The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial statistical analysis plan

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Introduction

The Australasian Resuscitation In Sepsis Evaluation (ARISE) study is an international, multicentre, randomised, controlled trial designed to evaluate the effectiveness of early goal-directed therapy (EGDT), compared with standard care, for patients presenting to the emergency department (ED) with severe sepsis. In keeping with current practice,[1-5] and taking into consideration aspects of trial design and reporting that are specific to non-pharmacological interventions,[6,7] our plan for statistical analysis outlines the principles and methods for analysing and reporting the trial results, updating and elaborating on the statistical methods as described in the trial protocol (see http://www.arise.org.au).

This plan has been prepared before completion of patient recruitment into the ARISE study, without knowledge of the results of the interim analysis conducted by the data safety and monitoring committee (DSMC), and before completion of the two related international studies (the Protocolised Care for Early Septic Shock [ProCESS] and Protocolised Management in Sepsis [ProMISe] trials) conducted in the United States and the United Kingdom, respectively. The ARISE trial is funded by the National Health and Medical Research Council (grants 491075 and 1021165) and is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12608000053325) and the US National Institutes of Health registry ClinicalTrials.gov (NCT00975793). The trial protocol and the expanded statistical analysis plan can be accessed via the ARISE website (http://www.arise.org.au).

Population

Trial centres

Expressions of interest to participate in the ARISE trial have been sought by coordinating centres before trial commencement and throughout the recruitment period. To be included, sites need to be able to provide EGDT, ie, medical and nursing staff from the ED and/or the intensive care unit who are skilled in all procedural aspects of EGDT delivery, and a critical care environment where EGDT can be delivered for 6 hours. Trial centres are encouraged to provide these components 24 hours per day, 7 days per

ABSTRACT

Background: The Australasian Resuscitation in Sepsis Evaluation (ARISE) study is an international, multicentre, randomised, controlled trial designed to evaluate the effectiveness of early goal-directed therapy compared with standard care for patients presenting to the emergency department with severe sepsis.

Objective: In keeping with current practice, and considering aspects of trial design and reporting specific to non-pharmacological interventions, our plan outlines the principles and methods for analysing and reporting the trial results. The document is prepared before completion of recruitment into the ARISE study, without knowledge of the results of the interim analysis conducted by the data safety and monitoring committee and before completion of the two related international studies.

Methods: Our statistical analysis plan was designed by the ARISE chief investigators, and reviewed and approved by the ARISE steering committee. We reviewed the data collected by the research team as specified in the study protocol and detailed in the study case report form. We describe information related to baseline characteristics, characteristics of delivery of the trial interventions, details of resuscitation, other related therapies and other relevant data with appropriate comparisons between groups. We define the primary, secondary and tertiary outcomes for the study, with description of the planned statistical analyses.

Results: We have developed a statistical analysis plan with a trial profile, mock-up tables and figures. We describe a plan for presenting baseline characteristics, microbiological and antibiotic therapy, details of the interventions, processes of care and concomitant therapies and adverse events. We describe the primary, secondary and tertiary outcomes with identification of subgroups to be analysed.

Conclusion: We have developed a statistical analysis plan for the ARISE study, available in the public domain, before the completion of recruitment into the study. This will minimise analytical bias and conforms to current best practice in conducting clinical trials.

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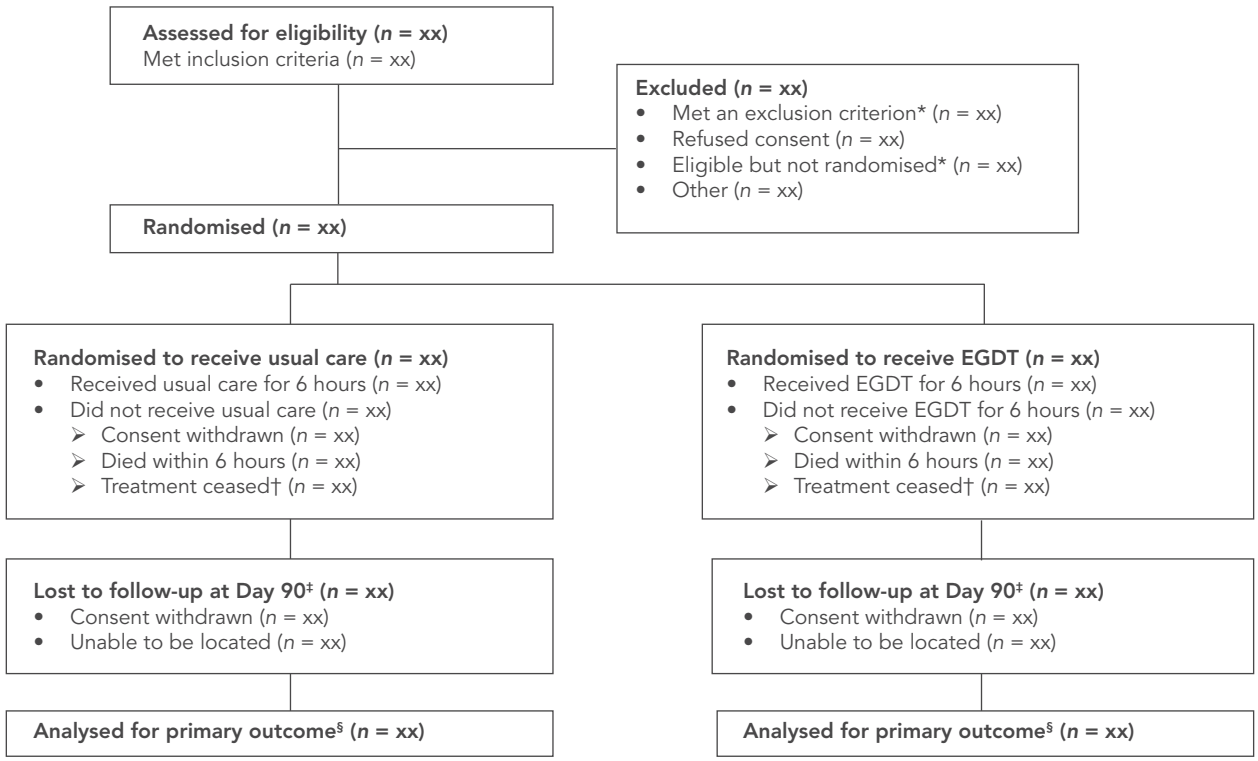
Figure 1. Flow of participants through the Australasian Resuscitation in Sepsis Evaluation trial



EGDT = early goal-directed therapy. * Exclusion criteria met (reasons for eligible patients not being enrolled will be shown in supplementary Table X). † Reasons for non-completion of 6 hours' therapy for each group will be shown in supplementary Table X. ‡ Trial participants for whom the primary outcome was not available. § Trial participants for whom the primary outcome was available.

week, although we emphasise maintaining compliance with the trial protocol over extending the hours of potential recruitment.

Inclusion criteria

All inclusion criteria must be met in the ED within 6 hours of admission to the ED (defined as the triage time), and randomisation must occur within 2 hours of meeting the final physiological inclusion criterion. The inclusion criteria are:

- suspected or confirmed infection; *and*
- two or more systemic inflammatory response syndrome criteria;[8] *and*
- evidence of refractory hypotension *or* hypoperfusion:
  - refractory hypotension is confirmed by the presence of a systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 65 mmHg after a 1000 mL intravenous (IV) fluid challenge within 60 minutes;
  - hypoperfusion is confirmed by the presence of a blood lactate concentration ⩾ 4 mmol/L; *and*
- the first dose of IV antimicrobial therapy being commenced before randomisation.

Exclusion criteria

Patients with any of the following are excluded:

- age < 18 years
- contraindication to insertion of a central venous catheter (CVC) in the superior vena cava
- contraindication to receiving blood products
- inability to commence EGDT within 1 hour of randomisation or to complete 6 hours of EGDT
- haemodynamic instability due to active bleeding
- pregnancy (confirmed or suspected)
- inpatient transfer from another acute health care facility
- underlying disease process with a life expectancy < 90 days
- death is deemed imminent and inevitable
- documented "limitation of therapy" order restricting implementation of the study protocol, or the treating clinician deems aggressive care unsuitable.

Aim and hypotheses

The aim of the trial is to determine whether EGDT, compared with standard care, is associated with a reduction in 90-day all-cause mortality in patients presenting to the ED

Table 1. Data collection in the Australasian Resuscitation in Sepsis Evaluation trial case report form

Time and type of data	Data
Randomisation	Patient demographics, eligibility criteria, exclusion criteria
Baseline	Patient demographics (date of birth, sex, weight, usual place of residence, chronic comorbidity score based on the Charlson comorbidity index), concurrent acute medical conditions, vital signs (temperature; heart rate; blood pressure; respiratory rate; central venous pressure (CVP); oxygen saturation; urine output; Glasgow coma scale score; arterial blood gas (ABG); lactate; biochemical, haematological and coagulation measurements; vasopressor administration; total intravenous (IV) fluids administered before randomisation, including IV fluids administered in prehospital setting; time of randomisation
Intervention period (0 hours – 6 hours)	Hourly vital signs including oxygen saturation; CVC; mean arterial pressure; central venous oxygen saturation ($ScvO_2$); haematocrit; ABG; biochemical, haematological and coagulation measurements; fluid therapy; blood product, vasoactive and sedative medication administration; neuromuscular paralysis; details of personnel delivering early goal-directed therapy
Invasive monitoring and cointerventions	Time and date of insertion of invasive monitoring devices (arterial catheter, central venous catheter (CVC), CVC with $ScvO_2$ monitoring, peripheral arterial continuous cardiac output monitoring, pulmonary artery catheter, other vascular catheter); surgical intervention for source control; activated protein C; corticosteroid therapy; coenrolment in another clinical trial
24 hours – 72 hours	Vital signs; ABG; biochemical, haematological and coagulation results; fluid therapy; blood products; vasoactive medications
Microbiological data	Date and time of antimicrobial therapy given (within initial 72 hours), positive cultures, resistance patterns of positive cultures, primary source of sepsis
Outcomes	Vital status at Day 28 and Day 90; date, place and cause of death; requirement for and duration of invasive mechanical ventilation, non-invasive ventilation, vasopressor support and renal replacement therapy; emergency department vital status, and discharge date, time and destination; requirement for intensive care unit admission; ICU discharge date, time and vital status; opinion of the principal investigator on whether the patient would have been admitted to the ICU if not enrolled in the study; hospital discharge date, time, destination and vital status
Protocol deviations	Ineligible patients randomised, early goal-directed therapy not delivered as planned, and the reasons for deviation from protocol
Adverse events and serious adverse events	Description of adverse events (complications related to CVCs and arterial catheters, acute pulmonary oedema, acute myocardial infarction, arrhythmia, blood transfusion reaction, other), severity of adverse events and relation to treatment

with severe sepsis. The null hypothesis is that there is no difference in 90-day all-cause mortality between patients with severe sepsis presenting to the ED who are randomised to receive either EGDT or standard care.

Definitions of outcomes

Primary outcome

The primary outcome of the trial is all-cause mortality measured at 90 days after randomisation. Minimal loss to follow-up is anticipated and missing values will not be imputed.

Secondary outcomes

The secondary outcomes include:

- survival time from randomisation to Day 90
- cause-specific mortality within the 90-day follow-up period. The primary cause of death will be classified as:[9]
  - cardiovascular: septic shock
  - cardiovascular: arrhythmia
  - cardiovascular: hypovolaemic shock
  - cardiovascular: cardiogenic shock
  - respiratory: hypoxic respiratory failure
  - metabolic
  - neurological
  - other
- duration of stay in the ED (hours)
- duration of ICU stay (days)
- duration of hospital stay (days)
- requirement for and duration of mechanical ventilation postrandomisation
- requirement for and duration of vasopressor support postrandomisation
- requirement for and duration of renal replacement therapy postrandomisation.

Tertiary outcomes

The tertiary outcomes include:

- 28-day all-cause mortality
- mortality at ICU discharge
- hospital mortality (censored at 60 days postrandomisation)
- proportion of trial participants with a limitation of medical treatment order at the time of death
- destination at hospital discharge, for trial participants who survive to hospital discharge.

Table 2. Baseline characteristics to be collected from trial participants

Baseline characteristics	
Age	Laboratory values
Sex	pH
Weight	$PaCO_2$
APACHE II score	Bicarbonate
Usual residence	Lactate
Home	Creatinine
Long-term care facility	Bilirubin
Chronic comorbidity variables	Glucose
Cardiovascular	Haemoglobin
Central nervous system	White cell count
Renal	Platelet count
Liver	International normalised ratio
Respiratory	Treatment before randomisation
Endocrine	Time from ED presentation to first dose of IV antibiotics
Gastrointestinal	Time from ED presentation to randomisation
Haematological or oncological	Mechanical ventilation
Immunological	Vasopressor support
Connective tissue	Total IV fluids
Physiological variables	
Temperature	
Heart rate	
Mean arterial pressure	
Central venous pressure	
Respiratory rate	
Peripheral oxygen saturation	
Urine output	
Glasgow coma score	

Additional baseline variables (to be reported in a supplementary table)	
Acute concurrent medical disease	Active gastrointestinal bleeding
Cardiac arrhythmia	Seizure
Acute pulmonary oedema	Drug overdose
Acute coronary syndrome	Burn injury
Cerebrovascular accident	Trauma
Status asthmaticus	Neutrophil count $< 0.5 \times 10^9$/L

APACHE = Acute Physiology and Chronic Health Evaluation. ED = emergency department. IV = intravenous.

Safety variables

There are several potential adverse effects associated with treatments that are essential components of EGDT. The safety variables include the numbers and proportions of trial participants who experience:

- a serious adverse event other than death
- complications of CVC insertion, including:
  - bleeding
  - pneumothorax
  - arterial puncture
  - venous thrombosis
  - CVC-related bloodstream infection
- arterial thrombosis as a complication of arterial line insertion
- within 72 hours of randomisation:
  - acute pulmonary oedema
  - acute myocardial infarction
  - a blood transfusion reaction.

Design

Sample size

ARISE is a multicentre, unblinded, randomised controlled trial.

The sample size calculation assumes a baseline hospital mortality rate in the control group of 28%[10-12] with an additional subsequent mortality of 10%, leading to a 90-day mortality of 38%.[13,14] Based on these figures, a trial of 1600 evaluable participants has a power of 85%–90% (α = 0.05) to exclude a 7.6% absolute risk reduction (20% relative risk reduction) associated with EGDT implementation, allowing for the plausible ranges of loss to follow-up. These are conservative estimates relative to the 12.6% absolute risk reduction reported at 60 days in the original EGDT trial.[15]

Consent

Due to the specific nature of the trial, prior informed consent is not always possible; in these circumstances, where allowed under appropriate regional legislation, and when approved by the appropriate human research ethics committee, the patient or their legal surrogate are asked for delayed consent. Two situations may result in cessation of trial treatment:

- the patient or legal surrogate may withdraw consent to participate in the trial; or
- the patient or legal surrogate may refuse consent to continue trial treatments from the time delayed consent is sought.

In both cases, trial treatment will cease and the patient will continue therapy as prescribed by the treating medical team. When this situation occurs, consent to data already collected is sought, and if this consent is withheld, the patient's data are removed from the analysis, apart from data related to randomisation and consent. For trial participants who refuse consent to ongoing study treatment, but allow use of data already collected, their data will be included and analysed on an intention-to-treat basis. Vital status at Day 28 and Day 90 will not be imputed if missing.

Randomisation and treatment allocation

Eligible patients are randomly allocatted in a 1:1 ratio to receive either usual care (as determined by the treating clinicians) or EGDT. Randomisation uses a permuted block method with variable block sizes and stratification by site. Allocation concealment is maintained using a centralised telephone interactive voice response system which is accessible 24 hours per day.

Data collection and follow-up

Table 1 shows a summary of the data collected in the case report form.

Table 3. Microbiological and antibiotic therapy variables to be collected from trial participants

Medical infection site
Respiratory tract
Urinary tract
Soft tissue
Central nervous system
Blood
Other
Surgical infection site
Intra-abdominal
Soft tissue
Other
Positive cultures
Blood
Respiratory tract
Urine
Soft tissue
Cerebrospinal fluid
Other
Causative organism
Gram-positive
Gram-negative
Fungal
Parasitic
Viral
Other
Culture-negative
Multidrug-resistant
Time from emergency department presentation to first dose of antimicrobial agent appropriate for presumed causative organism

Interim analysis

Unblinded data on patient characteristics, compliance with the trial protocol and study outcomes are regularly reviewed by an independent DSMC, chaired by an experienced clinical researcher without other connection to this research trial. The terms of reference of the DSMC are to advise the trial steering committee whether the results of all available evidence provide both:

- "proof beyond reasonable doubt" that, for all or some specific types of patients, EGDT is clearly indicated or contraindicated in terms of an overall difference in 90-day mortality; and
- evidence that might reasonably be expected to materially influence the patient management of many clinicians who are already aware of the main results of any other clinical trials.

The DSMC has reviewed available outcome data from 200 trial participants and has reviewed data at least annually to assess potential safety issues and to review

compliance with the study protocol, without specific analysis of the primary outcome. A single, planned, formal interim analysis was performed once 90-day outcome data from the first 800 participants enrolled were available. The DSMC recommended continuation of enrolment.

Statistical analysis

Analysis principles

All analyses will be conducted on an intention-to-treat basis, with subjects retained in their original assigned groups, and will be unadjusted for the effects of other covariates except where indicated. There will be no imputation of missing values unless otherwise specified. Where there are missing observations, the number of observations used in the analysis will be reported. Subgroup analyses will be carried out irrespective of whether there is strong evidence of a treatment effect associated with the primary outcome. All tests will be two-sided and the nominal type I error (α) will be 5%. Significance levels (*P* values) will not be adjusted for multiplicity.

Trial profile

The flow of patients through the study will be displayed in a modified consolidated standards of reporting trials (CONSORT) diagram,[7] as shown in Figure 1. We will report the number of trial participants who met the inclusion criteria based on refractory hypotension, and the number of trial participants who met the inclusion criteria based on elevated lactate.

Participants and baseline comparisons

A description of the baseline characteristics of the trial participants will be presented by treatment group. Discrete variables will be summarised as numbers. Percentages will be calculated according to the number of trial participants for whom data are available. When values are missing, the denominator will be stated in the table or in a footnote to the corresponding summary table. Continuous variables will be summarised by standard measures of central tendency and dispersion, either mean and standard deviation for normally distributed variables, or median and interquartile range (IQR) for non-normally distributed variables. Baseline characteristics are detailed in Table 2, and Table 3 shows microbiological and antibiotic therapy data.

Interventions, process measures and concomitant treatments

Sites

We will report details of the care providers and centres involved in the study, including details of the medical and nursing teams involved in delivery of the EGDT.[6] We will report the following details for each site involved in the trial in a supplementary table:

- country
- hospital type
- number of hospital beds
- number of ED presentations per year
- members of the ARISE team
- location of EGDT delivery
- recruitment period
- total number of trial participants.

Treatments

We will present details of all resuscitation-specific therapies delivered in the first 6 hours, and up to 72 hours, after randomisation. Categorical variables will be summarised as number and percentage, and the two groups will be compared using the Fisher exact test. Continuous variables will be summarised using the same measures of central tendency and dispersion: mean and SD for normally distributed variables, and median and IQR for non-normally distributed variables. The continuous variables will be compared using student *t* tests or Wilcoxon rank-sum tests as appropriate.

We will present the following measures of resuscitation treatment from randomisation (T0) to Hour 6 (T6), and from Hour 7 (T7) to 72 hours (T72) after randomisation, as number and percentage, as well as time from randomisation, where appropriate:

- supplemental oxygen
- requirement for non-invasive mechanical ventilation
- requirement for invasive mechanical ventilation
- volume of IV fluids
- blood products
  - red cell transfusion
  - platelets
  - fresh frozen plasma
  - other
- volume of red blood cell transfusion
- vasopressor use
- dobutamine use
- surgical intervention for source control
- corticosteroid therapy
- arterial line insertion
- CVC insertion
- CVC with continuous central venous oxygen saturation ($ScvO_2$) monitoring
- pulse contour cardiac output catheter insertion (PiCCO)
- pulmonary artery catheter insertion
- the intended location of care after ED discharge (determined by the treating ED clinician) if the patient had not been enrolled into the ARISE trial (ie, ICU, high dependency unit, general ward).

Resuscitation goals and end points

We will produce graphs showing the mean and SD for each of the primary EGDT resuscitation goals (Spo_2, central venous pressure [CVP], MAP and $Scvo_2$) each hour for the initial 6-hour period for both treatment groups. We will also report the number and percentage of trial participants randomised to receive EGDT who achieve the resuscitation goals at each time point, using the total number of trial participants with data available for the denominator at each time point. We will report (by treatment group) physiological and laboratory values at the end of the 6-hour intervention period and at 72 hours, as detailed below, with the denominators for each being the number of trial participants with data available:

- Spo_2
- heart rate
- MAP
- CVP
- $Scvo_2$
- lactate level
- bicarbonate level
- pH
- haemoglobin level
- international normalised ratio
- activated partial thromboplastin time.

We will also report compliance with the EGDT resuscitation algorithm for patients not meeting the primary resuscitation goals (Spo_2, CVP, MAP and $Scvo_2$) for patients randomised to receive EGDT.

Consent and permanent discontinuation of trial treatment

We will report consent data (number and percentage for each category) for the following groups:

- prior informed consent obtained from trial participant
- prior informed consent obtained from legal surrogate
- delayed consent obtained from trial participant
- delayed consent obtained from legal surrogate
- consent obtained from other legal body before or after trial participant's death
- no consent obtained; data withdrawn.

We will report data (number and percentage for each category) for the following categories of trial participants for whom study treatment was permanently discontinued:

- informed consent was withdrawn
- informed consent was withheld
- treatment was discontinued due to transfer to the operating theatre and EGDT unable to be continued
- study treatment was discontinued due to transfer to another hospital during the 6-hour EGDT period
- treatment was discontinued due to cardiopulmonary arrest
- treatment was discontinued for other reason.

Analyses

Primary outcome

A Fisher exact test will be used to assess the effect of treatment allocation on 90-day all-cause mortality. The numbers at risk in each group and the number and proportion of events observed will be reported, as well as the equivalent absolute risk difference and relative risk ratio, and each corresponding 95% confidence interval.

Secondary and tertiary outcomes

We will report, as secondary outcomes, effect estimates derived from multivariable logistic regression models with 90-day all-cause mortality as the dependent variable. These models will adjust for the independent baseline covariates of age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, SBP < 90 mmHg, use of invasive mechanical ventilation, and country. We will also perform additional sensitivity analyses incorporating other covariates if they exhibit an apparent baseline imbalance between the two treatment groups. If more than 5% of the 90-day all-cause mortality primary outcome data are missing, sensitivity analyses will be performed to estimate the dependency of the reported effect estimates on the pattern of missing data.

Survival time from randomisation until Day 90, according to treatment group, will be displayed as Kaplan–Meier curves and analysed using a log-rank test. Estimates of hazard ratios for survival, with corresponding 95% CI and *P* values, will be obtained from Cox proportional hazards models incorporating the treatment group alone, and also the independent covariates used in the multivariable logistic models as detailed above.

The durations of ED and hospital stay will be calculated from the time of randomisation respectively, and the duration of ICU stay will be calculated from the time of ICU admission. These durations will be summarised as median and IQR, and compared between treatment groups using a Wilcoxon rank-sum test. Similar analyses will occur for the duration of mechanical ventilation, vasopressor support and renal replacement therapy.

The proportional use of mechanical ventilation, vasopressor support and renal replacement therapy after randomisation will be presented in each treatment group, with the effect of treatment allocation on the relative risk for each outcome assessed using Fisher exact tests with corresponding 95% CI and *P* values. Differences between treatment groups regarding cause-specific mortality and destination at hospital discharge will be compared using Fisher exact tests and corresponding 95% CIs.

The estimated differential mortality at 28 days, ICU discharge and hospital discharge (censored at 60 days), by treatment group, will be presented as absolute risk differ-

ences, relative risk ratios and corresponding 95% CIs, with these differences assessed using Fisher exact tests. The proportion of trial participants with a limitation of medical treatment order at the time of death in each treatment group will be presented similarly and compared using a Fisher exact test. Additionally, analyses adjusted for the same variables as the primary outcome will be performed for the secondary and tertiary outcomes as subsidiary analyses. These will be based on linear, logistic or Cox regression models as appropriate.

Safety outcomes and adverse events

The occurrence of adverse events, as summarised above under Safety variables, will be presented as frequencies and proportions per treatment group. The differences in proportions of trial participants in each group experiencing each event will be compared using relative risks, 95% CIs and Fisher exact tests. There will be no adjusted analyses performed for the adverse events.

Subgroup analysis

Potential heterogeneity of the primary end point (90-day all-cause mortality) will be assessed using logistic regression with treatment group and the subgroup identifier incorporated as main effects, with a multiplicative interaction term. All such subgroup analyses will be exploratory, and the potential low power of such tests to find evidence of significant interactions is acknowledged.

The number of deaths, the total number of trial participants in the subgroup, the estimate of the odds ratio and the 95% CI for each category will be presented along with the *P* value for the interaction test. The subgroup analyses representing those covariates incorporated in the secondary analyses, as well as three further binary categories noted below, will be presented as a forest plot.

Pre-identified subgroup analyses will be:

- age (dichotomised at 65 years)
- APACHE II score ≥ 25 or < 25
- requirement for invasive mechanical ventilation
- refractory hypotension (SBP < 90 mmHg or MAP < 65 mmHg after a 1000 mL IV fluid challenge within 60 minutes)
- hypoperfusion (lactate ≥ 4 mmol/L)
- trial participants who received ≥ 20 mL/kg of IV fluid for resuscitation before randomisation compared with those with < 20 mL/kg
- country.

Tables and figures

Planned figures are:

- a CONSORT-style diagram illustrating the flow of patients through the study
- line graphs showing the hourly mean and SD, Spo_2, CVP, MAP and $Scvo_2$ for each treatment group from T0–T6 after randomisation, the number and percentage of trial participants achieving the resuscitation goals at each time point, and the number and percentage of trial participants in whom the EGDT resuscitation algorithm was not followed when the physiological goals were not achieved (for patients randomised to receive EGDT)
- a forest plot of OR for death at 90 days after randomisation for all trial participants, according to treatment allocation and the a-priori subgroups as described above under Subgroup analysis
- a Kaplan–Meier curve showing survival to 90 days after randomisation, according to treatment group.

Planned tables include:

- baseline characteristics of the trial participants, according to study group
- source of infection, positive cultures, organisms and time to appropriate antibiotics, according to study group
- therapies received and invasive monitoring performed in the first 72 hours after randomisation, according to study group
- resuscitation goals, physiological, biochemical and haematological parameters at 6 hours and 72 hours after randomisation, according to study group
- primary, secondary and tertiary outcomes, according to study group
- adverse events until 72 hours after randomisation, according to study group.

Additional tables will include:

- baseline concurrent diseases, according to study group
- most commonly cultured specific organisms, according to study group.

Control of type 1 error

A twin-boundary symmetric O'Brien–Fleming design was used for the single interim analysis, with a two-sided *P* value of 0.005, meaning that for the final analysis, a *P* value of 0.0491 will be used to allow the overall type I error to remain at 5%.

Future analyses

We plan to use the data collected in the trial to contribute to an economic analysis to assess the cost–utility of EGDT compared with usual care, with quality-of-life follow-up continued for 12 months after randomisation. We will also use data collected in this trial to contribute to an individual patient data meta-analysis, where the data will be combined with data from the ProCESS and ProMISe studies.[16] Further hypothesis-generating exploratory analyses beyond

those described above may occur with future analyses of these important clinical datasets.

Competing interests

None declared.

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Appendix. The Australasian Resuscitation in Sepsis Evaluation investigators

Steering committee

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The Alfred Hospital, Melbourne, Victoria: P Cameron, DJ Cooper, V Bennett
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Auckland City Hospital, Auckland, New Zealand: P Jones, F Sawtell, K Schimanski
Austin Health, Melbourne, VIC: R Bellomo, F Kerr, L Peak
Bendigo Hospital, Bendigo, VIC: J Edington, J Fletcher, J Smith
Blacktown Hospital, Sydney, New South Wales: D Ghelani, K Nand, T Sara
Box Hill Hospital, Melbourne, VIC: A Cross, M Grummisch, A Purdue
Canberra Hospital, Canberra, Australian Capital Territory: K Grove, I Mitchell, H Rodgers, E Fulton
Central Gippsland Health Service, Sale, VIC: J Dennett, T Coles, R Ziffer
Christchurch Hospital, Christchurch, New Zealand: S Barrington-Onslow, S Henderson, J Mehrtens
Coffs Harbour Base Hospital, Coffs Harbour, NSW: A Tankel
Dandenong Hospital, Melbourne, VIC: G Braitberg, B O'Bree, K Shepherd, S Vij
Frankston Hospital, Melbourne, VIC: K Haji, L Goh, S Allsop
Geelong Hospital, Geelong, VIC: A Bone, N Orford, M Ragg
Gosford Hospital, Gosford, NSW: S Kelly, D Stewart, N Woodward
Helsinki University Hospital, Helsinki, Finland: V Pettila, S Sutinen, M Abo
Hornsby Hospital, Sydney, NSW: J Fratzia, J Halkhoree, T Solano, S Treloar
Ipswich Hospital, Ipswich, Queensland: K Ryan, T Sandford, J Walsham
John Hunter Hospital, Newcastle, NSW: C Jenkins, D Williamson
Joondalup Health Campus, Perth, Western Australia: S Brown, D Hawkins, C Tang
Liverpool Hospital, Sydney, NSW: A Dimakis, A Holdgate, M Parr
Logan Hospital, Meadowbrook, QLD: H White, L Morrison, K Sosnowski
Lyell McEwin Hospital, Adelaide, South Australia: R Ramadoss, J Wood
Manly Hospital, Sydney, NSW: M Franks
Middlemore Hospital, Auckland, New Zealand: T Williams, C Hogan
Modbury Hospital, Adelaide, SA: R Wells
Monash Medical Centre, Melbourne, VIC: P Galt, D Lightfoot, T Lamac
Nepean Hospital, Sydney, NSW: K Braid, T Clarke, I Seppelt
Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong: R Lam, S Lam, W Yan
Port Macquarie Base Hospital, Port Macquarie, NSW: A Altea, B Lancashire
Prince of Wales Hospital, Shatin, Hong Kong: C Gomersall, C Graham, P Leung
Prince of Wales Hospital, Sydney, NSW: S Arora, F Bass, Y Shehabi
Princess Alexandra Hospital, Brisbane, QLD: K Isoardi, S Lawrence
Royal Adelaide Hospital, Adelaide, SA: A Ankor, L Chester, S O'Connor, K Sundararajan
Royal Brisbane and Women's Hospital, Brisbane, QLD: J Williams, J Greenslaid
Royal Melbourne Hospital, Melbourne, VIC: C MacIsaac, A Jordan, T Caf
Royal North Shore Hospital, Sydney, NSW: S Bird, A O'Connor, A Delaney
Royal Perth Hospital, Perth, WA: J Chamberlain, S Webb
Royal Prince Alfred Hospital, Sydney, NSW: H Buhr, D Gattas, D Rajbhandari
Sir Charles Gairdner Hospital, Perth, WA: S Baker, B Roberts
St Vincent's Hospital, Melbourne, VIC: E Faraone, J Holmes, C Winter
St Vincent's Hospital, Sydney, NSW: P Nair, C Reynolds
St Vincent's University Hospital, Dublin, Ireland: A Nichol
Sydney Adventist Hospital, Sydney, NSW: R Harris, L Shields
Tampere University Hospital, Tampere, Finland: A Kuitunen, J Tenhunen, S Karlsson, S Varila
Tamworth Hospital, Tamworth, NSW: J Burrows, N Ryan, C Trethewy
Townsville Hospital, Townsville, QLD: G Gordon, S Reeves
Western Hospital, Melbourne, VIC: S Bates, J Butler, C French
Westmead Hospital, Sydney, NSW: J Kwans, M Murphy, D O'Flynn
The Queen Elizabeth Hospital, Adelaide, SA: C Kurenda, S Peake, P Williams
The Queen Elizabeth Hospital, Hong Kong: A Leung, Hiu Fai Ho.