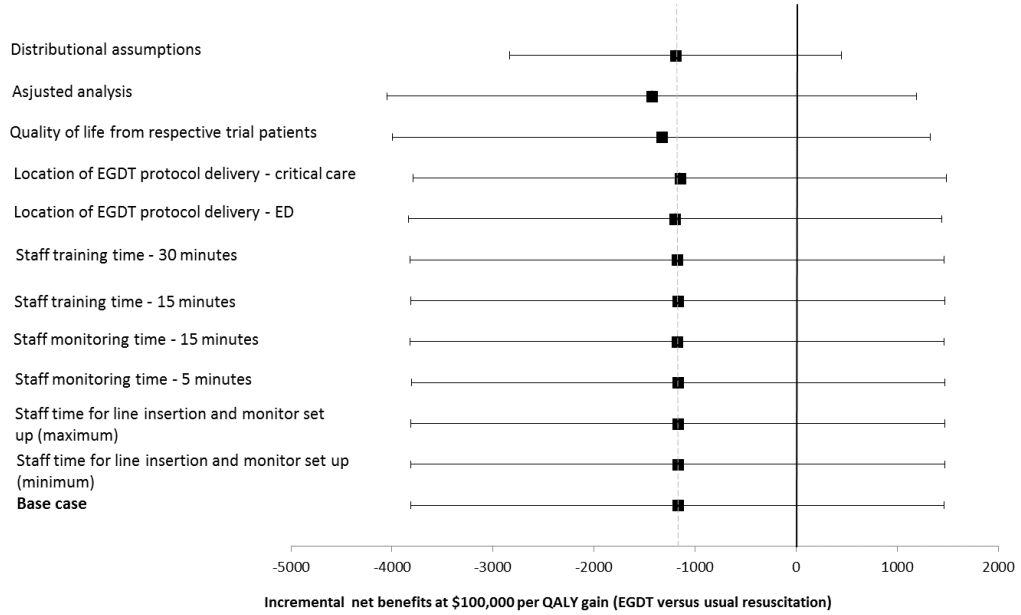

Vertical dashed line indicates incremental net benefits in the base case analysis. Solid vertical line indicates no difference in net monetary benefits between comparator groups.

### (S4b) ARISE




Vertical dashed line indicates incremental net benefits in the base case analysis. Solid vertical line indicates no difference in net monetary benefits between comparator groups.

## (S4c) ProMISe




Vertical dashed line indicates incremental net benefits in the base case analysis. Solid vertical line indicates no difference in net monetary benefits between comparator groups.

These results are for the time horizon of 90 days post-randomization. The mean (95% CI) incremental net benefit (at $100,000 per QALY) according to alternative assumptions compared to the base case

ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; EGDT – early, goal-directed therapy; ED – emergency department; CI – confidence interval; QALY – quality-adjusted life-year.

## Supplementary Tables

### Table S1 Data harmonization

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| **Identifier** | | | | | |
| Trial | Trial identifier | Category | 1 | C – ProCESS, A – ARISE, M – ProMISe | |
| Site | Site identifier | Category | 2 | XX | • Numbered from 01 to NN |
| Patient | Patient unique identifier | Category | 4 | XXXX | • Numbered in order of randomization |
| **Group** | | | | | |
| Randomly allocated group | EGDT or usual care | Category | 1 | E – EGDT, U – usual care | |
| **Patient** | | | | | |
| Age | Age of patient | Number (years) | 2 | NN | • Actual or estimated<br>• Maximum value is 90 – patients aged >90 are recorded as 90 to reduce identifiability of the data |
| Age extra | Additional information about age variable | Category | 1 | O – over 89, K – unknown | • Either unknown age if no age provided or estimated age when age provided |
| Sex | Sex of patient | Category | 1 | M – male, F – female | |
| Weight | Weight of patient | Number (kg) | 3 | NNN | • Actual or estimated |
| Weight extra | Additional information about bodyweight variable | Category | 1 | K – unknown | • Either unknown bodyweight if no bodyweight provided or estimated bodyweight when bodyweight provided |
| Nursing home residence prior to admission | Admitted from nursing home | Boolean | 1 | 1 – yes, 0 – no | • Variation in nursing home definition:<br>○ ProCESS – personal care homes, skilled or unskilled assisted living or extended care facilities<br>○ ARISE – high or low level care facility or assisted living facility<br>○ ProMISe – nursing home |
| Severe coexisting | Severe liver condition in | Boolean | 1 | 1 – yes, 0 – no | • APACHE II defined |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| condition – liver | past medical history | | | | • Mapped from Charlson for ProCESS and ARISE |
| Severe coexisting condition – respiratory | Severe respiratory condition in past medical history | Boolean | 1 | 1 – yes, 0 – no | • APACHE II defined<br>• Mapped from Charlson for ProCESS and ARISE |
| Severe coexisting condition – cardiovascular | Severe cardiovascular condition in past medical history | Boolean | 1 | 1 – yes, 0 – no | • APACHE II defined<br>• Mapped from Charlson for ProCESS and ARISE |
| Severe coexisting condition – renal | Severe renal condition in past medical history | Boolean | 1 | 1 – yes, 0 – no | • APACHE II defined<br>• Mapped from Charlson for ProCESS and ARISE |
| Severe coexisting condition – immunocompromised state | Severe immunocompromised condition in past medical history | Boolean | 1 | 1 – yes, 0 – no | • APACHE II defined<br>• Mapped from Charlson for ProCESS and ARISE |
| **Eligibility** | | | | | |
| Time from ED presentation to inclusion criteria met | Duration from ED presentation to meeting inclusion criteria | Number (minutes) | 3 | NNN | • Variation in eligibility timing definition:<br>o ProCESS – maximum time to meet eligibility was 12 hours<br>o ARISE / ProMISe – maximum time to meet eligibility was 6 hours<br>• Variation in meeting eligibility definition:<br>o ProCESS – time to specific refractory hypotension or hyperlactatemia criterion being met<br>o ARISE / ProMISe – time to final physiological criterion being met |
| Refractory hypotension | Met refractory hypotension criterion | Boolean | 1 | 1 – yes, 0 – no | • Variation in refractory hypotension definition:<br>o ProCESS – SBP <90 mm Hg (including patients requiring vasopressor therapy to |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| | | | | | maintain SBP at 90 mm Hg) after 1L fluid challenge (initially minimum 20 ml $kg^{-1}$ crystalloid bolus) within 30 minutes<br>○ ARISE / ProMISe – SBP <90 or MAP <65 mm Hg after 1L fluid challenge within 60 minutes |
| Eligibility SBP | Actual value for meeting refractory hypotension criterion | Number (mm Hg) | 2 | NN | • Only for those who met criterion |
| Eligibility MAP | Actual value for meeting refractory hypotension criterion | Number (mm Hg) | 2 | NN | • Only for those who met criterion<br>• Only SBP was collected in ProCESS |
| Hyperlactatemia | Met hyperlactatemia criterion | Boolean | 1 | 1 – yes, 0 – no | • Blood lactate concentration ≥4 mmol $l^{-1}$ |
| Eligibility serum lactate level | Actual value for meeting hyperlactatemia criterion | Number (mmol $l^{-1}$) | 4 | NN.N | • Only for those who met criterion |
| Reported as would have been admitted direct to ICU from ED if not enrolled into trial | Would have been admitted direct to ICU from ED if not in trial | Boolean | 1 | 1 – yes, 0 – no | • Assessed at eligibility/ randomization<br>• Not collected in ProCESS |
| **Before hospital presentation until randomization** | | | | | |
| IV fluids administered before hospital presentation until randomization | Receipt of IV fluids administered pre-hospital presentation to randomization | Boolean | 1 | 1 – yes, 0 – no | • IV crystalloid, colloid and blood products<br>• Blood products were not collected pre-hospital for ARISE |
| Volume administered | Volume of IV fluids administered pre-hospital to randomization | Number (ml) | 4 | NNNN | • 0 if no fluids received |
| **ED presentation to randomization** | | | | | |
| Time from ED presentation to | Duration from ED presentation to | Number (minutes) | 3 | NNN | |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| randomization | randomization | | | | |
| **Last value before randomization** | | | | | |
| SBP | Last value prior to randomization | Number (mm Hg) | 3 | NNN | • Only first SBP measurement upon presentation to ED was collected in ProCESS |
| MAP | Last value prior to randomization | Number (mm Hg) | 3 | NNN | • Recorded MAP may be measured or calculated<br>• Only first SBP/associated DBP measurement upon presentation to ED was collected in ProCESS |
| Serum lactate level | Last value prior to randomization | Number (mmol $l^{-1}$) | 4 | NN.N | |
| APACHE II Acute Physiology Score | Acute Physiology Score (APACHE II) | Number | 2 | NN | • Uses last values prior to randomization<br>• Recorded MAP may be measured or calculated<br>• Only first temperature, SBP/associated DBP, heart rate and respiratory rate measurement upon presentation to ED were collected in ProCESS |
| APACHE II score | APACHE II score | Number | 2 | NN | |
| SOFA score | SOFA score | Number | 2 | NN | • Uses last values prior to randomization<br>• Only first SBP/associated DBP measurement upon presentation to ED were collected in ProCESS<br>• Urine output was not used in the calculation of the SOFA renal score for ARISE and ProMISe |
| **At randomization** | | | | | |
| Day of week randomized | Day of week randomized | Category | 1 | 1 – Monday, 2 – Tuesday, 3 – Wednesday, 4 – Thursday, 5 – Friday, 6 – Saturday, 7 – Sunday | |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| Time of day randomized | Hour of day randomized | Number (hr) | 2 | NN | • 24-hour clock (e.g. 14:52 is 14:00) |
| On invasive mechanical ventilation at randomization | Patient receiving invasive mechanical ventilation at randomization | Boolean | 1 | 1 – yes, 0 – no | • Variation in invasive mechanical ventilation definition:<br>○ ProCESS – delivered via endotracheal tube, tracheostomy, laryngeal mask airway or Combitube<br>○ ARISE / ProMISe – positive pressure ventilation via endotracheal tube, nasotracheal tube or tracheostomy |
| On vasopressor infusion at randomization | Patient receiving/on vasopressors at randomization | Boolean | 1 | 1 – yes, 0 – no | • Variation in vasopressor infusion definition:<br>○ ProCESS / ProMISe – between ED presentation and randomization<br>○ ARISE – continuous infusion for ≥30 minutes within 1 hour of randomization (including if started <30 minutes prior to randomization but continued for total of ≥30 minutes) |
| Receiving antimicrobial agents at randomization | Patient receiving/on IV antimicrobial agents at randomization | Boolean | 1 | 1 – yes, 0 – no | • Antimicrobial agents mandated prior to randomization in ARISE and ProMISe, but not in ProCESS |
| **ED presentation to beyond randomization** | | | | | |
| Time from ED presentation to first IV antimicrobial agents | Duration from ED presentation to first IV antimicrobial agents | Number (minutes) | 4 | NNNN | • Time not collected in ProMISe |
| Site of infection | Site of known or presumed infection | Category | 1 | L – lungs, A – abdomen, C – central nervous system, B – blood, S – soft tissue, U – urinary tract, O – other site(s), K – unknown site, N – determined ultimately to have no | • Mapped into common categories |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| | | | | infection | |
| **Lines** | | | | | |
| CVC with continuous $ScvO_2$ monitoring capability | Placement of a CVC with continuous $ScvO_2$ monitoring capability | Boolean | 1 | 1 – yes, 0 – no | • Up to 6 hours post-randomization |
| CVC without continuous $ScvO_2$ monitoring capability | Placement of a CVC without continuous $ScvO_2$ monitoring capability | Boolean | 1 | 1 – yes, 0 – no | • Up to 6 hours post-randomization |
| Arterial line | Placement of an arterial line | Boolean | 1 | 1 – yes, 0 – no | • Up to 6 hours post-randomization |
| **After randomization** | | | | | |
| Volume of IV fluids administered from randomization to T6 (or death) | Volume of IV fluids administered from randomization to T6 hours (or death) | Number (ml) | 5 | NNNNN | • IV crystalloid, colloid and albumin<br>• 0 if no fluids received |
| Volume of blood products administered from randomization to T6 (or death) | Volume of blood products administered from randomization to T6 (or death) | Number (ml) | 4 | NNNN | • Packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate<br>• 0 if no blood products received |
| Vasopressor(s) from randomization to T6 hours (or death) | Patient receiving vasopressors from randomization to T6 hours (or death) | Boolean | 1 | 1 – yes, 0 – no | • Variation in recorded receipt of vasopressors:<br>○ ProCESS / ARISE – received on the hour<br>○ ProMISe – given during the hour |
| Volume of IV fluids administered from randomization to T72 hours (or death) | Volume of IV fluids administered from randomization to T72 hours (or death) | Number (ml) | 5 | NNNNN | • IV crystalloid, colloid and albumin<br>• 0 if no fluids received |
| Volume of blood products administered from randomization to T72 (or death) | Volume of blood products administered from randomization to T72 (or death) | Number (ml) | 4 | NNNN | • Packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate<br>• 0 if no blood products received |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| **Outcomes – duration of stay** | | | | | |
| In ED | Duration of stay in ED from randomization | Category | 2 | 0 – <1 hour, 1 – 1 to <2 hours, 2 – 2 to <3 hours, 3 – 3 to <4 hours, 4 – 4 to <5 hours, 5 – 5 to <6 hours, 6 – 6 to <12 hours, 12 – 12 to <24 hours, 24 – 24 to <48 hours, 48 – 48 to <72 hours, 72 – ≥72 hours | • Location recorded at whole hours up to Hour 6, then at Hour 12, 24, 48 and 72 in ProCESS<br>• 0 if randomized post-ED |
| In ICU – first stay | Duration of first stay in ICU | Number (days) | 4 | NNNN | • Calculated from dates<br>• 0 if not admitted to ICU<br>• 1 if admitted and death or discharge on same day |
| In ICU – total stay | Total duration of stay in ICU (including readmissions) | Number (days) | 4 | NNNN | • Calculated from dates<br>• Includes if readmitted during same hospital stay<br>• 0 if not admitted to ICU<br>• 1 if admitted and death or discharge on same day |
| In hospital | Duration of stay in hospital from randomization | Number (days) | 5 | NNNNN | • Calculated from dates<br>• Acute hospital = hospital randomized in<br>• Censored at 60 days post-randomization in ProCESS<br>• 1 if randomized and death or discharge on same day |
| **Outcomes – mortality** | | | | | |
| Trial day died | Trial day died from randomization to date of death | Number | 3 | NNN | • 0 = day of randomization<br>• Up to 365 days<br>• Blank if survived to 365 days (even if died after 365 days) |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| Location of death | Location of death | Category | 1 | E – ED, I – ICU, H – hospital (not ED or ICU), A – after discharge | • Hospital = hospital randomized in<br>• Up to 365 days |
| Hospital mortality | Hospital mortality | Boolean | 1 | 1 – dead, 0 – alive | • Hospital = hospital randomized in |
| Lost to follow-up at one-year | Lost to follow-up at one-year | Boolean | 1 | 1 – yes, 0 – no | |
| Trial day last known alive | If lost to follow-up at one-year, then trial day last known alive from randomization | Number | 3 | NNN | • 0 = day of randomization<br>• Up to 365 days |
| **Outcomes – organ support in ICU** | | | | | |
| Respiratory support – receipt | Received invasive mechanical ventilation in ICU | Boolean | 1 | 1 – yes, 0 – no | • Variation in invasive mechanical ventilation definition:<br>○ ProCESS – delivered via endotracheal tube, tracheostomy, laryngeal mask airway or Combitube<br>○ ARISE / ProMISe – positive pressure ventilation via endotracheal tube, nasotracheal tube or tracheostomy |
| Respiratory support – duration | Days received invasive mechanical ventilation in ICU | Number (days) | 2 | NN | • Number of calendar days (00:00-23:59) on which respiratory support in ICU was given at any time<br>• Days were counted if patients were free from respiratory support for, or died within, <48 hours after last recorded use in ProCESS<br>• Days were counted if patients were free from respiratory support for <24 hours after last recorded use in ARISE<br>• 1 if admitted and discharged on same day and received respiratory support |
| Cardiovascular support – | Received vasopressors | Boolean | 1 | 1 – yes, 0 – no | • Variation in cardiovascular support |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| receipt | and/or inotropes in ICU | | | | definition:<br>○ ProCESS / ARISE – need for vasopressors<br>○ ProMISe – indicated by one or more of: receipt of multiple IV 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 |
| Cardiovascular support – duration | Days received vasopressors and/or inotropes in ICU | Number (days) | 2 | NN | • Number of calendar days (00:00-23:59) on which cardiovascular support in ICU was given at any time<br>• Days were counted if patients were free from cardiovascular support for <24 hours after last recorded use in ARISE<br>• 1 if admitted and discharged on same day and received cardiovascular support |
| Renal support – receipt | Received renal replacement therapy/dialysis in ICU | Boolean | 1 | 1 – yes, 0 – no | |
| Renal support – duration | Days received renal replacement therapy/dialysis in ICU | Number (days) | 2 | NN | • Number of calendar days (00:00-23:59) on which renal support in ICU was given at any time<br>• Days were counted if patients were free from renal support for <72 hours after last recorded use in ProCESS (manual adjustments made if patient either died or |

| Variable | Description | Data type (units) | Data length | Data format | Notes |
|---|---|---|---|---|---|
| | | | | | discharged within 72 hours of last recorded use)<br>• Days were counted if patients were free from renal support for <7 days after last recorded use in ARISE<br>• 1 if admitted and discharged on same day and received renal support |
| **EGDT group only** | | | | | |
| EGDT protocol delivery location | Location of delivery of six-hour EGDT protocol | Category | 2 | ED – ED, IC – ICU, WA – ward, EI – ED and ICU, EW – ED and ward, IW – ICU and ward, AL – ED, ICU and ward | • Operating room/theatre not included |
| Hours of EGDT protocol delivered in ED | Hours of six-hour EGDT protocol delivered in ED from date/time of randomization | Number (whole hr) | 1 | N | • Location recorded at each hourly time point<br>• If in operating room/theatre at any hour, added to subsequent location<br>• 0 if randomized post-ED or left ED before Hour 1 |
| Hours of EGDT protocol delivered in ICU | Hours of six-hour EGDT protocol delivered in ICU from date/time of randomization | Number (whole hr) | 1 | N | • Location recorded at each hourly time point<br>• If in operating room/theatre at any hour, added to subsequent location |
| Hours of EGDT protocol delivered in ward | Hours of six-hour EGDT protocol delivered in ward from date/time of randomization | Number (whole hr) | 1 | N | • Location recorded at each hourly time point<br>• If in operating room/theatre at any hour, added to subsequent location |

ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; EGDT – early, goal-directed therapy; kg – kilogram; APACHE II – Acute Physiology and Chronic Health Evaluation II; ED – emergency department; SBP – systolic blood pressure; MAP – mean arterial pressure; mm Hg – millimeter of mercury; mmol – millimole; l – liter; ICU – intensive care unit; IV – intravenous; ml – milliliter; DBP – diastolic blood pressure; SOFA – Sequential Organ Failure Assessment; hr – hour; CVC – central venous catheter.

**Table S2 Patient and care-delivery characteristics at baseline[a]**

| Characteristic | EGDT (N = 1857) | Usual resuscitation (N = 1880) |
|---|---|---|
| **Patient characteristics** | | |
| Age[b] (yr) – median (IQR) | 65 (53-75) [1857] | 65 (53-76) [1879] |
| Male sex – no. (%) | 1065 (57.4) | 1104 (58.7) |
| Weight (actual or estimated in kg) – median (IQR) | 75 (65-90) [1734] | 76 (65-90) [1696] |
| Nursing home residence prior to admission – no. (%) | 126 (6.8) [1852] | 126 (6.7) [1879] |
| Severe coexisting conditions (APACHE II) – no. (%) | [1854] | [1880] |
| Liver | 59 (3.2) | 58 (3.1) |
| Respiratory | 191 (10.3) | 180 (9.6) |
| Cardiovascular | 49 (2.6) | 47 (2.5) |
| Renal | 62 (3.3) | 63 (3.4) |
| Immunocompromised state | 281 (15.2) | 264 (14.0) |
| One or more | 546 (29.4) | 526 (28.0) |
| Site of infection – no. (%) | | |
| Lungs | 657 (35.4) | 620 (33.0) |
| Abdomen | 172 (9.3) | 163 (8.7) |
| Blood | 172 (9.3) | 172 (9.1) |
| Central nervous system | 28 (1.5) | 19 (1.0) |
| Soft tissue | 154 (8.3) | 153 (8.1) |
| Urinary tract | 356 (19.2) | 371 (19.7) |
| Other | 113 (6.1) | 149 (7.9) |
| Unknown | 196 (10.6) | 218 (11.6) |
| Determined ultimately to have no infection | 9 (0.5) | 15 (0.8) |
| Entry criterion met[c] – no. (%) | | |
| Refractory hypotension only | 821 (44.3) | 833 (44.3) |
| Hyperlactatemia only | 717 (38.7) | 732 (38.9) |
| Both refractory hypotension and hyperlactatemia | 316 (17.0) | 315 (16.8) |
| Refractory hypotension (SBP <90 or MAP <65 mm Hg) – no. (%) | 1137 (61.2) | 1148 (61.1) |
| Eligibility SBP (mm Hg) – median (IQR) | 80 (73-85) [953] | 81 (74-85) [979] |
| Eligibility MAP (mm Hg) – median (IQR) | 58 (53-61) [325] | 58 (53-61) [331] |
| Hyperlactatemia (lactate ≥4 mmol $l^{-1}$) – no. (%) | 1033 (55.6) | 1047 (55.7) |
| Eligibility serum lactate level (mmol $l^{-1}$) – median (IQR) | 5.6 (4.6-7.6) [1033] | 5.6 (4.6-7.5) [1047] |
| Last values before randomization | | |
| SBP (mm Hg) – median (IQR) | 94 (83-112) [1809] | 94 (82-111) [1824] |
| MAP (mm Hg) – median (IQR) | 67 (59-78) [1318] | 67 (59-78) [1352] |
| Serum lactate (mmol $l^{-1}$) – median (IQR) | 4.3 (2.5-5.9) [1626] | 4.2 (2.4-5.9) [1645] |
| APACHE II Acute Physiology Score[d] – median (IQR) | 11 (7-15) | 11 (7-15) |
| APACHE II score[d] – median (IQR) | 16 (12-21) | 16 (12-21) |
| SOFA score[e] – median (IQR) | 4 (2-6) | 4 (2-6) |
| Customized risk of death – median (IQR) | 0.21 (0.11-0.37) [1849] | 0.22 (0.11-0.36) [1878] |
| At randomization – no. (%) | | |
| On invasive mechanical ventilation | 182 (9.8) | 164 (8.7) |
| On vasopressor infusion | 293 (15.8) [1855] | 277 (14.7) [1878] |
| Reported as would have been admitted direct to ICU from ED if not enrolled into trial[f] – no. (%) | 1027 (76.1) [1350] | 1044 (81.1) [1288] |

| Characteristic | EGDT (N = 1857) | Usual resuscitation (N = 1880) |
|---|---|---|
| **Care-delivery characteristics** | | |
| Time from ED presentation to inclusion criteria met – median (IQR) | 85 (40-150) [1853] | 81 (36-145) [1878] |
| Time from ED presentation to randomization – median (IQR) | 162 (119-223) | 159 (115-221) |
| Day of week randomized – no. (%) | | |
| Monday | 342 (18.4) | 334 (17.8) |
| Tuesday | 333 (17.9) | 377 (20.1) |
| Wednesday | 337 (18.1) | 315 (16.8) |
| Thursday | 337 (18.1) | 301 (16.0) |
| Friday | 277 (14.9) | 297 (15.8) |
| Saturday | 118 (6.4) | 125 (6.6) |
| Sunday | 113 (6.1) | 131 (7.0) |
| Weekday (Monday to Friday) | 1626 (87.6) | 1624 (86.4) |
| Weekend (Saturday to Sunday) | 231 (12.4) | 256 (13.6) |
| Time of day randomized – no. (%) | | |
| Day (08:00 to 19:59) | 1569 (84.5) | 1574 (83.7) |
| Night (20:00 to 07:59) | 288 (15.5) | 306 (16.3) |
| Receiving antimicrobial agents at randomization – no. (%) | 1726 (93.0) [1856] | 1742 (92.7) [1880] |
| Time from ED presentation to first IV antimicrobial agents[g] (minutes) – median (IQR) | 75 (42-120) [1091] | 72 (42-119) [1095] |
| IV fluids administered before hospital presentation until randomization – no. (%) | 1801 (97.6) [1846] | 1818 (97.2) [1871] |
| Volume administered (ml) – median (IQR) | 2000 (1250-3000) [1846] | 2000 (1200-3000) [1871] |
| Volume administered per body weight (ml $kg^{-1}$) – median (IQR) | 27.5 (16.5-42.3) [1723] | 27.7 (16.2-41.7) [1687] |

EGDT – early, goal-directed therapy; IQR – interquartile range; % – percentage; kg – kilogram; APACHE II – Acute Physiology and Chronic Health Evaluation II; SBP – systolic blood pressure; MAP – mean arterial pressure; mm Hg – millimeter of mercury; mmol – millimole; l – liter; SOFA – Sequential Organ Failure Assessment; ICU – intensive care unit; ED – emergency department; IV – intravenous; ml – milliliter.

[ ] indicate where one or both groups have missing data

[a] Please see Table S1 in the Supplementary Appendix for details on data harmonization

[b] Age estimated for seven patients in ProMISe

[c] Three patients did not meet the refractory hypotension or hyperlactatemia eligibility criteria

[d] Scores on the APACHE II Acute Physiology range from 0 to 60, with higher scores indicating greater severity of illness. Scores on the APACHE II range from 0 to 71, with higher scores indicating greater severity of illness

[e] Scores on the SOFA range from 0 to 24, with higher scores indicating a greater degree of organ failure; baseline urine output was not used in the calculation of the renal SOFA score for ARISE and ProMISe.

[f] Only recorded for patients in two of the trials (ARISE, ProMISe)

[g] Only for patients who received IV antimicrobial agents prior to randomization (ProCESS, ARISE); all patients in ProMISe received IV antimicrobial agents prior to randomization – time not recorded

**Table S3 Patient and care-delivery characteristics at baseline by trial[a]**

| | ProCESS | | ARISE | | ProMISe | |
|---|---|---|---|---|---|---|
| **Characteristic** | **EGDT (N = 439)** | **Usual resuscitation (N = 456)** | **EGDT (N = 793)** | **Usual resuscitation (N = 798)** | **EGDT (N = 625)** | **Usual resuscitation (N = 626)** |
| **Patient characteristics** | | | | | | |
| Age[b] (years) – median (IQR) | 60 (50-73) [439] | 62 (51-75) [455] | 65 (50-74) [793] | 65 (52-76) [798] | 68 (58-78) [625] | 67 (54-76) [626] |
| Male sex – no. (%) | 232 (52.8) | 264 (57.9) | 477 (60.2) | 473 (59.3) | 356 (57.0) | 367 (58.6) |
| Weight (actual or estimated in kg) – median (IQR) | 77 (64-93) [438] | 76 (65-92) [452] | 75 (64-90) [767] | 77 (65-90) [763] | 75 (65-85) [529] | 75 (65-89) [481] |
| Nursing home residence prior to admission – no. (%) | 64 (14.6) [437] | 73 (16.0) [455] | 44 (5.5) [793] | 39 (4.9) [798] | 18 (2.9) [622] | 14 (2.2) [626] |
| One or more severe coexisting conditions (APACHE II) – no. (%) | 140 (31.9) [439] | 154 (33.8) [456] | 213 (26.9) [793] | 201 (25.2) [798] | 193 (31.0) [622] | 171 (27.3) [626] |
| Site of infection – no. (%) | | | | | | |
| Lungs | 140 (31.9) | 151 (33.1) | 289 (36.4) | 262 (32.8) | 228 (36.5) | 207 (33.1) |
| Abdomen | 69 (15.7) | 51 (11.2) | 63 (7.9) | 61 (7.6) | 40 (6.4) | 51 (8.1) |
| Blood | [*Not recorded*][c] | [*Not recorded*][c] | 75 (9.5) | 86 (10.8) | 97 (15.5) | 86 (13.7) |
| Central nervous system | 3 (0.7) | 4 (0.9) | 13 (1.6) | 6 (0.8) | 12 (1.9) | 9 (1.4) |
| Soft tissue | 25 (5.7) | 38 (8.3) | 90 (11.3) | 76 (9.5) | 39 (6.2) | 39 (6.2) |
| Urinary tract | 100 (22.8) | 94 (20.6) | 148 (18.7) | 160 (20.1) | 108 (17.3) | 117 (18.7) |
| Other | 40 (9.1) | 40 (8.8) | 52 (6.6) | 72 (9.0) | 21 (3.4) | 37 (5.9) |
| Unknown | 57 (13.0) | 66 (14.5) | 63 (7.9) | 75 (9.4) | 76 (12.2) | 77 (12.3) |
| Determined ultimately to have no infection | 5 (1.1) | 12 (2.6) | 0 (0) | 0 (0) | 4 (0.6) | 3 (0.5) |
| Entry criterion met[d] – no. (%) | | | | | | |
| Refractory hypotension only | 178 (40.5) | 179 (39.3) | 427 (53.8) | 427 (53.5) | 216 (34.6) | 227 (36.3) |
| Hyperlactatemia only | 193 (44.0) | 213 (46.7) | 237 (29.9) | 241 (30.2) | 287 (45.9) | 278 (44.4) |
| Both refractory hypotension and hyperlactatemia | 66 (15.0) | 64 (14.0) | 128 (16.1) | 130 (16.3) | 122 (19.5) | 121 (19.3) |

| | ProCESS | | ARISE | | ProMISe | |
|---|---|---|---|---|---|---|
| **Characteristic** | **EGDT (N = 439)** | **Usual resuscitation (N = 456)** | **EGDT (N = 793)** | **Usual resuscitation (N = 798)** | **EGDT (N = 625)** | **Usual resuscitation (N = 626)** |
| Refractory hypotension (SBP <90 or MAP <65 mm Hg) – no. (%) | 244 (55.6) | 243 (53.3) | 555 (70.0) | 557 (69.8) | 338 (54.1) | 348 (55.6) |
| Eligibility SBP (mm Hg) – median (IQR) | 79 (70-84) [137] | 78 (72-84) [158] | 81 (75-85) [500] | 82 (75-85) [503] | 80 (73-85) [316] | 81 (73-85) [318] |
| Eligibility MAP (mm Hg) – median (IQR) | [*Not recorded*] | [*Not recorded*] | 58 (53-61) [275] | 59 (53-62) [267] | 58 (53-60) [50] | 57 (52-61) [64] |
| Hyperlactatemia (lactate ≥4 mmol $l^{-1}$) – no. (%) | 259 (59.0) | 277 (60.7) | 365 (46.0) | 371 (46.5) | 409 (65.4) | 399 (63.7) |
| Eligibility serum lactate level (mmol $l^{-1}$) – median (IQR) | 5.5 (4.5-6.8) [259] | 5.5 (4.6-7.3) [277] | 5.4 (4.6-7.5) [365] | 5.8 (4.6-7.4) [371] | 5.8 (4.6-8.0) [409] | 5.7 (4.7-7.8) [399] |
| Last values before randomization | | | | | | |
| SBP (mm Hg) – median (IQR) | 95 (81-114) [439] | 92 (80-116) [456] | 95 (84-109) [782] | 95 (85-110) [784] | 92 (82-115) [588] | 91 (81-110) [584] |
| MAP (mm Hg) – median (IQR) | 69 (59-81) [439] | 67 (58-83) [456] | 66 (59-77) [772] | 67 (60-77) [771] | 65 (56-77) [107] | 62 (55-70) [125] |
| Serum lactate (mmol $l^{-1}$) – median (IQR) | 4.4 (2.6-6.0) [411] | 4.5 (2.8-5.9) [426] | 4.0 (2.2-5.3) [636] | 3.8 (2.5-5.0) [632] | 4.5 (2.8-6.4) [579] | 4.4 (2.8-6.3) [587] |
| APACHE II Acute Physiology Score[e] – median (IQR) | 10 (7-14) | 10 (7-15) | 10 (6-14) | 10 (6-14) | 12 (8-17) | 12 (8-17) |
| APACHE II score[e] – median (IQR) | 15 (11-20) | 16 (12-21) | 15 (11-20) | 15 (11-20) | 18 (13-23) | 17 (13-22) |
| SOFA score[f] – median (IQR) | 5 (3-7) | 5 (3-7) | 3 (2-6) | 4 (2-5) | 4 (2-5) | 4 (3-6) |
| Customized risk of death – median (IQR) | 0.200 (0.106-0.326) [435] | 0.221 (0.112-0.352) [454] | 0.169 (0.096-0.302) [792] | 0.186 (0.091-0.313) [798] | 0.288 (0.157-0.453) [622] | 0.249 (0.140-0.412) [626] |
| At randomization – no. (%) | | | | | | |
| On invasive mechanical ventilation | 71 (16.2) | 72 (15.8) | 71 (9.0) | 64 (8.0) | 40 (6.4) | 28 (4.5) |
| On vasopressor infusion | 84 (19.1) [439] | 69 (15.1) [456] | 173 (21.8) [793] | 173 (21.7) [798] | 36 (5.8) [623] | 35 (5.6) [624] |
| Reported as would have been admitted direct to ICU from ED if not enrolled into trial – no. (%) | [*Not recorded*] | [*Not recorded*] | 608 (83.9) [725] | 617 (93.2) [662] | 419 (67.0) [625] | 427 (68.2) [626] |

| | ProCESS | | ARISE | | ProMISe | |
|---|---|---|---|---|---|---|
| **Characteristic** | **EGDT (N = 439)** | **Usual resuscitation (N = 456)** | **EGDT (N = 793)** | **Usual resuscitation (N = 798)** | **EGDT (N = 625)** | **Usual resuscitation (N = 626)** |
| **Care-delivery characteristics** | | | | | | |
| Time from ED presentation to inclusion criteria met (minutes) – median (IQR) | 92 (55-164) [436] | 88 (50-145) [454] | 82 (35-150) [792] | 76 (30-145) [798] | 79 (31-138) [625] | 79 (34-145) [626] |
| Time from ED presentation to randomization (minutes) – median (IQR) | 170 (128-227) | 166 (121-219) | 167 (125-234) | 161 (117-233) | 147 (106-209) | 150 (109-209) |
| Day of week randomized – no. (%) | | | | | | |
| Monday | 77 (17.5) | 84 (18.4) | 154 (19.4) | 140 (17.5) | 111 (17.8) | 110 (17.6) |
| Tuesday | 88 (20.0) | 98 (21.5) | 131 (16.5) | 148 (18.5) | 114 (18.2) | 131 (20.9) |
| Wednesday | 83 (18.9) | 71 (15.6) | 134 (16.9) | 130 (16.3) | 120 (19.2) | 114 (18.2) |
| Thursday | 70 (15.9) | 78 (17.1) | 144 (18.2) | 123 (15.4) | 123 (19.7) | 100 (16.0) |
| Friday | 82 (18.7) | 64 (14.0) | 97 (12.2) | 119 (14.9) | 98 (15.7) | 114 (18.2) |
| Saturday | 20 (4.6) | 27 (5.9) | 71 (9.0) | 64 (8.0) | 27 (4.3) | 34 (5.4) |
| Sunday | 19 (4.3) | 34 (7.5) | 62 (7.8) | 74 (9.3) | 32 (5.1) | 23 (3.7) |
| Weekday (Monday to Friday) | 400 (91.1) | 395 (86.6) | 660 (83.2) | 660 (82.7) | 566 (90.6) | 569 (90.9) |
| Weekend (Saturday to Sunday) | 39 (8.9) | 61 (13.4) | 133 (16.8) | 138 (17.3) | 59 (9.4) | 57 (9.1) |
| Time of day randomized – no. (%) | | | | | | |
| Day (08:00 to 19:59) | 384 (87.5) | 386 (84.6) | 637 (80.3) | 643 (80.6) | 548 (87.7) | 545 (87.1) |
| Night (20:00 to 07:59) | 55 (12.5) | 70 (15.4) | 156 (19.7) | 155 (19.4) | 77 (12.3) | 81 (12.9) |
| Receiving antimicrobial agents at randomization – no. (%) | 332 (75.6) [439] | 347 (76.1) [456] | 769 (97.1) [792] | 769 (96.4) [798] | 625 (100) [625] | 626 (100) [626] |
| Time from ED presentation to first IV antimicrobial agents[g] (minutes) – median (IQR) | 88 (56-134) [322] | 96 (55-138) [327] | 69 (37-109) [769] | 64 (38-104) [768] | [*Not recorded*] | [*Not recorded*] |
| IV fluids administered before hospital presentation until randomization – no. (%) | 419 (95.4) [439] | 438 (96.1) [456] | 771 (98.6) [782] | 780 (98.9) [789] | 611 (97.8) [625] | 600 (95.8) [626] |
| Volume administered (ml) – median (IQR) | 2000 (1000-3000) [439] | 2000 (1000-3000) [456] | 2400 (1700-3200) [782] | 2500 (1750-3280) [789] | 1912 (1000-2500) [625] | 2000 (1000-2500) [626] |
| Volume administered per body weight (ml $kg^{-1}$) – median (IQR) | 25.7 (16.0-40.6) [438] | 24.7 (12.7-39.2) [452] | 33.0 (20.0-46.2) [756] | 31.9 (20.0-46.1) [754] | 22.7 (14.3-33.8) [529] | 24.2 (15.3-38.5) [481] |

ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; EGDT – early, goal-directed therapy; IQR – interquartile range; % – percentage; kg – kilogram; APACHE II – Acute Physiology and Chronic Health Evaluation II; SBP – systolic blood pressure; MAP – mean arterial pressure; mmHg – millimeter of mercury; mmol – millimole; l – liter; SOFA – Sequential Organ Failure Assessment; ICU – intensive care unit; ED – emergency department; IV – intravenous; ml – milliliter.

[ ] indicate where one or both groups have missing data

[a] Please see Table S1 for details on data harmonization

[b] Age estimated for seven patients in ProMISe

[c] ProCESS assigned all positive blood cultures to the most likely anatomic source

[d] Three patients did not meet the refractory hypotension or hyperlactatemia eligibility criteria

[e] Scores on the APACHE II Acute Physiology range from 0 to 60, with higher scores indicating greater severity of illness. Scores on the APACHE II range from 0 to 71, with higher scores indicating greater severity of illness

[f] Scores on the SOFA range from 0 to 24, with higher scores indicating a greater degree of organ failure

[g] Only for patients who received IV antimicrobial agents prior to randomization (ProCESS, ARISE). All patients in ProMISe received IV antimicrobial agents prior to randomization – time not recorded

**Table S4 Impact of harmonization on precision of length of stay**

| | ARISE | | ProMISe | |
|---|---|---|---|---|
| | **EGDT (N = 1857)** | **Usual resuscitation (N = 1880)** | **EGDT (N = 1857)** | **Usual resuscitation (N = 1880)** |
| **Before harmonization** | | | | |
| In ED (hours) – median (IQR) / mean (SD) | 1.4 (0.5-2.7) / 2.4 (3.8) | 2.0 (1.0-3.8) / 3.2 (4.1) | 1.5 (0.4-3.1) / 2.3 (3.2) | 1.3 (0.4-2.9) / 2.0 (2.1) |
| In ICU (days) | | | | |
| First stay | | | | |
| Median (IQR) among those admitted | 2.7 (1.3-5.0) | 2.8 (1.5-5.2) | 2.7 (1.1-5.4) | 3.1 (1.1-5.9) |
| Mean (SD) overall | 4.3 (6.4) | 3.8 (5.3) | 4.3 (7.1) | 3.9 (7.9) |
| Total stay (including readmissions) | | | | |
| Median (IQR) among those admitted | 2.8 (1.4-5.1) | 2.8 (1.5-5.7) | 3.0 (1.3-6.2) | 3.8 (1.7-6.9) |
| Mean (SD) overall | 4.5 (7.0) | 4.0 (5.6) | 5.0 (7.8) | 4.8 (8.9) |
| **After harmonization** | | | | |
| In ED (hours) – median (IQR) / mean (SD) | 1 (0-2) / 1.6 (3.1) | 1 (0-3) / 2.2 (3.1) | 1 (0-3) / 1.8 (2.9) | 1 (0-2) / 1.5 (1.9) |
| In ICU (days) | | | | |
| First stay | | | | |
| Median (IQR) among those admitted | 3 (2-6) | 3 (2-6) | 4 (2-6) | 4 (2-7) |
| Mean (SD) overall | 4.7 (6.4) | 4.1 (5.3) | 5.2 (7.1) | 4.6 (8.0) |
| Total stay (including readmissions) | | | | |
| Median (IQR) among those admitted | 3 (2-6) | 3 (2-6) | 4 (2-7) | 5 (3-8) |
| Mean (SD) overall | 4.9 (7.1) | 4.3 (5.6) | 5.9 (7.9) | 5.5 (9.1) |

ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; EGDT – early, goal-directed therapy; ED – emergency department; IQR – interquartile range; SD – standard deviation; ICU – intensive care unit.

**Table S5 Customized risk of death model[a,b]**

| Factor | Odds ratio (95% confidence interval) | P value |
|---|---|---|
| Age[c] (years) | 1.03 (1.03-1.04) | <0.001 |
| Male sex | 1.04 (0.82-1.31) | 0.75 |
| Nursing home residence prior to admission | 1.87 (1.22-2.87) | 0.004 |
| One or more severe coexisting conditions (APACHE II) | 2.19 (1.71-2.81) | <0.001 |
| Site of infection | | |
| Soft tissue | 1 | <0.001 |
| Lungs | 3.25 (1.83-5.78) | |
| Abdomen | 2.78 (1.44-5.38) | |
| Blood | 4.20 (2.20-7.99) | |
| Central nervous system | 4.27 (1.33-13.70) | |
| Urinary tract | 2.06 (1.12-3.78) | |
| Other | 2.50 (1.25-4.97) | |
| Unknown | 2.69 (1.43-5.07) | |
| Determined ultimately to have no infection | 4.57 (1.29-16.21) | |
| Entry criterion met[d] | | |
| Refractory hypotension only | 1 | <0.001 |
| Hyperlactatemia only | 1.84 (1.41-2.39) | |
| Both refractory hypotension and hyperlactatemia | 1.92 (1.39-2.66) | |
| Last APACHE II Acute Physiology Score before randomization[e] | 1.11 (1.09-1.13) | <0.001 |

APACHE II – Acute Physiology and Chronic Health Evaluation II.

[a] Please see Table S1 for details on data harmonization

[b] Model derived using data from 1870 usual care patients; area under the receiver operating characteristic curve 0.756 (95% confidence interval 0.732-0.781)

[c] Age estimated for seven patients in ProMISe

[d] Three patients did not meet the refractory hypotension or hyperlactatemia eligibility criteria

[e] Scores on the APACHE II Acute Physiology range from 0 to 60, with higher scores indicating greater severity of illness

## Table S6 Vasopressor use model[a,b]

| Factor | Odds ratio (95% confidence interval) | P value |
|---|---|---|
| Age[c] (years) | 1.01 (1.00-1.02) | 0.002 |
| Male sex | 1.03 (0.84-1.25) | 0.79 |
| Nursing home residence prior to admission | 0.95 (0.64-1.42) | 0.81 |
| One or more severe coexisting conditions (APACHE II) | 1.00 (0.80-1.25) | 0.98 |
| Site of infection | | |
| Soft tissue | 1 | 0.11 |
| Lungs | 1.16 (0.79-1.72) | |
| Abdomen | 1.35 (0.83-2.19) | |
| Blood | 1.50 (0.93-2.41) | |
| Central nervous system | 2.59 (0.92-7.30) | |
| Urinary tract | 1.13 (0.75-1.71) | |
| Other | 1.10 (0.67-1.79) | |
| Unknown | 0.82 (0.52-1.30) | |
| Determined ultimately to have no infection | 0.61 (0.18-2.11) | |
| Entry criterion met[d] | | |
| Refractory hypotension only | 1 | <0.001 |
| Hyperlactatemia only | 0.65 (0.51-0.83) | |
| Both refractory hypotension and hyperlactatemia | 1.23 (0.93-1.64) | |
| Last APACHE II Acute Physiology Score before randomization[e] | 1.07 (1.05-1.09) | <0.001 |
| On invasive mechanical ventilation at randomization | 1.37 (0.94-2.00) | 0.10 |
| On vasopressor infusion at randomization | 1.24 (0.93-1.66) | 0.14 |
| Day of week randomized | | |
| Sunday | 1 | 0.31 |
| Monday | 1.09 (0.70-1.70) | |
| Tuesday | 1.22 (0.79-1.87) | |
| Wednesday | 1.08 (0.69-1.68) | |
| Thursday | 1.23 (0.79-1.92) | |
| Friday | 1.14 (0.73-1.79) | |
| Saturday | 0.70 (0.41-1.20) | |
| Time of day randomized – Day (08:00 to 19:59) | 1.39 (1.07-1.82) | 0.01 |
| Volume (liters) of IV fluids administered before hospital until randomization | 1.30 (1.20-1.42) | <0.001 |
| Volume (liters) of IV fluids administered during the first six hours after randomization | 1.14 (1.07-1.22) | <0.001 |
| Volume (liters) of blood products administered during the first six hours after randomization | 1.22 (0.83-1.79) | 0.32 |

APACHE II – Acute Physiology and Chronic Health Evaluation II; IV – intravenous.

[a] Please see Table S1 for details on data harmonization

[b] Model derived using data from 1866 usual care patients, of whom 807 (43%) received vasopressors during the first six hours after randomization; area under the receiver operating characteristic curve 0.702 (95% confidence interval 0.678-0.725)

[c] Age estimated for seven patients in ProMISe

[d] Three patients did not meet the refractory hypotension or hyperlactatemia eligibility criteria

[e] Scores on the APACHE II Acute Physiology range from 0 to 60, with higher scores indicating greater severity of illness

**Table S7 Fluid volume use model[a,b]**

| Factor | Coefficient (95% confidence interval) | P value |
|---|---|---|
| Age[c] (years) | -0.008 (-0.013 to -0.003) | 0.001 |
| Male sex | 0.053 (-0.096 to 0.202) | 0.49 |
| Weight (actual or estimated in kg) | 0.001 (-0.002 to 0.004) | 0.41 |
| Nursing home residence prior to admission | 0.121 (-0.164 to 0.406) | 0.41 |
| One or more severe coexisting conditions (APACHE II) | -0.007 (-0.169 to 0.155) | 0.93 |
| Site of infection | | |
| Soft tissue | 0 | 0.08 |
| Lungs | -0.173 (-0.462 to 0.116) | |
| Abdomen | 0.161 (-0.191 to 0.513) | |
| Blood | -0.108 (-0.462 to 0.246) | |
| Central nervous system | -0.160 (-0.904 to 0.584) | |
| Urinary tract | 0.042 (-0.261 to 0.345) | |
| Other | 0.253 (-0.110 to 0.616) | |
| Unknown | -0.061 (-0.397 to 0.275) | |
| Determined ultimately to have no infection | 0.353 (-0.535 to 1.241) | |
| Entry criterion met[d] | | |
| Refractory hypotension only | 0 | 0.01 |
| Hyperlactatemia only | 0.161 (-0.016 to 0.338) | |
| Both refractory hypotension and hyperlactatemia | 0.322 (0.107 to 0.537) | |
| Last APACHE II Acute Physiology Score before randomization[e] | 0.023 (0.010 to 0.036) | 0.001 |
| On invasive mechanical ventilation at randomization | -0.120 (-0.393 to 0.153) | 0.39 |
| On vasopressor infusion at randomization | -0.207 (-0.418 to 0.004) | 0.05 |
| Time (minutes) from ED presentation to randomization | -0.125 (-0.179 to -0.071) | <0.001 |
| Day of week randomized | | |
| Sunday | 0 | 0.67 |
| Monday | 0.188 (-0.134 to 0.510) | |
| Tuesday | 0.296 (-0.022 to 0.614) | |
| Wednesday | 0.259 (-0.066 to 0.584) | |
| Thursday | 0.244 (-0.084 to 0.572) | |
| Friday | 0.275 (-0.053 to 0.603) | |
| Saturday | 0.192 (-0.199 to 0.583) | |
| Time of day randomized – Day (08:00 to 19:59) | 0.191 (-0.006 to 0.388) | 0.06 |
| Volume (liters) of IV fluids administered before hospital until randomization | -0.034 (-0.095 to 0.027) | 0.28 |
| Volume (liters) of blood products administered during the first six hours after randomization | 0.374 (0.102 to 0.646) | 0.01 |
| Vasopressor infusion initiated in the first six hours after randomization | 0.250 (0.099 to 0.401) | 0.001 |

APACHE II – Acute Physiology and Chronic Health Evaluation II; ED – emergency department; IV – intravenous.

[a] Please see Table S1 for details on data harmonization

[b] Model derived using data from 1683 usual care patients; mean (SD) volume of IV fluids administered during the first six hours after randomization was 1.9 (1.5) liters; $R^2$ 7.9%, adjusted $R^2$ 6.2%

[c] Age estimated for seven patients in ProMISe

[d] Three patients did not meet the refractory hypotension or hyperlactatemia eligibility criteria

[e] Scores on the APACHE II Acute Physiology range from 0 to 60, with higher scores indicating greater severity of illness

**Table S8 Equipment and staff time for catheter insertion and monitor set-up**

| Catheter | Physician time (catheter insertion) | Nurse time (monitor set-up) |
|---|---|---|
| PreSep™ central venous oximetry catheter | 30 minutes (ProCESS/ARISE/ProMISe) | 20 minutes[a] (ProCESS/ProMISe)<br>15 minutes[a] (ARISE)<br>+<br>30 minutes[b,c] (ProCESS/ARISE/ProMISe) |
| Standard CVC | 30 minutes (ProCESS/ARISE/ProMISe) | 20 minutes[a] (ProMISe/ProCESS)<br>15 minutes[a] + 15 minutes[c] (ARISE) |
| Arterial catheter | 20 minutes (ProCESS/ProMISe)<br>15 minutes (ARISE) | 20 minutes[a] (ProCESS/ProMISe)<br>10 minutes[a] + 15 minutes[c] (ARISE) |

ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; CVC – central venous catheter.

[a] It is assumed that same amount of nurse time is required whether single or multiple catheters are inserted
[b] Additional nurse time for setting up the monitor
[c] Additional nurse time for calibration of lines, take and process arterial blood gas

**Table S9 Unit cost in US dollars ($)[a]**

| Items | ProCESS | ARISE | ProMISe | Source |
|---|---|---|---|---|
| **Equipment & consumables** | | | | |
| Monitor | 99 | 100 | 99 | Manufacturer's price |
| PreSep™ central venous oximetry catheter | 236 | 275 | 183 | Huang et al[1] (ProCESS)<br>Manufacturer's price (ARISE/ProMISe) |
| Standard CVC | 47 | 29 | 34 | UPMC database (ProCESS)<br>Participating sites (ARISE)<br>Local NHS finance department (ProMISe) |
| Arterial catheter | 131 | 14 | 18 | |
| Ultrasound | N/A | 18 | N/A | Participating sites |
| **Blood products[b]** | | | | |
| PRBC | 200 | 240 | 172 | UPMC database (ProCESS)<br>National Blood Authority[9] (ARISE)<br>NHS Blood & Transplant[10] (ProMISe) |
| Platelets | 60 | 257 | 293 | |
| Frozen fresh plasma | 375 | 195 | 39 | |
| **Staff time** | | | | |
| Senior physician (per hour) | 136 | 90 | 98 | Salary.com[11] & Medscape[12] (ProCESS)<br>Enterprise Agreement Salary (ARISE)<br>PSSRU[13] (ProMISe) |
| Junior physician (per hour) | 28 | 42 | 42 | |
| Nurse (per hour) | 35 | 29 | 35 | |
| Staff training (per patient) | 12 | 18 | 12 | |
| **Hospital bed** | | | | |
| ED (per hour) | 247 | 111 | 38 | Henneman et al[14] (ProCESS)<br>Cullen et al[15] (ARISE)<br>Dixon et al[16] (ProMISe) |
| ICU (per bed day) | 3,154 | 2,938 | 1,645 | Milbrandt et al[17] (ProCESS)<br>NSW costs of care standard[18] (ARISE)<br>NHS Reference Costs[19] (ProMISe) |
| Floor/ ward (per bed day) | 1,943 | 976 | 373 | Milbrandt et al[17] (ProCESS)<br>APH Costs Report[20] (ARISE)<br>NHS Reference Costs[19] (ProMISe) |

ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; CVC – central venous catheter; UPMC – University of Pittsburgh Medical Centre; NHS – UK National Health Service; PRBC – packed red blood cells; PSSRU – Personal Social Services Research Unit; ED – emergency department; ICU – intensive care unit; NSW – New South Wales; APH – Australian Public Hospitals.

[a] Unit costs in GBP (ProMISe) and AUD (ARISE) were converted to USD using 2012 World Bank purchasing power parity (PPP) at exchange rates of £1 GBP = $1.41 USD and $1 AUD=$0.66 USD (http://data.worldbank.org/indicator/PA.NUS.PPP)

[b] Unit size of PRBC, platelets and frozen fresh plasma considered in ProCESS were 300ml, 275ml and 45ml, respectively; in ARISE the unit sizes were 200ml, 160ml and 295ml, respectively; in ProMISe the unit sizes were 280ml, 200ml and 250ml, respectively

## Table S10 Variables considered for multiple imputation and form of imputation model

| Variable | Missing values | Imputation model |
|---|---|---|
| Baseline variables | | |
| Randomized group | 0 (0) | None required |
| Age | 1 (<0.1) | Mean imputation |
| Sex | 0 (0) | None required |
| Nursing home residence prior to admission | 6 (0.2) | Assumed no |
| Severe coexisting conditions | 3 (0.1) | Assumed no |
| Site of infection | 0 (0) | None required |
| SOFA score | 0 (0) | None required |
| Resource use variables | | |
| Days in ICU | 6 (0.2) | None required / mean imputation[a] |
| Days on floor/ ward | 19 (0.5) | None required / mean imputation[a,b] |
| Quality-of-life variables | | |
| EQ-5D at 90 days | 2127 (56) | Predictive mean matching |

Values are number and percentage.

SOFA – Sequential Organ Failure Assessment; ICU – intensive care unit; EQ-5D – EuroQol questionnaire.

[a] There were six withdrawals whose duration of stay up to the point of withdrawal was counted

[b] There were 13 patients in ProCESS whose duration of stay was truncated at 60 days; additional days for these patients were mean imputed (see Methods)

**Table S11 Alternative assumptions for sensitivity analysis**

| Assumptions | Base case | Sensitivity analysis |
|---|---|---|
| Staff time for line insertion and monitor set up | Trial specific duration used | Duration was varied over max/min across the trials |
| 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 ICU | Protocol implemented exclusively either in ED or in ICU |
| Imputation of missing QOL | Imputed across the trials using observed QOL in ProMISe | Using trial-specific QOL |
| Baseline covariates | Unadjusted analysis | Adjusted for baseline covariates |
| Distributional assumptions | Costs and QALYs normally distributed | Costs and QALYs gamma distributed |

ED – emergency department; ICU – intensive care unit; QOL – quality of life; ProMISe – Protocolised Management in Sepsis; QALY – quality-adjusted life-year.

## Table S12 Resource use up to 90 days post-randomization

| Resource use category | Statistic | ProCESS | | ARISE | | ProMISe | |
|---|---|---|---|---|---|---|---|
| | | EGDT (N=439) | Usual resuscitation (N=456) | EGDT (N=793) | Usual resuscitation (N=798) | EGDT (N=625) | Usual resuscitation (N=626) |
| **Interventions** | | | | | | | |
| PreSep™ central venous oximetry catheter | N | 391 | 19 | 705 | 3 | 545 | 2 |
| | % | 89% | 4% | 89% | 0% | 87% | 0% |
| Standard CVC | N | 72 | 246 | 109 | 494 | 48 | 316 |
| | % | 16% | 54% | 14% | 62% | 8% | 50% |
| Arterial line | N | 166 | 134 | 725 | 609 | 462 | 389 |
| | % | 38% | 29% | 91% | 76% | 74% | 62% |
| Duration of protocol delivered (hours) | Mean | 5.88 | 0.00 | 5.95 | 0.00 | 5.81 | 0.00 |
| | SD | 0.74 | 0.00 | 0.50 | 0.00 | 0.88 | 0.00 |
| Duration of protocol delivered in ED (hours) | Mean | 2.99 | N/A | 1.36 | N/A | 1.59 | N/A |
| | SD | 2.35 | N/A | 1.89 | N/A | 1.93 | N/A |
| Volume of blood products (ml) | Mean | 290 | 221 | 254 | 261 | 181 | 158 |
| | SD | 710 | 570 | 698 | 917 | 484 | 520 |
| **Additional staff time** | | | | | | | |
| Line insertion and set-up (hours) | Mean | 1.24 | 0.55 | 1.19 | 0.75 | 1.22 | 0.52 |
| | SD | 0.30 | 0.42 | 0.21 | 0.39 | 0.34 | 0.38 |
| Monitoring (hours) | Mean | 0.50 | N/A | 0.23 | N/A | 0.27 | N/A |
| | SD | 0.39 | N/A | 0.32 | N/A | 0.32 | N/A |
| Training (hours) | Mean | 0.50 | N/A | 0.20 | N/A | 0.30 | N/A |
| | SD | 0.00 | N/A | 0.00 | N/A | 0.00 | N/A |
| **Hospital length of stay** | | | | | | | |
| ED (hours) | Mean | 3.34 | 3.08 | 1.58 | 2.17 | 1.76 | 1.54 |
| | SD | 3.80 | 3.60 | 3.05 | 3.12 | 2.86 | 1.86 |
| ICU (days) | Mean | 5.80 | 5.31 | 4.93 | 4.28 | 5.88 | 5.50 |
| | SD | 7.38 | 6.78 | 7.07 | 5.56 | 7.88 | 9.00 |
| Floor/ ward (days) | Mean | 6.03 | 6.46 | 9.85 | 10.05 | 10.54 | 9.72 |
| | SD | 9.22 | 9.73 | 12.63 | 12.34 | 14.87 | 13.42 |
| **Total length of stay up to 90 days** | Mean | 11.97 | 11.89 | 14.84 | 14.42 | 16.49 | 15.28 |
| | SD | 12.11 | 12.46 | 15.30 | 14.75 | 18.17 | 16.73 |

ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; EGDT – early, goal-directed therapy; CVC – central venous catheter; ED – emergency department; ICU – intensive care unit.

## Table S13 Costs ($) up to 90 days post-randomization

| Cost category | Statistic | ProCESS | | ARISE | | ProMISe | |
|---|---|---|---|---|---|---|---|
| | | EGDT (N=439) | Usual resuscitation (N=456) | EGDT (N=793) | Usual resuscitation (N=798) | EGDT (N=625) | Usual resuscitation (N=626) |
| **Intervention costs** | | | | | | | |
| Monitor and consumables | Mean | 386 | 74 | 414 | 41 | 236 | 29 |
| | SD | 133 | 83 | 134 | 31 | 83 | 26 |
| Blood products | Mean | 883 | 791 | 284 | 292 | 141 | 123 |
| | SD | 936 | 752 | 780 | 1,025 | 377 | 405 |
| **Additional staff costs** | | | | | | | |
| Line insertion and set-up | Mean | 40 | 17 | 41 | 26 | 46 | 20 |
| | SD | 10 | 13 | 7 | 14 | 13 | 15 |
| Monitoring | Mean | 17 | N/A | 7 | N/A | 9 | N/A |
| | SD | 14 | N/A | 9 | N/A | 11 | N/A |
| Training | Mean | 23 | N/A | 7 | N/A | 12 | N/A |
| | SD | 0 | N/A | 0 | N/A | 0 | N/A |
| **Hospital costs** | | | | | | | |
| ED | Mean | 825 | 761 | 175 | 241 | 67 | 59 |
| | SD | 938 | 888 | 339 | 346 | 109 | 71 |
| ICU | Mean | 18,289 | 16,741 | 14,471 | 12,562 | 9,670 | 9,050 |
| | SD | 23,261 | 21,372 | 20,780 | 16,323 | 12,959 | 14,801 |
| Floor/ ward | Mean | 11,714 | 12,546 | 9,615 | 9,811 | 3,931 | 3,625 |
| | SD | 17,908 | 18,908 | 12,326 | 12,041 | 5,547 | 5,006 |
| **Total costs up to 90 days** | **Mean** | **32,178** | **30,930** | **25,014** | **22,973** | **14,112** | **12,906** |
| | **SD** | **30,215** | **30,183** | **25,753** | **22,836** | **15,132** | **16,029** |

ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; EGDT – early, goal-directed therapy; ED – emergency department; ICU – intensive care unit.

## Table S14 Incremental net benefit by subgroups[a]

| Subgroup | ProCESS | | | ARISE | | | ProMISe | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | Lower CI | Upper CI | Mean | Lower CI | Upper CI | Mean | Lower CI | Upper CI |
| **Patient characteristics** | | | | | | | | | |
| Age[b] (years) | | | | | | | | | |
| < 57 | 110 | -4,712 | 4,932 | -2,989 | -6,968 | 990 | -2,495 | -7,567 | 2,577 |
| 57-71 | 2,648 | -5,572 | 10,868 | -451 | -8,209 | 7,307 | 42 | -4,443 | 4,527 |
| ≥ 72 | 1,438 | -6,671 | 9,547 | -1,660 | -9,302 | 5,982 | -1,167 | -5,439 | 3,105 |
| Sex | | | | | | | | | |
| Female | -2,265 | -6,926 | 2,396 | -1,739 | -5,437 | 1,959 | 24 | -4,049 | 4,097 |
| Male | -4,335 | -11,352 | 2,682 | -3,809 | -10,233 | 2,615 | -2,046 | -5,522 | 1,430 |
| Site of infection | | | | | | | | | |
| Lungs | -228 | -14,759 | 14,303 | 2,233 | -11,167 | 15,633 | -787 | -5,263 | 3,689 |
| Abdomen | 2,246 | -6,304 | 10,796 | -192 | -8,507 | 8,123 | -3,212 | -12,973 | 6,549 |
| Blood[c] | -- | -- | -- | -2,667 | -17,060 | 11,726 | -5,686 | -12,575 | 1,203 |
| Soft tissue | 12,020 | -4,534 | 28,574 | 9,581 | -6,855 | 26,017 | 6,562 | -3,942 | 17,066 |
| Urinary tract | 6,640 | -7,577 | 20,857 | 4,202 | -9,881 | 18,285 | 1,182 | -5,012 | 7,376 |
| Other or unknown[d] | 3,910 | -10,228 | 18,048 | 1,472 | -12,531 | 15,475 | -1,548 | -7,562 | 4,466 |
| Severity of illness | | | | | | | | | |
| Eligibility criterion met[e] | | | | | | | | | |
| Refractory hypotension | -9,009 | -19,883 | 1,865 | -2,340 | -11,629 | 6,949 | 11 | -4,393 | 4,415 |
| Hyperlactatemia | -11,634 | -22,311 | -957 | -4,965 | -14,024 | 4,094 | -2,614 | -6,512 | 1,284 |
| Both | -9,363 | -17,441 | -1,285 | -2,694 | -8,466 | 3,078 | -342 | -6,288 | 5,604 |
| Last lactate level before randomization (mmol $l^{-1}$) | | | | | | | | | |
| < 2.1 | -1,227 | -8,792 | 6,338 | 1,118 | -4,211 | 6,447 | -557 | -7,161 | 6,047 |
| 2.1-4.0 | -1,557 | -12,991 | 9,877 | 788 | -9,314 | 10,890 | -886 | -6,544 | 4,772 |
| ≥ 4.1 | -2,140 | -12,628 | 8,348 | 204 | -8,803 | 9,211 | -1,470 | -4,802 | 1,862 |
| APACHE II Acute Physiology Score[f] | | | | | | | | | |
| < 9 | -221 | -5,273 | 4,831 | -1,315 | -4,918 | 2,288 | -664 | -5,712 | 4,384 |
| 9-13 | 849 | -7,583 | 9,281 | -245 | -7,901 | 7,411 | 406 | -4,195 | 5,007 |
| ≥ 14 | -2,354 | -10,484 | 5,776 | -3,447 | -10,768 | 3,874 | -2,796 | -6,815 | 1,223 |
| APACHE II score[f] | | | | | | | | | |
| < 14 | -806 | -5,884 | 4,272 | -1,401 | -5,045 | 2,243 | 86 | -4,975 | 5,147 |
| 14-19 | -1,653 | -10,136 | 6,830 | -2,248 | -9,961 | 5,465 | -761 | -5,420 | 3,898 |
| ≥ 20 | -3,180 | -11,345 | 4,985 | -3,775 | -11,138 | 3,588 | -2,288 | -6,337 | 1,761 |

| Subgroup | ProCESS | | | ARISE | | | ProMISe | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | Lower CI | Upper CI | Mean | Lower CI | Upper CI | Mean | Lower CI | Upper CI |
| SOFA score[g] | | | | | | | | | |
| < 3 | 1,929 | -5,277 | 9,135 | -146 | -4,102 | 3,810 | -1,114 | -6,395 | 4,167 |
| 3-4 | 1,292 | -8,660 | 11,244 | -782 | -8,709 | 7,145 | -1,751 | -6,313 | 2,811 |
| ≥ 5 | 1,927 | -7,790 | 11,644 | -148 | -7,782 | 7,486 | -1,116 | -5,143 | 2,911 |
| Customized risk of death | | | | | | | | | |
| < 14% | -896 | -6,194 | 4,402 | -1,157 | -4,810 | 2,496 | -609 | -5,972 | 4,754 |
| ≥ 14% and <30% | 960 | -7,801 | 9,721 | 698 | -7,181 | 8,577 | 1,246 | -3,368 | 5,860 |
| ≥ 30% | -3,428 | -11,863 | 5,007 | -3,689 | -11,204 | 3,826 | -3,141 | -7,096 | 814 |
| Invasive mechanical ventilation | | | | | | | | | |
| No | -1,580 | -4,936 | 1,776 | -1,632 | -4,061 | 797 | -1,221 | -3,912 | 1,470 |
| Yes | 2,606 | -9,465 | 14,677 | 2,554 | -9,294 | 14,402 | 2,965 | -8,334 | 14,264 |
| Vasopressor infusion | | | | | | | | | |
| No | 102 | -3,298 | 3,502 | -1,641 | -4,276 | 994 | -1,277 | -3,991 | 1,437 |
| Yes | 3,039 | -8,704 | 14,782 | 1,296 | -10,253 | 12,845 | 1,661 | -9,271 | 12,593 |
| **Care-delivery characteristics** | | | | | | | | | |
| Time to randomization (minutes) | | | | | | | | | |
| < 132 | -3,024 | -8,732 | 2,684 | -6,729 | -10,902 | -2,556 | -2,769 | -6,934 | 1,396 |
| 132-197 | -1,523 | -9,952 | 6,906 | -5,228 | -12,705 | 2,249 | -1,268 | -5,968 | 3,432 |
| ≥ 198 | 665 | -7,852 | 9,182 | -3,040 | -10,613 | 4,533 | 920 | -3,932 | 5,772 |
| Randomization | | | | | | | | | |
| Day of week | | | | | | | | | |
| Weekday (Mon-Fri) | 2,958 | -10,053 | 15,969 | 4,053 | -6,514 | 14,620 | -951 | -3,721 | 1,819 |
| Weekend (Sat-Sun) | 701 | -8,790 | 10,192 | 1,796 | -3,900 | 7,492 | -3,208 | -11,821 | 5,405 |
| Time of day | | | | | | | | | |
| Day (08:00 to 19:59) | 3,356 | -8,046 | 14,758 | -105 | -9,518 | 9,308 | -1,036 | -3,858 | 1,786 |
| Night (20:00 to 07:59) | 2,245 | -6,101 | 10,591 | -1,215 | -6,531 | 4,101 | -2,147 | -9,547 | 5,253 |
| Time from ED presentation to first IV antimicrobial agents[h] (minutes) | | | | | | | | | |
| < 51 | -2,005 | -10,647 | 6,637 | -6,266 | -10,545 | -1,987 | -- | -- | -- |
| 51-90 | 3,703 | -6,903 | 14,309 | -558 | -5,210 | 4,094 | -- | -- | -- |
| ≥ 100 | 6,740 | -4,030 | 17,510 | 2,479 | -2,534 | 7,492 | -- | -- | -- |
| Intensity of underlying care | | | | | | | | | |
| Standardized vasopressor use | | | | | | | | | |
| 1 (lowest use) | 594 | -4,992 | 6,180 | -7,127 | -11,360 | -2,894 | -1,892 | -6,846 | 3,062 |
| 2 (intermediate use) | 1,610 | -7,205 | 10,425 | -6,111 | -14,135 | 1,913 | -876 | -5,682 | 3,930 |

| Subgroup | ProCESS | | | ARISE | | | ProMISe | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | Lower CI | Upper CI | Mean | Lower CI | Upper CI | Mean | Lower CI | Upper CI |
| 3 (highest use) | 1,403 | -7,077 | 9,883 | -6,318 | -13,968 | 1,332 | -1,083 | -5,238 | 3,072 |
| Standardized fluid volume use | | | | | | | | | |
| 1 (lowest use) | -3,836 | -11,898 | 4,226 | -2,200 | -5,542 | 1,142 | -1,140 | -6,462 | 4,182 |
| 2 (intermediate use) | -4,004 | -14,953 | 6,945 | -2,368 | -10,496 | 5,760 | -1,308 | -6,565 | 3,949 |
| 3 (highest use) | -3,956 | -14,323 | 6,411 | -2,321 | -9,649 | 5,007 | -1,260 | -5,166 | 2,646 |

These results are for the time horizon of 90 days post-randomization. Values are incremental net benefit in USD ($), expressed at $100,000 per QALY

QALY – quality-adjusted life-year; ProCESS – Protocolized Care for Early Septic Shock; ARISE – Australasian Resuscitation in Sepsis Evaluation; ProMISe – Protocolised Management in Sepsis; CI – confidence interval; APACHE II – Acute Physiology and Chronic Health Evaluation II; SOFA – Sequential Organ Failure Assessment; ED – emergency department; IV – intravenous.

[a] Please see Table S1 for details on data harmonization

[b] Age estimated for seven patients in ProMISe

[c] ProCESS assigned all positive blood cultures to the most likely anatomic source

[d] Includes patients whose site of infection was in the central nervous system or were determined ultimately to have no infection

[e] Three patients did not meet the refractory hypotension or hyperlactatemia eligibility criteria

[f] Scores on the APACHE II Acute Physiology range from 0 to 60, with higher scores indicating greater severity of illness. Scores on the APACHE II range from 0 to 71, with higher scores indicating greater severity of illness

[g] Scores on the SOFA range from 0 to 24, with higher scores indicating a greater degree of organ failure

[h] Only for patients who received IV antimicrobial agents prior to randomization (ProCESS, ARISE); all patients in ProMISe received antimicrobial agents prior to randomization – time not recorded

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