

Statistical analysis plan for the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial

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The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial will be the largest study to date of corticosteroid therapy in patients with septic shock.¹ We describe the pre-specified statistical analysis plan (SAP), finalised before patient enrolment is completed (expected by May 2017) and the database is locked for analysis.

This SAP was written by the trial statistician and the principal investigator, both of whom are blinded to the treatment allocation. All analyses specified in this SAP have been defined prospectively.

Study design

The ADRENAL trial is a multicentre, randomised, concealed, parallel-group trial comparing the administration of intravenous (IV) hydrocortisone with placebo in patients with septic shock. A total of 3800 patients will be enrolled at 69 study sites. Eligible patients will be randomised to receive hydrocortisone 200 mg per day or placebo for 7 days.

The primary hypothesis is that the administration of hydrocortisone reduces 90-day all-cause mortality in patients admitted to an intensive care unit with septic shock, compared with placebo.

Patient population

Adult patients with septic shock receiving vasopressor and mechanical ventilator support are eligible for enrolment.

Inclusion criteria

The inclusion criteria are:

- age 18 years or older
- documented site of infection or strong suspicion of infection
- two of the four signs of the systemic inflammatory response syndrome (SIRS):²
 - core temperature > 38°C or < 36°C
 - heart rate > 90 beats/min
 - respiratory rate > 20 breaths/min, or $\text{Paco}_2 < 32$ mmHg, or treatment with mechanical ventilation
 - white cell count > $12 \times 10^9/\text{L}$, or < $4 \times 10^9/\text{L}$, or > 10% immature neutrophils
- treatment with mechanical ventilation, via an

ABSTRACT

Background: The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial, a 3800-patient, multicentre, randomised controlled trial, will be the largest study to date of corticosteroid therapy in patients with septic shock.

Objective: To describe a statistical analysis plan (SAP) and make it public before completion of patient recruitment and data collection. The SAP will be adhered to for the final data analysis of this trial, to avoid analysis bias arising from knowledge of study findings.

Methods: The SAP was designed by the chief investigators and statisticians and approved by the ADRENAL management committee. All authors were blind to treatment allocation and to the unblinded data produced during two interim analyses conducted by the Data Safety and Monitoring Committee. The data shells were produced from a previously published protocol. Statistical analyses are described in broad detail. Trial outcomes were selected and categorised into primary, secondary and tertiary outcomes, and appropriate statistical comparisons between groups are planned and described in a way that is transparent, available to the public, verifiable and determined before completion of data collection.

Results: We developed a standard SAP for the ADRENAL trial, and have produced a trial profile outline and list of mock tables. We describe analyses of baseline characteristics, processes of care, measures of efficacy and outcomes. Six pre-specified subgroups were defined, and statistical comparisons between groups in these subgroups are described.

Conclusion: We have developed an SAP for the ADRENAL trial. This plan accords with high-quality standards of internal validity to minimise analysis bias.

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endotracheal tube or non-invasively, at the time of randomisation

- treatment with vasopressors or inotropes to maintain a systolic blood pressure > 90 mmHg, or mean arterial blood pressure (MAP) > 60 mmHg, or an MAP target set

by the treating clinician for maintaining perfusion

- administration of vasopressors or inotropes for ≥ 4 hours and at time of randomisation.

Exclusion criteria

The exclusion criteria are patients:

- who met all inclusion criteria more than 24 hours earlier
- for whom the treating clinician expects to prescribe systemic corticosteroids, for an indication other than septic shock (excluding inhaled corticosteroids)
- who are receiving treatment with etomidate
- who are receiving treatment with amphotericin B for systemic fungal infections at time of randomisation
- who have documented cerebral malaria at the time of randomisation
- who have documented *Strongyloides* infection at the time of randomisation
- for whom death is deemed inevitable or imminent during this admission and either the attending physician or the patient or surrogate legal decision maker is not committed to active treatment
- for whom death from underlying disease is likely within 90 days
- who have previously been enrolled in the ADRENAL trial.

Randomisation and blinding

Randomisation will be conducted using a minimisation algorithm via a password-protected, encrypted, web-based interface, stratified according to participating site and an operative or non-operative diagnosis on admission to the ICU. After randomisation, each patient will be assigned a unique patient study number and a unique medication kit number. The unique medication kit number is matched to blinded study drug with sufficient supply to last a 7-day course of treatment. Patients, treating clinicians and study personnel are blinded to study treatment allocation.

Intervention

Trial participants will receive a continuous IV infusion of hydrocortisone 200 mg per day or placebo, for 7 days or until discharge from the ICU (whichever is earlier).

Primary outcome

The primary outcome is all-cause mortality 90 days after randomisation.

Secondary outcomes

The secondary outcomes are:

- all-cause mortality 28 days and 6 months after randomisation
- time to resolution of shock, defined as the time taken to achieve a clinician-prescribed MAP goal for > 24 hours without the use of vasopressors or inotropes

- recurrence of shock, defined as a new episode of haemodynamic instability requiring treatment with vasopressors or inotropes after reversal of the initial episode, where reversal is defined as being vasopressor-free and inotrope-free for at least 24 hours
- length of ICU stay
- length of hospital stay
- frequency and duration of mechanical ventilation, where cessation of mechanical ventilation is defined as not receiving any mode of positive pressure ventilation for 1 day; conversely, re-institution of mechanical ventilation is defined as the need for any mode of positive pressure ventilation after cessation of mechanical ventilation
- frequency and duration of renal replacement therapy (RRT)
- development of any new episodes of bacteraemia or fungaemia between 2 and 14 days after randomisation
- episodes of clinically important bleeding in the ICU, defined by the requirement for blood transfusion
- quality of life at 6 months after randomisation, using the EuroQol (five dimensions, five levels) (EQ-5D-5L) questionnaire.³

Safety outcomes

The safety outcomes are:

- adverse drug reactions
- serious adverse drug reactions
- suspected unexpected serious adverse reactions.

Sample size

The study population will be 3800 patients, calculated using 90% power to detect a 15% relative reduction, or 5% absolute risk reduction, in the risk of death from an estimated baseline mortality rate of 33%. The baseline mortality rate in the control population was based on data from sepsis surveys performed in Australia and New Zealand by the Australian and New Zealand Intensive Care Society Clinical Trials Group⁴ and the Catecholamine Comparison Trial study.⁵ These mortality rates are consistent with the mortality rates in the control arms of other international randomised controlled trials of septic shock.⁶⁻⁸ This study population allows for a potential withdrawal and loss to follow-up rate of 1%.

Statistical analysis

Analysis principles

Analysis principles are as follows:

- Analyses will be conducted on an intention-to-treat basis (ie, analysing all patients according to the group to which they were assigned, regardless of treatment compliance).
- All tests will be two-sided and the nominal level of statistical significance (α) will be 5%.

- This analysis plan, and the primary manuscript, will only include analyses up to 90 days after randomisation.
- Analyses at 6 months after randomisation will be presented separately.
- Pre-specified subgroup analyses will be conducted regardless of whether statistically significant treatment effect on the primary outcome is observed in the overall sample.
- No formal adjustments for multiplicity of testing will be applied, but outcomes will be ordered by degree of importance (ie, primary versus secondary) and significant test results will be interpreted in light of the multiple comparisons made.
- The main analyses of primary and secondary outcomes will be adjusted for stratification variables (study centre and admission type).
- Continuous variables will be analysed using parametric methods (eg, *t* test or linear regression).
- Tests of normality will not be conducted.
- Analyses will be conducted primarily using SAS, version 9.3 or later.

Interim analyses

An independent Data Safety and Monitoring Committee (DSMC) has reviewed unblinded data to examine patient characteristics, treatment compliance, outcomes and adverse events, on two occasions (availability of primary outcome for 950 and 2500 patients). The DSMC charter is in Appendix 1 (online at cicm.org.au/Resources/Publications/Journal).

Datasets analysed

All analyses will be performed on the intention-to-treat population; that is, by analysing all patients according to the group to which they were randomised and regardless of protocol compliance. To comply with relevant laws, data for which consent is not obtained or is withdrawn will be excluded from the analyses.

Trial profile

The flow of patients through the trial will be shown using a Consolidated Standards of Reporting Trials diagram,⁹ as shown in Figure 1.

The report will include the number of screened patients who met study inclusion criteria, the number of patients who were included and reasons for exclusion of non-included patients. A separate figure will describe consent status (Figure 2).

Patient characteristics and baseline comparisons

A description of the baseline characteristics will be presented by treatment group, as outlined in the tables (see Appendix 2 online).

Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised using mean with standard deviation (SD) or median with quartiles (Q1–Q3).

Baseline measures for all patients will be tabulated for the following variables:

- sociodemographic and admission characteristics:
 - sex
 - age
 - weight
 - admission source
 - geographical region (Australia, New Zealand, United Kingdom, Denmark, Kingdom of Saudi Arabia)
 - time from ICU admission to randomisation
- vital signs and laboratory data (in the 24 hours before randomisation)
 - most recent core temperature
 - most recent heart rate
 - most recent central venous pressure (CVP)

Figure 1. CONSORT flowchart

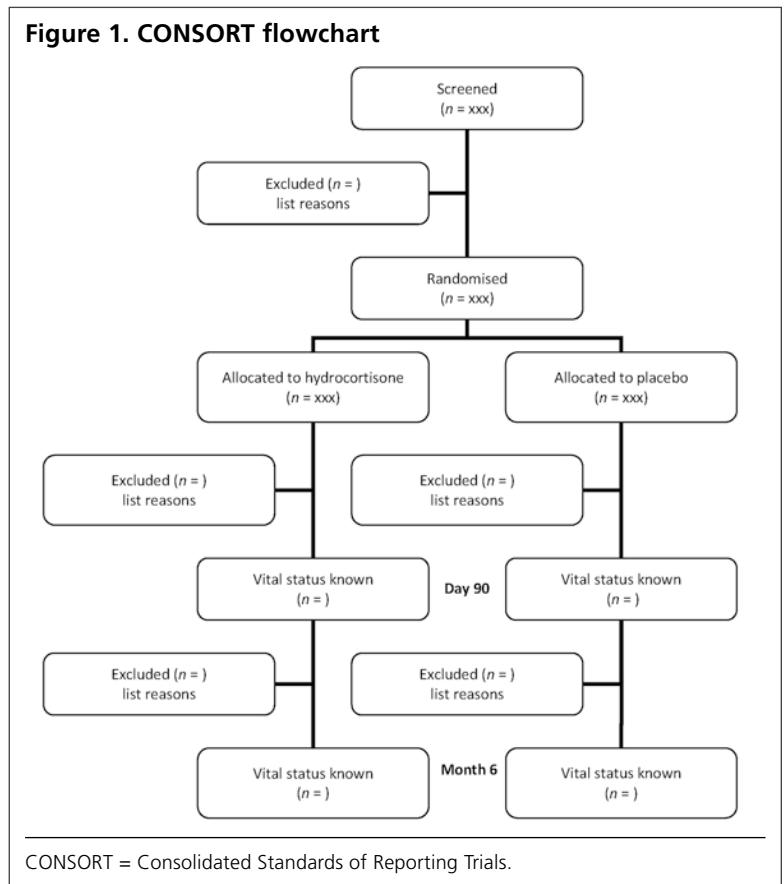
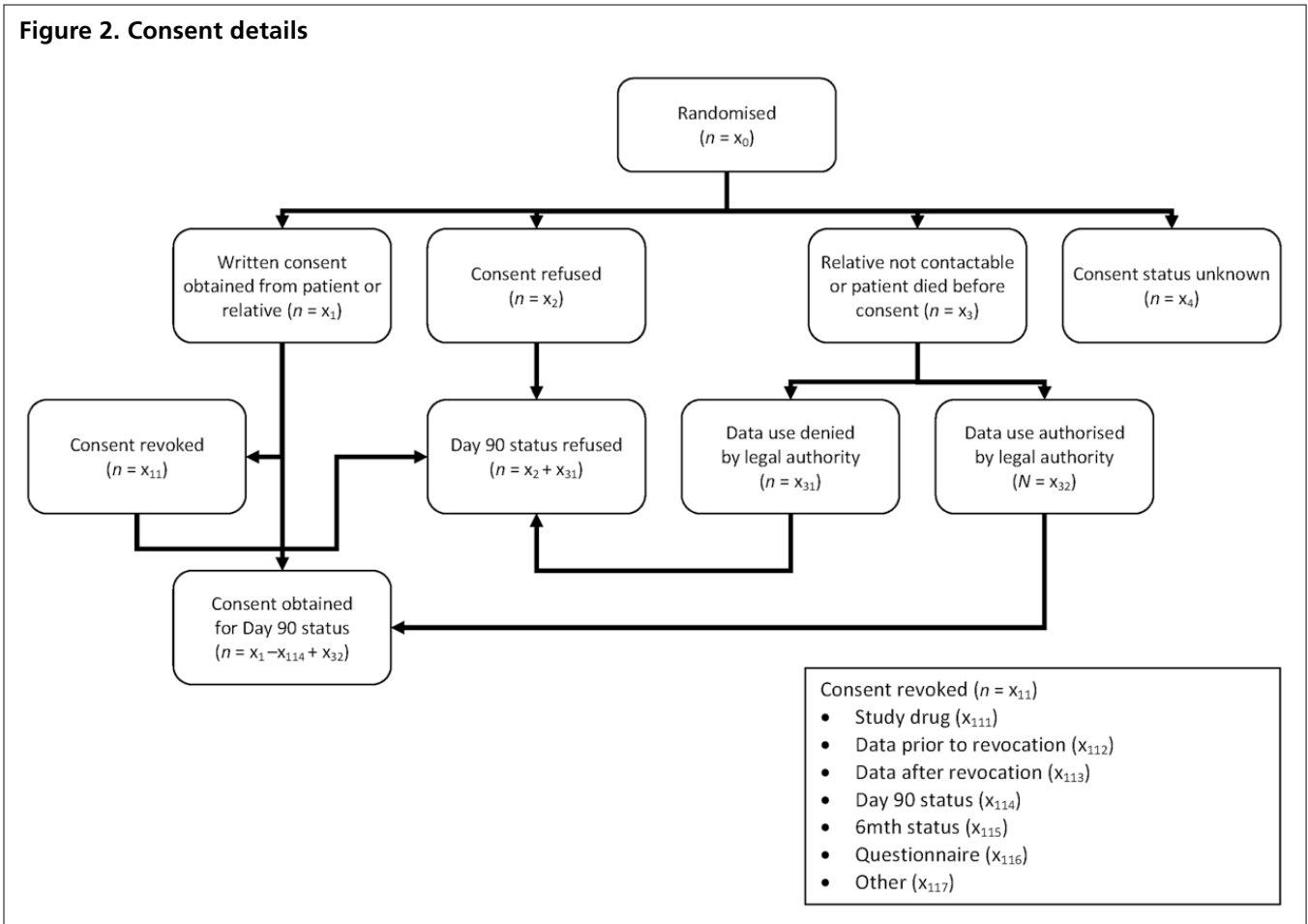


Figure 2. Consent details



- most recent MAP
- lowest MAP
- lowest Pao2:Flo2 ratio
- highest arterial lactate level
- highest plasma bilirubin level
- highest serum creatinine level
- lowest haemoglobin level
- highest white cell count
- lowest platelet count
- highest international normalised ratio:prothrombin ratio
- severity of illness (in the 24 hours before randomisation)
 - SIRS² (deranged value closest to randomisation)
 - APACHE (Acute Physiology and Chronic Health Evaluation) II score and chronic health categories (worst score)¹⁰
- concomitant therapy:
 - use of steroid therapy, defined as any IV dosing in the 24 hours before randomisation or a prescribed course of steroids for > 2 weeks in the past 12 months (yes/no)
 - inotropic and vasopressor drugs at the time of randomisation (yes/no)
- antimicrobial agents in the 24 hours before randomisation (yes/no)
- RRT in the 24 hours before randomisation (yes/no)
- dialysis for chronic renal failure in the 12 months before randomisation (yes/no)
- volume of packed red cells and/or whole blood in the 24 hours before randomisation (mL)
- use of HMG-CoA reductase inhibitor (statin) therapy for more than 14 days before randomisation and/or received a dose in the last 72 hours before randomisation (yes/no)
- primary admission diagnosis to the ICU for the index admission:
 - cardiovascular
 - respiratory
 - gastrointestinal
 - neurological
 - sepsis
 - trauma
 - metabolic
 - musculoskeletal or skin
 - gynaecological
 - haematological

- renal or genitourinary
- other
- site of infection
- inotropic and vasopressor drugs at the time of randomisation:
 - norepinephrine
 - epinephrine
 - dopamine
 - dobutamine
 - metaraminol
 - vasopressin
 - levosimendan
 - milrinone
 - other.

Analysis of compliance and concomitant therapies

Compliance with the administration of study drug

Compliance with study drug will be summarised using the following variables:

- time from randomisation to the first administration of study drug (minutes)
- time on study treatment, defined as the number of days between the first and last study drug administration
- cumulative dose of study drug received (mg or mg equivalent)
- cumulative dose duration (hours)
- overall compliance, defined as the number of doses given divided by the number of expected doses (a dose will be expected if the patient is alive and in the ICU)
- reasons for not receiving study drug.

Time from randomisation to administration of study drug, time on study treatment, cumulative dose, cumulative duration and overall compliance will be summarised using means and SDs, and medians and quartiles, with differences between treatment groups tested using a *t* test.

Reasons for not receiving the study drug will be summarised, by reason, as the proportion of patients selecting the reason at least once.

Protocol deviations

Protocol deviations will be summarised as the number of deviations by type (randomisation of ineligible patient, failure to comply with study treatment, and other). All protocol deviations will be listed with a description of the deviation and the corrective action taken.

Concomitant therapies

The following concomitant therapies will be summarised:

- inotropic and vasopressor drugs
- HMG-CoA reductase inhibitors
- open-label corticosteroids
- etomidate
- antibiotics.

The number and proportion of patients receiving each therapy during the first 90 days (28 days for antimicrobials) will be summarised, with differences between treatments tested using the Fisher exact test.

Laboratory tests and vital signs

Heart rate, MAP, CVP and arterial lactate level (last available values on the chart day) will be summarised as means and SDs, medians and quartiles, and minimums and maximums for each day between Day 1 and Day 14. Means and 95% confidence intervals over time will be presented, by treatment, using longitudinal plots. The overall mean difference (and 95% CI) between treatment arms will be calculated using a repeated-measure, linear mixed model including a random centre effect. Fixed effects will include the baseline value of the parameter, the allocated treatment, admission type, study day (as a categorical variable) and the interaction between treatment and study day. Within-patient correlations will be modelled via a repeated effect with an unstructured covariance matrix or, in case of convergence issues, a compound-symmetry covariance matrix.

Analysis of the primary outcome

To account for the variables used for stratifying the randomisation, the main analyses will be adjusted for site and admission type (operative v non-operative), as this has been shown to lead to more accurate type I error rates and increases in power.¹¹

The primary analysis will be conducted without imputation of missing data, but imputations will be performed in the event that the primary outcome is missing for more than 5% of patients (see Treatment of missing data, below).

Main analysis

The primary endpoint is the proportion of patients dead at 90 days. To account for stratification variables, the main analysis will be performed using logistic regression with treatment allocation and admission type (operative v non-operative) as fixed effects and site as a random effect.¹²

The effect of the intervention will be presented as the odds ratio (OR) of death and its 95% CI. Crude proportions by treatment arm will also be reported with an unadjusted OR and 95% CI, and a χ^2 test *P* value.

Adjusted analyses

Additional adjusted analyses will be performed by adding the following covariates to the main logistic regression model: sex, age (as a continuous variable), APACHE II score at randomisation (as a continuous variable), time from onset of shock to randomisation (as a continuous variable) and use of RRT in the 24 hours before randomisation (yes/no). Given that the APACHE II score includes age in the calculation, we will test for collinearity between age and the APACHE II score. In the case of a Pearson correlation coefficient

greater than 0.8, we will only include the variable with the lowest univariate *P* value in the adjusted model.

The adjusted treatment effect will be reported as the adjusted OR and 95% CI. If more than 5% of observations are lost after adding covariates, multiple imputations will be used (see Treatment of missing data).

In the case of unexpected important imbalances in baseline variables not already included in the adjusted analyses described above, we will run a second adjusted model by adding the unbalanced variables.

Subgroup analyses

We will undertake six pre-specified subgroup analyses defined by the following baseline criteria:

- admission source: post-operative (admitted to the ICU from the operating theatre or recovery room) v non-operative
- catecholamine dose (epinephrine or norepinephrine) at randomisation: $\leq 15 \mu\text{g}/\text{min}$ v $> 15 \mu\text{g}/\text{min}$
- site of sepsis: pulmonary v other sites
- APACHE II score: < 25 v ≥ 25
- time from onset of shock to randomisation (divided into four groups): < 6 hours, 6–12 hours, 12–18 hours and > 18 hours
- sex: male v female

The analysis for each subgroup will be performed by adding the subgroup variable as well as its interaction with the intervention as fixed effects to the main logistic regression model (see Main analysis, above). Within each subgroup, summary measures will include raw counts and percentages within each treatment arm, as well as the OR for treatment effect with the 95% CI.

The results will be shown on a Forest plot including *P* for heterogeneity corresponding to the interaction term between the intervention and the subgroup variable.

Treatment of missing data

If more than 5% of patients from the intention-to-treat population are excluded from the analysis of death at 90 days due to missing data, missing data will be imputed using fully conditional specification.¹³ Data could be missing due to missing vital status data at 90 days or, for the adjusted analyses, due to missing covariates.

The imputation model will include death at 90 days, the randomised treatment arm, study site and admission type (operative v non-operative), as well as all the covariates listed under Adjusted analyses). Binary variables (eg, vital status at 90 days) will be imputed using a logistic model, categorical variables using a discriminant function method and continuous variables using linear regression. Ten sets of imputed data will be created and analysed using the methods described under Main analysis and Adjusted analyses. OR estimates from the 10 imputed analyses will

be combined to obtain a pooled common OR and 95% CI. The same 10 imputed datasets will be used for all analyses described under Main analysis and Adjusted analyses.

Other analyses of mortality

Analyses at Day 28

The analysis of death described under Main analysis will be replicated to compare the proportion of patients dead at Day 28. No additional adjusted or subgroup analyses will be conducted on 28-day mortality.

Survival analysis of time to death

We will perform a survival analysis of time to death. The analysis will be censored at 90 days or at the time when the patient was last known to be alive, whichever occurs earlier. A Kaplan–Meier plot will be used to describe survival rates. Differences in survival will be tested using a Cox proportional hazard model including the randomised treatment arm, admission type and a random centre effect (ie, using a shared frailty model).¹⁴ In the case of convergence issues, we will remove the random centre effect. The treatment effect will be summarised as the hazard ratio and 95% CI. We will visually assess the proportional hazard assumption using a plot of log-negative-log of the Kaplan–Meier estimator by treatment arm.

Cause and place of death

Causes and places (ICU, ward, home or other) of death at 90 days will be categorised, and the distribution compared between the two treatment arms using a χ^2 test. The categorisation of the causes of death will be performed by a researcher blinded to the treatment allocation.

Analysis of other secondary outcomes

Other secondary outcomes include shock resolution and recurrence, ICU and hospital length of stay, mechanical ventilation, bacteraemia or fungaemia and use of RRT.

All will be analysed as both the number of days alive and free of outcome (eg, days alive and free of shock, or days alive and free of ICU) and time from randomisation to resolution or discharge (eg, time from randomisation to resolution of shock, or time from randomisation to ICU discharge).

In addition, we will analyse recurrence of shock, recurrence of mechanical ventilation, recurrence of bacteraemia or fungaemia and occurrence of RRT.

Days alive and free of outcome

Days alive and free of outcome (eg, days alive and free of shock) will be calculated between randomisation and 90 days. They will be summarised using means and SDs, or medians and minimum and maximum quartiles. Differences between treatment groups will be tested using linear

regression, including treatment allocation and admission type (operative v non-operative) as fixed effects, and site as a random effect. The effect of the intervention will be presented as the mean difference and its 95% CI.

Time to resolution or discharge

A survival analysis of time to resolution or discharge (eg, time to shock resolution) will be performed with censoring at Day 90 or when the patient was last known to be alive, whichever occurs earlier.

Death will be handled in this analysis by assigning the worst observed time to event (up to 90 days) to patients who died before experiencing the event of interest. This simple method has been shown to be equivalent to a formal competing risk approach.¹⁵

Time to resolution or discharge will be summarised using median survival times and quartiles. A Kaplan–Meier plot will be used to describe survival rates. Differences in survival will be tested using the same strategy as for time to death (see Survival analysis of time to death, above).

Analysis of recurrence (of shock, mechanical ventilation and bacteraemia or fungaemia) will be summarised as the proportion of patients who experience a new episode after reversal of the initial episode. Differences in proportions will be assessed using logistic regression with treatment allocation and admission type (operative v non-operative) as fixed effects and site as a random effect. The same analysis will be applied to the proportion of patients receiving RRT at any time between randomisation and 90 days.

Blood transfusion

The volume of packed cells and whole blood (mL) will be summarised as means and SDs, medians and quartiles, and minimums and maximums for each day between Day 1 and Day 14 and overall (total volume received between Day 1 and Day 14). In addition, means and 95% CIs over time will be shown by treatment using longitudinal plots. The overall mean difference (and 95% CI) between treatment arms will be calculated using a repeated-measure linear mixed model similar to the one described for the analysis of laboratory tests and vital signs (see Laboratory tests and vital signs, above).

Quality of life at Month 6

The information obtained from the EQ-5D-5L questionnaire will be used to conduct a cost–utility analysis at 6 months after randomisation.³ This will be part of an extended program of health economic and outcomes research that will be conducted after publication of the main trial findings.

Analysis of safety outcomes

Adverse drug reactions deemed possibly, probably or definitely related to study treatment, as determined by the onsite treating physician, will be summarised as the number

and proportion of patients experiencing at least one adverse event. These will be summarised by category of event and overall numbers of events. In addition to the number of patients with at least one event, we will report the total number of events. Proportions of patients with adverse drug reactions will be compared between treatment arms using the Fisher exact test, both overall and by category. This will be repeated for serious adverse drug reactions. A list of all adverse drug reactions will be reported in an appendix. A list of proposed figures is in Box 1 and a list of proposed tables is in Box 2. The proposed tables are included in Appendix 2.

Competing interests

None declared.

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Box 1. Proposed figures**Figure 1. CONSORT flowchart****Figure 2. Consent details****Figure 3. Longitudinal mean plot of heart rate (Days 1–14)**

Programming note: show mean and 95% CI for each day by treatment group. Display overall mean difference, 95% CI and *P* value from repeated-measure linear mixed model. Show denominators each day.

Figure 4. Longitudinal mean plot of MAP (Days 1–14)

Programming note: show mean and 95% CI for each day by treatment group. Display overall mean difference, 95% CI and *P* value from repeated-measure linear mixed model. Show denominators each day.

Figure 5. Longitudinal mean plot of CVP (Days 1–14)

Programming note: show mean and 95% CI for each day by treatment group. Display overall mean difference, 95% CI and *P* value from repeated-measure linear mixed model. Show denominators each day.

Figure 6. Longitudinal mean plot of arterial lactate level (Days 1–14)

Programming note: show mean and 95% CI for each day by treatment group. Display overall mean difference, 95% CI and *P* value from repeated-measure linear mixed model. Show denominators each day.

Figure 7. Forest plot for subgroup analysis of mortality at Day 90**Figure 8. Kaplan–Meier plot of time to death**

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and *P* value from the Cox model.

Figure 9. Kaplan–Meier plot of time to shock resolution

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and *P* value from the Cox model.

Figure 10. Kaplan–Meier plot of time to ICU discharge

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and *P* value from the Cox model.

Figure 11. Kaplan–Meier plot of time to hospital discharge

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and *P* value from the Cox model.

Figure 12. Kaplan–Meier plot of time to cessation of mechanical ventilation

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and *P* value from the Cox model.

Figure 13. Kaplan–Meier plot of time to resolution of bacteraemia or fungaemia

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and *P* value from the Cox model.

Figure 14. Longitudinal mean plot of packed cell or whole blood transfusion requirements (Days 1–14)

Programming note: show mean and 95% CI for each day by treatment group. Display overall mean difference, 95% CI and *P* value from repeated-measure linear mixed model. Show denominators each day.

CONSORT = Consolidated Standards of Reporting Trials.
CI = confidence interval. MAP = mean arterial pressure. CVP = central venous pressure. ICU = intensive care unit.

Box 2. Proposed tables

Table 1. Study patient characteristics

Table 2. Baseline physiological and laboratory measurements

Table 3. Baseline therapies

Table 4. Admission diagnoses and infection sites

Table 5. Compliance with study treatment

Table 6. Reasons for discontinuing study drug

Table 7. Protocol deviations

Table 8. Concomitant therapies

Table 9. Physiological and laboratory values during trial period

Table 10. Analysis of mortality

Table 11. Cause and place of death by 90 days

Table 12. Continuous and binary secondary outcomes

Table 13. Volume of blood transfusion received

Table 14. Adverse drug reactions

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Correction

In “Direct cerebral perfusion and cooling in experimental cardiac arrest” in the December 2016 issue of the Journal (*Crit Care Resusc* 2016; 18: 255–60), two authors were listed with an incorrect affiliation. The authors were Junko Kosaka and Naoya Iguchi, whose correct affiliation is with the Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC, Australia.
