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

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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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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 $PaCO_2$ < 32 mmHg, or treatment with mechanical ventilation
  - white cell count > 12×10^9/L, or < 4×10^9/L, or > 10% immature neutrophils
- treatment with mechanical ventilation, via an 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 Group[4] 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

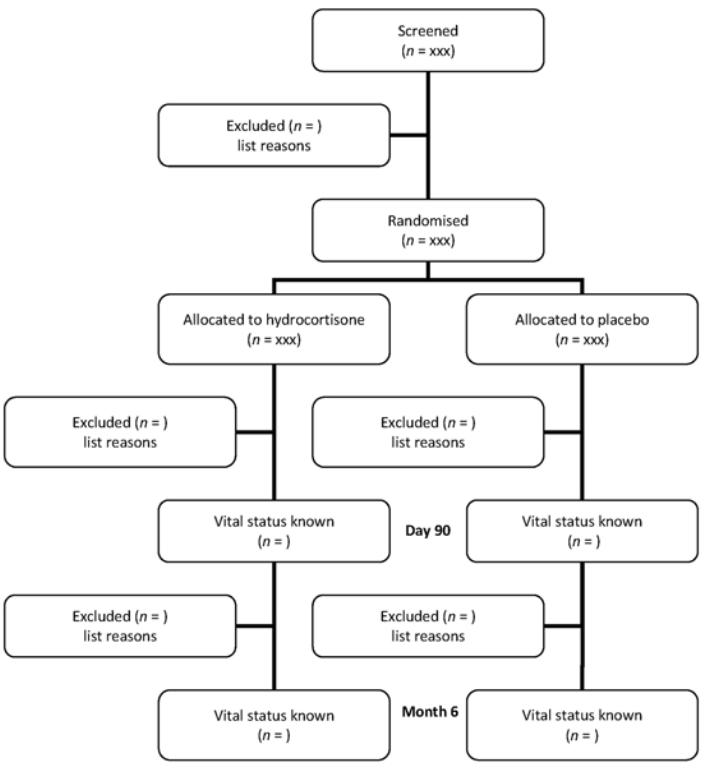
A description of the baseline characteristics will be presented by treatment group, as outlined in the tables (see Appendix 2 online).

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:

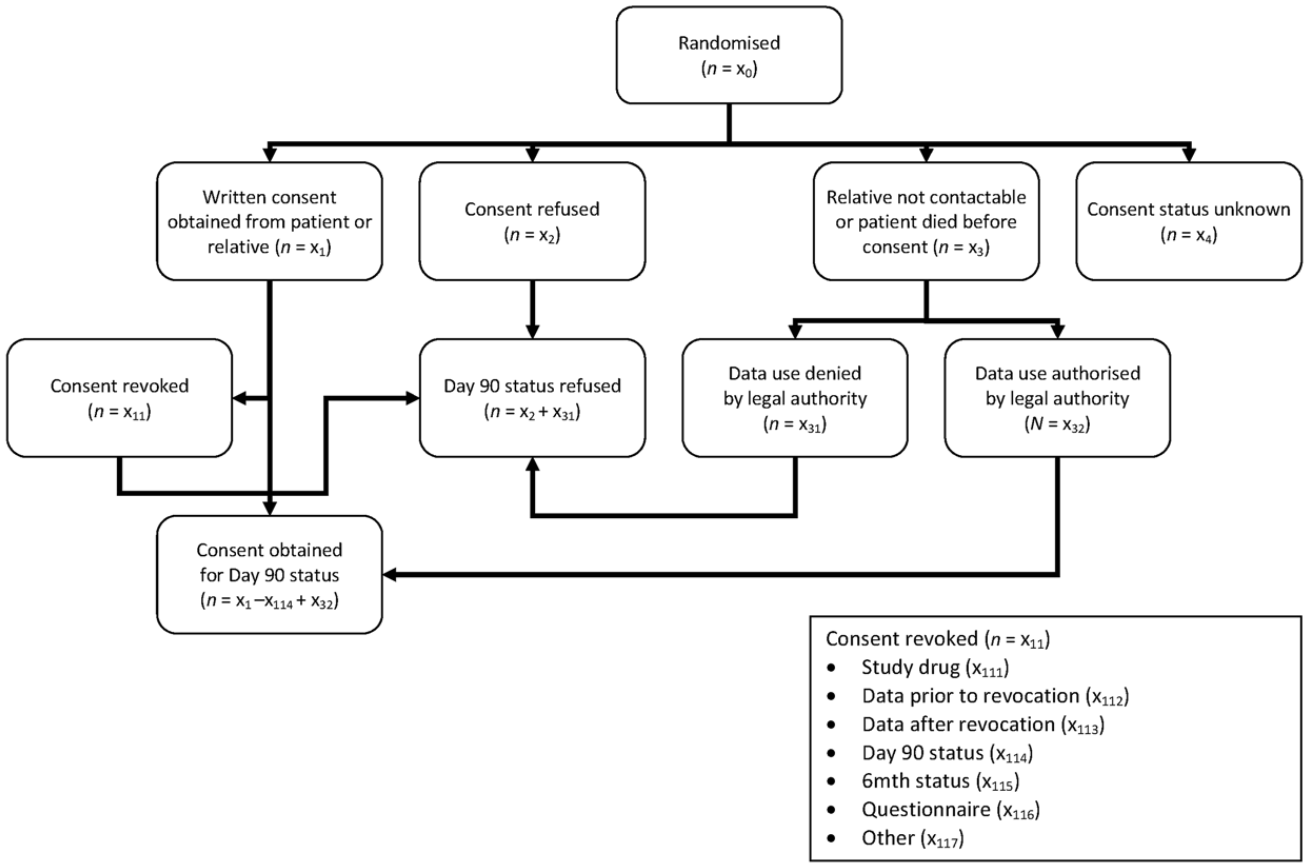
- sociodemographic and admission characteristics:
  - sex
  - age
  - weight
  - admission source
  - geographical region (Australia, New Zealand, United Kingdom, Denmark, Kingdom of Saudi Arabia)
  - time from ICU admission to randomisation
- vital signs and laboratory data (in the 24 hours before randomisation)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

Figure 1. CONSORT flowchart



CONSORT = Consolidated Standards of Reporting Trials.

Figure 2. Consent details



  - most recent MAP
  - lowest MAP
  - lowest Pao2:FIo2 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)
  - SIRS[2] (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: ≤ 15 μg/min v > 15 μg/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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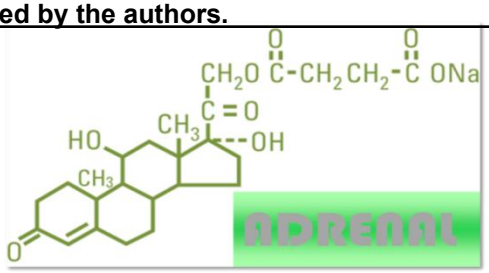
Correction

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.



DATA MONITORING COMMITTEE CHARTER

Full Title	A randomised blinded placebo controlled trial of Hydrocortisone in critically ill patients with septic shock
Short Title	ADRENAL Study ADjunctive coRticosteroid trEatment iN criticAlly ilL patients with septic shock
Acronym	ADRENAL
Protocol No.	GI-CCT372273
Version No.	4
Protocol Date	25 September 2012
ANZCTR registration No.	ACTRN12611001042932
ClinicalTrials.gov Identifier	NCT01448109

1. INTRODUCTION

Objectives of the trial, including interventions being investigated

Primary Objective:
The proposed study is a multi-centre blinded randomised-controlled trial. Critically ill patients with septic shock will be randomised to receive 200 mg of hydrocortisone or placebo in addition to conventional treatment. The primary end point will be 90 day all-cause mortality.
Secondary objectives:

Secondary endpoints will include shock resolution, recurrence of shock, 28 day, 6mth mortality, length of ICU and hospital stay, duration of ventilation, duration of renal replacement therapy, development of bacteraemia (2-14 days post randomisation), bleeding requiring blood transfusions while in ICU and index of functional survival (defined as Quality Adjusted Life years [QALY] at 6 months.

Outline of scope of charter

The purpose of this document is to describe the roles and responsibilities of the independent DMC for the ADRENAL study, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.

2. ROLES AND RESPONSIBILITIES

A broad statement of the aims of the committee

The DMC helps to safeguard the rights, safety and well-being of research participants. It does this by examining the data accumulated during the trial and other relevant information and advising the Trial Steering Committee (TSC) if there is proof beyond reasonable doubt that the

treatment is either definitely harmful or definitely beneficial for all, or a particular subcategory of patients.

The DMC has access to un-blinded data from the trial and will review interim analyses of the outcome data. It will consider these data and other relevant information when recommending to the TSC whether the study needs to continue, be changed, or be terminated.

Specific roles of DMC

The DMC will review the progress of the trial, including updated figures on recruitment, data quality, main outcomes and safety data.

A selection of specific aspects may be compiled from the following list:

- Monitoring evidence for treatment differences in the main efficacy outcome measures.
- Monitor evidence for treatment harm (e.g. unexpected serious ADRs, superinfections, duration of ventilation, reintubation rates, duration of ICU and hospital stay).
- Decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups.
- Assess data quality, including completeness.
- Review recruitment figures and monitor losses to follow-up.
- Monitor compliance with the protocol by participants and investigators.
- Monitor compliance with previous DMC recommendations considering the ethical implications of any recommendations made by the DMC.

3. PRE TRIAL COMMENCEMENT OR EARLY IN THE TRIAL

DMC input into the protocol

All potential DMC members will have sight of the protocol before finalising their agreeing to join the committee. Before recruitment begins the trial will have undergone review by a research ethics committee. Therefore, if a potential DMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the Study Management Committee (SMC) and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

DMC first meeting

The DMC will meet early in the course of the trial to discuss the protocol, the trial progress, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the Study Management Committee (SMC). The DMC should meet within 6 months of recruitment commencing.

An initial “dummy” report, including tables, to familiarise the DMC members with the format that will be used in the reports. The DMC will review the “dummy” report at the first meeting and confirm the final format of the report to be provided at subsequent meetings. Alterations to the report can be made at subsequent meetings to reflect the requirements of the DMC.

Issues specific to the disease under study

In accordance with the Protocol, the DMC has the responsibility for deciding whether, while randomisation is in progress, the un-blinded results (or the un-blinded results for a particular subgroup), should be revealed to the SMC.

Stopping rules

The DMC will reveal the un-blinded results to the SMC if, taking into account both statistical and clinical issues and exercising their best clinical and statistical judgement, the un-blinded results provide sufficient evidence that the trial treatment is on balance beneficial or harmful for all, or for a particular category of patients. Stopping rules will be based on the following:

- A responsibility to inform investigators if at any time the randomised comparisons provided evidence "beyond reasonable doubt" of a difference between randomised groups in total (all causes) mortality
- OR evidence that is likely to lead many clinicians conversant with the available evidence to change their practice with regard to the choice to use or not to use steroids.
- A three standard deviation difference in mortality (p-value < 0.00135) would constitute such evidence, unless the Data Monitoring Committee should itself decide in the circumstances of the trial that other evidence constitutes evidence beyond reasonable doubt.
- Additionally, while the primary focus of the committee should be on all cause mortality, this would not preclude the committee recommending termination of the study (or some modification to its design) if there emerged evidence of an important difference in some other major outcome (such as cause specific mortality).

Specific regulatory issues

All serious adverse drug reactions (expected and unexpected) are reported to the Trial Coordinating Centre (TCC). The TCC will provide all safety reports to the DMC for their consideration as part of their safety assessment.

Other issues specific to the treatment under study

The DMC will also consider information from other clinical trials of the same or similar compound and should be provided with any such information by the TCC.

DMC membership and their obligations

Members of a DMC are required to:

- Confirm their agreement to take on the responsibilities of membership as outlined in this Charter
- Agree to maintain the confidentiality of the data provided and the deliberations of the Committee
- Have no conflict of interest which will prejudice their role as a DMC member

By agreeing to adopt this Charter, all members confirm the above.

4. COMPOSITION

Membership and size of the DMC

Membership is international and includes previous expertise in trials of investigational medicinal products, the clinical setting of critical care medicine and previous DMC membership.

The members of the DMC for this trial are:

Dr Duncan Young (Chair)

Director of Research, UK Intensive Care Society
Consultant, Intensive care Medicine and Anaesthetics, John Radcliffe Hospital, Oxford, UK
Clinical Director for Critical Care Services at the Oxford Radcliffe Hospitals NHS Trust

Professor Ian Roberts
Director, Clinical trials unit.
Professor of Epidemiology and Public Health
London school of Hygiene & Tropical Medicine, Nutrition and Public Health
Intervention Research Unit, Keppel St, London WC1E 7HT, UK

Professor John Marshall
Director of Research
Critical Care Medicine,
St Michael's Hospital, 30 Bond St Toronto, Ontario M5B 1W8, Canada

Selection of the Chair

The Chair should have previous experience of serving on a DMC and experience of chairing meetings, and should be able to facilitate and summarise the DMC discussions. The Chair is expected to facilitate and summarise discussions.

The responsibilities of the DMC statistician

An independent statistician (i.e. independent of the trial team), Laurent Billot or designee from TGI is responsible for producing the report to the DMC. This is to ensure all trial related staff remain blind to the interim analysis. Laurent Billot will prepare the reports in accordance with the DMC reporting requirements and disseminate the required reports in a timely fashion to the DMC members. Laurent Billot may participate in DMC meetings if required for the purpose of guiding the DMC through the reports. DMC discussions will remain confidential and will not be communicated to the TCC

The responsibilities of the Chief Investigator (CI), other members of the TCC, members of the SMC

The CI is Prof Bala Venkatesh. He will be available to attend open sessions of the DMC meeting. Other TCC members may attend open sessions when necessary.

The ADRENAL Project Manager will provide inputs to the production of the non-confidential sections of the DMC report. The TCC are all George Institute (GI) employees and are comprised of:

Dorrilyn Rajbhandari
Project Manager with overall study responsibility

Meg Harward
Clinical Research Associate with responsibility for Queensland, Northern Territory and South Australian sites

Kelly Thompson
Clinical Research Associate with responsibilities for New Zealand, Western Australia, New South Wales, International sites and safety reporting

Ann Gould
Clinical Research Associate with responsibility for New South Wales, Tasmania and Victorian sites

The Study Management Committee is comprised of:

Bala Venkatesh	Chief Investigator, Principal Investigator (PI) Princess Alexandra & Wesley Hospitals, QLD

John Myburgh	PI St George's Hospital, NSW
Simon Finfer	PI Royal North Shore Hospital, NSW
Steve Webb	Chair ANZICS Clinical Trials Group
Jeremy Cohen	PI Royal Brisbane & Women's Hospital, QLD
Rinaldo Bellomo	PI Austin Hospital, VIC
Chris Joyce	PI Princess Alexandra Hospital, QLD
Colin McArthur	PI Auckland City Hospital, New Zealand
Dorrilyn Rajbhandari	Project Manager, Critical Care & Trauma Division, GI
Meg Harward	Clinical Research Associate, Critical Care & Trauma Division, GI
Parisa Glass	Deputy Director, Critical Care & Trauma Division, GI

5. RELATIONSHIP

Clarification of whether the DMC are advisory or executive

The DMC does not make decisions about the trial, but rather makes recommendations to the SMC.

Payments to DMC members

Members will be reimbursed for any travel and accommodation for DMC duties. All claims will be made to the TCC. The cost of telephone conferences will be the responsibility of the TCC.

The need for DMC members to disclose information about any competing interests

All competing interests should be disclosed prior to agreeing this Charter. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure helps to enhance credibility.

DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.

6. ORGANISATION OF DMC MEETINGS

Expected frequency of DMC meetings

The DMC will determine the frequency of their meeting. A minimum of one interim analysis will be performed after 1900 patients have been recruited and reached the 90 day follow up period.

Whether meetings will be face-to-face or by teleconference

The DMC will decide on the type of meeting required (face-to-face and/or teleconference). The TCC will make arrangements accordingly.

How DMC meetings will be organised - regarding open and closed sessions, including who will be present in each session

Only DMC members and others whom they specifically invite (e.g. independent Statistician) are present in closed sessions.

In open sessions, all those attending the closed session are joined by the CI and/or the other TCC/SMC members as required.

The format of the meetings will be as follows:

- Open session: Introduction and any "open" parts of the report
- Closed session: DMC discussion of "closed" parts of the report and, if necessary,
- Open session (if required by DMC): to address further questions to the CI/SPM.

7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION

Intended content of material to be available in open sessions

Open sessions: Accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented.

Intended content of material to be available in closed sessions

Closed sessions: In addition to all the material available in the open session, the closed session material will include safety and efficacy data by treatment group.

Will the DMC be blinded to the treatment allocation?

The DMC will be provided with full un-blinded data by Laurent Billot.

Who will see the accumulating data and interim analysis?

DMC members do not have the right to share confidential information with anyone outside the DMC, including the CI, TCC or SMC.

To whom the DMC will communicate the decisions / recommendations that are reached

The DMC will report its recommendations in writing to the SMC. This should be copied to the CI and, if possible, sent in time for consideration at a SMC meeting. If the trial is to continue largely unchanged the DMC may be asked to include a summary paragraph suitable for HREC reporting.

Whether reports to the DMC will be available before the meeting or only during the meeting

The DMC will receive all documents and reports for consideration at least 1 week before any meetings unless urgency prevails. Newest reports will be circulated by Laurent Billot before each meeting.

What will happen to the confidential papers after the meeting?

The DMC members must ensure the safety and confidentiality of unblinded data reports after each meeting. If in doubt, these may be destroyed and copies subsequently requested from the Independent Statistician with the newest report.

8. DECISION MAKING

What decisions / recommendations will be open to the DMC?

Possible recommendations could include:

- No action needed, trial continues as planned.
- Stopping recruitment within a subgroup or for the whole trial.
- Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up.
- Sanctioning and/or proposing protocol changes.

How decisions or recommendations will be reached within the DMC

It is recommended that every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the SMC as these may inappropriately convey information about the state of the trial data.

It is important that the implications (e.g. ethical, statistical, practical, regulatory) for the trial be considered before any recommendation is made. The role of the Chair is to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last.

When the DMC is quorate for decision-making

Effort should be made for all members to attend. The TCC will try to ensure that a date is chosen to enable this. Members who cannot attend in person at face-to-face meetings can attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if the Chair and one other member is present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent member as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC.

Can DMC members who cannot attend the meeting input?

If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC Chair for consideration during the discussions.

Whether different weight will be given to different endpoints (e.g. safety/efficacy)

The DMC will reveal the un-blinded results to the SMC if, taking into account both statistical and clinical issues and exercising their best clinical and statistical judgement, the un-blinded results provide compelling evidence that the trial treatment is on balance beneficial or harmful for all, or for a particular category of patients.

The DMC terms of reference state that they will do this if, and only if, two conditions are satisfied: (1) the results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of patients, in terms of the major outcome; (2) the results would, if revealed, be expected to substantially change the prescribing patterns of doctors who are already familiar with any other trial results that exist.

9. REPORTING

DMC reporting of their recommendations / decisions

This will be a letter sent to the CI within 3 weeks of the meeting. A copy of the letter should be sent to the TCC for the Trial Master File.

Disagreement between the DMC and the body to which it reports

If the DMC has serious problems or concerns with the SMC's decision, a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data may have to be revealed to all those attending such a meeting.

10. POST TRIAL

Publication of results

The SMC undertakes to publish the primary results within 1 year of the end of trial. The SMC will provide draft reports on these results to the DMC for their consideration prior to submission. The DMC may provide comments to the SMC on the draft reports, and give advice about data interpretation.

The information about the DMC included in published trial reports

DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings may be included if appropriate in the body of this paper.

Any constraints on DMC members divulging information about their deliberations after the trial has been published

The DMC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published. If a DMC needs to discuss their involvement any earlier, permission is required from the SMC.

This Charter was agreed by all members of the DMC:

Name	Agreement (signature)	Date
Professor Duncan Young		
Ian Roberts		
John Marshall		