

# The RENAL (Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy) study: statistical analysis plan

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## ABSTRACT

**Background:** The Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study is the largest interventional trial ever conducted in patients with acute renal failure.

**Objective:** To develop and report a pre-determined statistical analysis plan which the investigators will adhere to in analysing the data from the trial.

**Methods:** The data collected by the researchers as part of the trial protocol was reviewed and formally assessed. Information relevant to baseline characteristics was selected and, for each item, statistically relevant descriptive elements were described. Information relevant to the process of care and delivery of prescribed trial therapy was similarly classified and, for each item, appropriate descriptive statistical analysis was planned with appropriate comparison between groups. Finally, trial outcomes were selected, and an appropriate statistical comparison between groups was planned and described.

**Results:** A standard analysis plan for the RENAL trial results was developed, which allows a comprehensive description of baseline characteristics, features of the process of care and trial treatment delivery, and pre-determined statistical assessment of relevant outcome measures in a way that is transparent, available to the public, verifiable and pre-determined before the actual analysis of data.

**Conclusion:** We have developed a pre-determined statistical analysis plan for the RENAL trial. This plan will be adhered to in order to avoid introducing any analysis bias associated with prior knowledge of study findings.

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## 1 Introduction

### 1.1 Study overview

The RENAL study described below is approaching completion, and represents a major research project by the Australian and New Zealand Intensive Care Society Clinical Trial Group (ANZICS CTG) and the George Institute of Interna-

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tional Health. As part of a desire to maximise scientific rigour and transparency of analysis and to minimise any data manipulation, the RENAL Study Management Committee has agreed to develop, formally agree to, and abide by a pre-published statistical analysis plan. The plan, as described below, has been developed to precede any knowledge of study results, and we hope it will represent yet another important step toward making trials conducted by the ANZICS CTG the best that they can be in terms of execution and academic quality.

### 1.1.1 Title

The Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study is the largest interventional trial ever conducted in patients with acute renal failure. It is a multicentre, open-label, randomised controlled trial that compares the effects of two regimens of continuous renal replacement therapy (CRRT), targeting either a standard dose or a higher dose of continuous veno-venous haemodiafiltration (CVVHDF): 25 mL/kg/h of effluent generation versus 40 mL/kg/h of effluent generation.

### 1.1.2 Patient population

In previous studies<sup>1,2</sup> of CRRT control, the benefit of delivering a higher dose was shown in a broad population of adult patients with acute renal failure and, for this reason, this is the population we chose to study. However, we chose to exclude patients who are moribund and at imminent risk of death (brain death or cardiac standstill) on the basis that allocation to either study treatment is unlikely to alter the patient's outcome. In addition, because renal recovery was chosen as an outcome measure, we chose to exclude patients receiving long-term dialysis.

### 1.1.3 Inclusion criteria

- The treating clinician believes that CRRT is needed for acute renal failure (ARF).
- The clinician has equipoise with regard to the two treatments.
- Consent has been obtained.
- The patient fulfils at least one of the physiological criteria of ARF:<sup>3</sup>
  - Urine output < 100 mL/6 h.
  - Serum potassium concentration > 6.5 mmol/L.
  - pH < 7.2.
  - Serum urea concentration > 25 mmol/L.
  - Serum creatinine concentration > 300 µmol/L.
  - Clinically significant organ oedema in the setting of ARF.

### 1.1.4 Exclusion criteria

Patients will be excluded from the study if one or more of the following criteria are present:

- Age is less than 18 years.
- Death is imminent (cardiac standstill or brain death expected in less than 24 hours), and the treating clinicians are not committed to full supportive care. This should be confirmed by a documented treatment-limitation order that exceeds a "not-for-resuscitation" order.
- There is a strong likelihood that the trial protocol will not be continued.
- The patient has been treated with CRRT or any other form of dialysis during this hospital admission.
- The patient is receiving long-term dialysis.
- The patient's body weight is < 60 kg or > 120 kg.
- The patient has previously been enrolled in the study.

### 1.1.5 Objectives

The primary aim of the study is to compare the effects of the two regimens prescribed to deliver different doses of CVVHDF on 90-day all-cause mortality in intensive care patients with ARF requiring CRRT. The null hypothesis is that there is no difference in the relative risk of death between patients assigned to standard dose CVVHDF and those assigned to higher-dose CVVHDF.

## 1.2 Unblinding

Access to the interim data and results will be limited to members of the Data and Safety Monitoring Board (DSMB) and the statistician(s) in charge of writing the reports. The statistical analysis plan will be written by a statistician and the principal investigator, both of whom will be blinded to treatment allocations and study results until the final study results are released by the study statistician. Treatment allocations will be stored securely in a separate location for that purpose. Statistician(s) not involved in the writing of DSMB reports will remain blinded and work on dummy treatment until validation of their data analysis and computer instruction codes has been performed — this will be done in accordance with the Standard Operating Procedures of the George Institute for International Health.

## 1.3 Definition of efficacy variables

### 1.3.1 Definition of primary outcomes

The primary endpoint is all-cause mortality 90 days post-randomisation. As loss to follow-up is expected to be minimal, missing values will not be imputed.

### 1.3.2 Definition of secondary outcomes

The secondary outcomes will include:

- Survival time from randomisation to Day 90.
- Renal replacement dependence at Day 28 and Day 90.
- Renal replacement days from randomisation to Day 90.

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- ICU days from randomisation to Day 90.
- Hospital days from randomisation to Day 90.
- Mechanical ventilation days from randomisation to Day 28.

### 1.3.3 Definition of tertiary outcomes

The tertiary outcomes will include:

- 28-day all-cause mortality.
- Place of death (in study ICU, elsewhere in study hospital, or outside study hospital).
- Incidence of new organ failure at any time during the study. (A new organ failure is defined as a post-baseline SOFA score  $> 2$  in any domain where the baseline SOFA score in that domain was 0, 1 or 2).

### 1.4 Definition of safety variables

No specific adverse events have been described in association with higher-dose CVVHDF. However, it is conceivable that higher-dose CVVHDF might increase the risk of dialysis disequilibrium syndrome, hypophosphataemia and hypokalaemia.

The safety variables will include:

- Number and proportion of patients experiencing serious adverse events.
- Number and proportion of patients with suspected dialysis disequilibrium syndrome in each group.
- Number and proportion of patients with morning hypophosphataemia (morning serum phosphate concentration  $< 0.8$  mmol/L) in each group.
- Number of episodes of morning hypophosphataemia in each group.
- Number and proportion of patients with morning hypokalaemia (morning serum potassium concentration  $< 3.5$  mmol/L) in each group.
- Number of episodes of morning hypokalaemia in each group.
- Episodes of arrhythmia (any rhythm other than sinus rhythm) in each group.
- Number of episodes of arrhythmia requiring treatment in each group.
- Number of episodes of arrhythmia causing haemodynamic instability in each group.

### 1.5 Analysis principles

- All analyses will be conducted on an intention-to-treat basis.
- Results for all randomised patients will be analysed in the group to which they were assigned regardless of protocol violations. The only exception will be patients where consent to use their data in the analysis is withheld or withdrawn.

- All tests are two-sided, and the nominal level of  $\alpha$  will be 5%.
- All statistical analyses will be unadjusted except where indicated.
- Subgroup analyses will be carried out irrespective of whether there is a significant effect of treatment on the primary outcome.
- We will not impute missing values unless specified otherwise. We will report the number of observations used in the analysis.
- *P* values will not be adjusted for multiplicity. However, the outcomes are clearly categorised by degree of importance (primary to tertiary), and a limited number of subgroup analyses are pre-specified.

## 2 Design issues

### 2.1 Data collection and follow-up

The different stages of data collection and follow-up are summarised in Box 1.

Because of local legal considerations, patients or their legal surrogates may have an absolute right to request that their data be removed from the study database. As a result, there are potentially two datasets: the randomised patients, and the randomised patients who have data available. The latter is obtained after deleting the data for randomised patients who withheld or withdrew their consent and did not allow their data to be submitted or maintained in the database. Only the latter dataset can be used in the analysis.

### 2.2 Study design

The RENAL study is a multicentre, open-label, randomised, concealed controlled trial.

### 2.3 Treatment allocation

Eligible patients will be randomised to one of the two doses of CVVHDF using imbalance minimisation. Centralised randomisation will be achieved via a password-protected web-based program.

### 2.4 Study power

The study will assume a conservative 90-day mortality rate of 60% in the low-dose group. The study will also assume a conservative estimate for the relative reduction in mortality in patients of only 50% of that reported by Ronco et al<sup>1</sup> (ie, 14.5%) and a parallel absolute reduction in mortality of 8.5%. Based on these figures, a study of 1500 patients will have a 90% power of detecting an 8.5% absolute reduction

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from a 90-day mortality of 60% in the low-dose group to 51.5% in the higher-dose group ( $\alpha < 0.05$ ). Such a difference is clinically significant (number needed to treat = 12) and would likely lead to widespread change in the practice of CRRT in Australia, New Zealand and other countries.

### 2.5 Interim analyses

An independent Data and Safety Monitoring Board (DSMB), chaired by Professor Colin Baigent (University of Oxford, United Kingdom), will review unblinded data on patient characteristics, treatment compliance and study outcomes at two interim analyses when the primary outcome for about 500 and 1000 patients, respectively, are available, and at the final analysis. Recruitment will be reviewed during the trial at regular intervals, to be determined by the

DSMB, which will generate terms of reference. The DSMB will be charged with informing the Study Management Committees if at any time there emerges:

- evidence beyond reasonable doubt of a difference between randomised groups in all-cause mortality; or
- evidence likely to change the practice of many clinicians already familiar with the available evidence about the trial interventions.

### 2.6 Consent-related issues and dataset analysed

Due to the specific nature of the study, informed prior consent from participants or legal surrogates is not always possible, and patients or their legal surrogates may be asked for delayed consent after randomisation. Two important situations can lead to the cessation of study treatment:

#### Box 1. Data collected at different stages of the study

##### Randomisation

Patient demographics and inclusion/exclusion criteria.

##### Form 1. Baseline

Source and date of admission to ICU, Acute Physiology and Chronic Illness Evaluation III (APACHE III) score, ICU admission diagnosis, subgroup categories, operative or non-operative admission, emergency or elective surgery, presence or absence of "severe sepsis" and suspected site of infection, pre-admission treatment with HMG-CoA reductase inhibitors (statins), treatment with a statin at baseline, whether this is a readmission to ICU, Sequential Organ Failure Assessment (SOFA) scores (cardiovascular, respiratory, hepatic, renal and haematological), pre-morbid serum creatinine concentration, pre-randomisation serum creatinine and urea concentrations, treatment with mechanical ventilation. Haematological variables: international normalised ratio, activated partial thromboplastin time, haemoglobin concentration, white cell count, platelet count. Biochemical test results: serum sodium, potassium, chloride, bicarbonate, urea, creatinine, phosphate, albumin and magnesium concentrations, arterial blood gas variables (pH, carbon dioxide, base excess, ionised calcium) and glucose concentration.

##### Form 2. Daily, Days 1–28

Each day while in ICU: Daily volume of fluid infused as part of continuous renal replacement therapy (CRRT) (replacement fluid plus dialysate) and total CRRT effluent. Number of hours of CRRT treatment. CRRT machine used (make and model), number of filters used per day, anticoagulant treatment used, insertion of CRRT vascular access, site of CRRT vascular access catheter, brand, gauge and length of CRRT vascular access catheter. If intermittent haemodialysis given: whether net fluid balance was positive; and, if so, net positive haemodialysis fluid balance; whether fluid was removed from the patient, and, if so, net negative haemodialysis fluid balance. Daily blood product use and volume of red blood cells, platelets, fresh frozen plasma, cryoprecipitate, 4% albumin solution and 20% albumin solution. All morning haematological, biochemical and arterial blood gas variables as described for baseline. Whether the patient had an arrhythmia (any cardiac rhythm other than sinus rhythm), type of arrhythmia and treatment given; and whether the arrhythmia caused cardiovascular instability (defined by site investigator). Treatment with angiotensin-converting enzyme inhibitors. SOFA scores (cardiovascular, respiratory, hepatic and haematological domains), treatment with renal replacement therapy or mechanical ventilation, type (enteral versus parenteral) and volume of nutrition administered (total non-protein calories, protein, carbohydrate, and lipid will be calculated from type and volume of enteral and parenteral nutrition administered), all fluids administered. Urine output, recorded total blood loss, and recorded total loss of other fluids.

##### Form 3. 28-day summary

Vital status (alive or dead) at Day 28. Place, date and proximate cause of death. Treatment limitations and details. Whether patient is still in ICU; if not in ICU, date of discharge from index ICU admission. Whether patient is still in hospital; if not in hospital, date of discharge from index hospital admission, number of days in ICU and hospital. Whether patient is still receiving study treatment; if not, date of cessation of study treatment. Whether patient has been treated with any other form of renal replacement therapy; if so, whether this is still ongoing; if not, date of cessation of this treatment. Type of consent obtained for inclusion in RENAL study.

##### Form 4. 90-day summary

Vital status (alive or dead) at Day 90. Place, date and proximate cause of death. Treatment limitations and details. Whether patient is still in ICU; if not in ICU, date of discharge from index ICU admission. Whether patient is still in hospital; if not in hospital, date of discharge from index hospital admission, number of days in ICU and hospital. Whether patient is still receiving study treatment; if not, date of cessation of study treatment. Whether patient has been treated with any other form of renal replacement therapy; if so, whether this is still ongoing; if not, date of cessation of this treatment. Type of consent obtained for inclusion in RENAL study.

- A patient, next of kin or legal surrogate may withdraw consent; or
- They may refuse continuation of study treatment when delayed consent is sought (as opposed to withdrawing an existing consent).

In both cases, the study treatment will cease, and the patient will receive renal replacement therapy as prescribed by their treating clinicians. In this situation, specific consent is sought to continue study follow-up procedures and to use study data. If consent for use of data is withheld, that patient's data will be removed from the analysis, except for data related to randomisation (occurrence of randomisation and treatment assignment) and consent.

The efficacy and safety datasets comprise all patients randomised except those whose consent has been withdrawn or withheld. Refer to *Section 1.5, Analysis principles*.

### 2.7 Permanent discontinuation

The data of patients who withdraw or withhold consent to continued study treatment, but consent to the use of their data will be included and analysed on an intent-to-treat basis.

## 3 Statistical analysis

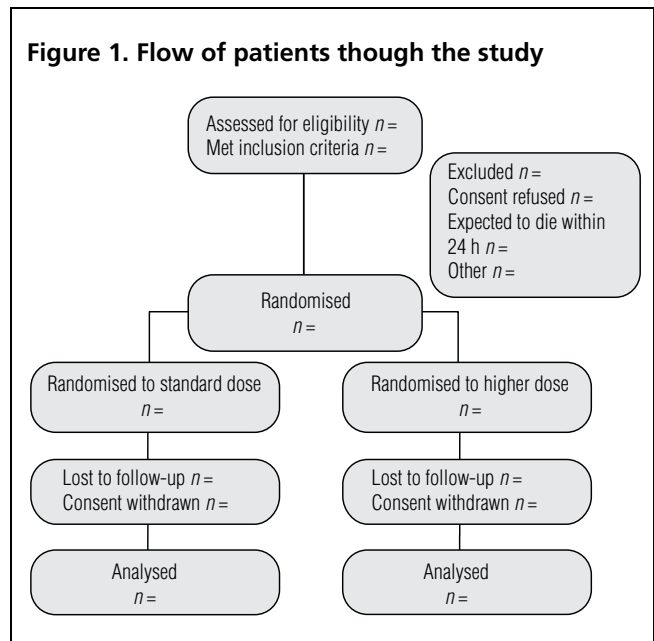
### 3.1 Trial profile

Flow of patients through the study will be displayed in a CONSORT diagram (Figure 1). We will report number of screened patients who met the study inclusion criteria and number included in the study, reasons for exclusion of those who met inclusion criteria, and information as below.

### 3.2 Characteristics of patients and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in the corresponding summary table, in either the body or a footnote. In some instances, additional frequencies and percentage of patients in each category will be reported as indicated below. Continuous variables will be summarised by standard measures of central tendency and dispersion, using mean and standard deviation, as well as quantile points at 0.25, 0.5 and 0.75 where appropriate.

Figure 1. Flow of patients through the study



### 3.3 Baseline characteristics of patients

- Sex.
- Age.
- Weight.
- Percentage of patients with measured weight, percentage of patients with estimated weight, and method of weight estimation.
- Source of admission to ICU (emergency department, hospital floor, another ICU, another hospital, operating room [OR] following emergency surgery, OR following elective surgery, readmission to the same ICU during same hospitalisation).
- Operative or non-operative admission.
- Operative admission diagnosis (number and % in each of the following categories):
  - Cardiovascular
  - Respiratory
  - Gastrointestinal
  - Neurological
  - Trauma without traumatic brain injury
  - Traumatic brain injury ± multiple trauma
  - Burns
  - Renal
  - Gynaecological
  - Other orthopaedic
  - Other surgical.
- Non-operative admission diagnosis (number and % in each of the following categories):
  - Cardiovascular
  - Respiratory

- Gastrointestinal
- Neurological
- Sepsis
- Trauma without traumatic brain injury
- Traumatic brain injury ± multiple trauma
- Metabolic
- Haematological
- Burns
- Renal
- Other medical.
- Severe sepsis at baseline.
- APACHE III score.
- SOFA score:
  - Cardiovascular domain
  - Respiratory domain
  - Hepatic domain
  - Haematological domain.

(SOFA score domains will be analysed both as continuous variables and as categorical variables divided into normal function (SOFA score, 0), dysfunction (score, 1–2), and failure (score, 3–4).

- Last serum urea concentration before randomisation.
- Last serum creatinine concentration before randomisation.
- Haematological variables (as described in Box 1).
- Biochemical variables (as described in Box 1).
- Treatment with mechanical ventilation.
- Estimated glomerular filtration rate (eGFR).
- Presence of an eGFR < 60 mL/min.

The eGFR will be calculated using the revised modification of diet in renal disease (MDRD) equation:<sup>4</sup>

$$\text{eGFR} = 175 \times (\text{SCr} \times 0.0113)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ [if female]})$$

where SCr = serum creatinine level (µmol/L).

### 3.4 Process measures and concomitant treatments

Continuous variables will be summarised by standard measures of central tendency and dispersion, using mean and standard deviation, as well as quantile points at 0.25, 0.5 and 0.75 where appropriate. Discrete variables will be summarised by counts and percentages. The *t* test or Welch test will be performed in the case of continuous data, after checking for equality of variances using the Levene or Fligner–Killeen test. A non-parametric test, such as the Wilcoxon rank-sum test, will be used in case of small samples (< 30). Discrete data will be compared using the Pearson  $\chi^2$  test. In cases where the expected count is less than 1, the Fisher exact test or Fisher–Irwin test (the preferred option) should be used, and odds ratio and 95% CI reported instead.<sup>5</sup> For repeated measurements, *P* values will not be computed.

#### 3.4.1 Process measures

- Days of study treatment.
- Days from cessation of study treatment to discharge from index ICU admission.
- Mean morning plasma urea concentration by day of treatment.
- Mean morning plasma creatinine concentration by day of treatment.
- Mean morning value for each biochemical variable (see Box 1) by day of treatment that is not already covered in the previous two items.
- Mean morning value for each haematological variable (see Box 1) by day of treatment
- Mean daily amount of effluent during study treatment.
- Mean daily amount of replacement fluid and dialysate during study treatment.
- Anticoagulant type, average treatment days received.
- Mean daily fluid balance during study treatment.
- Mean number of CRRT filters used daily during study treatment.
- Number of dialysis catheters used during study treatment.
- Mean daily urine output in mL.
- Number and percentage of patients treated with intermittent haemodialysis (IHD).
- Total number of treatments with IHD.
- Number and percentage of patients with a positive fluid balance during IHD.
- Number and percentage of patients with a negative fluid balance during IHD.

#### 3.4.2 Concomitant treatments

- Non-protein calories administered in the ICU (by day, up to Day 14).
- Non-protein calories by all routes (by day, up to Day 14).
- Non-protein calories by enteral route (by day, up to Day 14).
- Non-protein calories by parenteral route (by day, up to Day 14).

In the event that the number of patients remaining in the ICU becomes too small, the means will be truncated before 14 days. Conversely, the maximum of 14 days will be extended if more than 50% of patients remain in the ICU.

- Mean protein administration in g/day.
- Mean daily volumes of blood products while in ICU up to Day 28:
  - Red blood cells
  - Platelets
  - Fresh frozen plasma
  - Cryoprecipitate
  - 4% albumin solution
  - 20% albumin solution.

### 3.4.3 Limitation of treatment

For this section, only counts and frequencies will be reported.

- Patients for whom there was limitation of treatment.
- Patients for whom treatment was limited or withheld:
  - Patients for whom treatment was limited as terminal event.
  - Patients for whom maximal treatment was not indicated.
- Time from randomisation to first treatment limitation order (overall and for limitations indicated in specific study question in Day 90 study form).

Treatment limitation refers to withdrawing a treatment that might otherwise prolong life as it is no longer considered appropriate for that individual (ie, ceasing a previously provided treatment); or withholding treatment that might otherwise prolong life as it is not considered appropriate for that individual (ie, not commencing a treatment).

Each of these will have been authorised by a treating clinician independent of the study and documented in the medical record. The specific treatments limited or withdrawn will not be reported.

### 3.4.4 Consent and permanent discontinuation of study treatment

For this section, only counts and frequencies will be reported.

- Consent (number and % in each of the following categories):
  - Prior informed consent from patient.
  - Prior informed consent from a legal surrogate.
  - Delayed informed consent from patient.
  - Delayed informed consent from a legal surrogate.
  - Consent from other legal body before or after patient's death.
  - No consent obtained.
  - Consent withdrawn (no. and % of all consent obtained).
- Patients for whom study treatment permanently discontinued (number and % in each of the following categories):
  - Patient requested withdrawal.
  - Legal surrogate requested withdrawal.
  - Study treatment discontinued by treating clinician (not due to a serious adverse event or palliative care).
  - Study treatment discontinued due to serious adverse event.
  - Study treatment discontinued as focus of treatment changed to palliative care (derived from treatment limitation question on Day 90 form).
  - Study treatment discontinued for other reason.

### 3.5 Primary outcome

We will compare the difference in number and proportion of all-cause mortality at Day 90 between the two groups, using standard  $\chi^2$  tests, and a 95% confidence interval (CI) will be computed. Frequency and count for primary outcome per

group will also be reported. A sensitivity analysis (assuming the best and worst possible case) will be performed if more than 5% of the 90-day mortality data are missing. A full logistic regression analysis examining the effect of treatment group, incorporating all the variables specified in the subgroup analysis below, might also be carried out, with or without transformation of variables, as necessary.

### 3.6 Secondary and tertiary outcomes

Survival time from randomisation to Day 90, duration of ICU stay and duration of hospital stay will be analysed using a log-rank test. The number of events and the median survival (if available) or event times or hazard ratio (including 95% CI) will also be reported. Kaplan–Meier curves will be used to display probability of survival or of experiencing an event, by treatment group. Survival times will be censored at the time when the patient was last known to be alive or to experience an event (for ICU or hospital discharge calculations). On the rare occasion that assumptions are needed as to the time patients were last known to be alive or to experience an event, they must be explicitly specified and consistently applied between treatment groups.

Renal replacement days up to Day 90, and mechanical ventilation days up to Day 28 will be analysed as continuous variables, without censoring, with reporting of mean and standard deviation, as well as quantile points at 0.25, 0.5 and 0.75. Comparison of differences in mean and median between the two groups will be carried out using the *t*/Welch or Wilcoxon rank-sum test, as outlined in *Section 3.4*.

A standard  $\chi^2$  test and 95% CI testing the difference in proportion between two treatment groups will be used to assess the effect of treatment on binary or categorical outcomes (ie, 28-day all-cause mortality, cause of death, place of death, renal replacement dependence at Day 28 and Day 90, incidence of a new organ failure at any time since baseline [from no failure up to five failures]). In case of an expected count less than 1, the Fisher exact test or Fisher–Irwin test (the preferred option) should be used, and odds ratio and 95% CI will be reported instead.

### 3.7 Safety outcomes

Safety outcomes as defined in *Section 1.4* will be analysed via frequencies and percentages per treatment group. The difference in proportions of patients experiencing a particular event (at least once) will be tested across treatment arm by means of a  $\chi^2$  or Fisher/Fisher–Irwin test. Additionally, the difference in number of episodes between treatment groups for morning hypophosphataemia (measured serum phosphate concentration < 0.8 mmol/L) at any time in the ICU will be compared using Welch, *t* or Wilcoxon rank-sum

tests, with 95% CI reported. The same will apply to episodes of morning hypokalaemia (serum potassium concentration < 3.5 mmol/L). Denominators for discrete variables are based on all patients randomised.

### 3.8 Subgroup analyses

All subgroups will be defined by the presence or absence of a pre-randomisation variable; we will not select any subgroups based on post-randomisation events.

The primary outcome for planned subgroup analyses will be the same as for the main analysis: 90-day all-cause mortality.

#### 3.8.1 Analysis

The main analysis for each subgroup will be a test of interaction in a logistic model to determine whether the effect of treatment differs significantly across categories (eg, in patients with sepsis versus those without sepsis). Odds ratio and 95% CI for each category will be reported, as well as the *P* value for the interaction test.

We will conduct subgroup analyses for patients with the following baseline characteristics:

- Patients with severe sepsis versus those without severe sepsis.
- Patients with at least one non-renal failing organ versus those with single (kidney) organ failure.
- Patients with SOFA cardiovascular score of 3–4 versus those with a SOFA cardiovascular score of < 3 at baseline.
- Patients with known premorbid chronic renal disease (pre-admission eGFR < 60 mL/min, using MDRD equation) versus those with premorbid eGFR ≥ 60 mL/min.

#### 3.8.2 Rationale

The rationale for considering these subgroups is as follows. Patients with sepsis, multiorgan failure, vasopressor requirements or premorbid renal dysfunction have been reported as potentially having different outcomes and responses to therapy, or have been studied separately in other major studies of CRRT or haemodialysis.<sup>1,2,6-13</sup> They are considered likely to differ in terms of clinical course and potential response to therapy from the populations in epidemiological studies.<sup>14</sup>

#### 3.8.3 Presentation of results

Subgroup results for categorical variables will be presented as forest plots, with *P* values for heterogeneity (interaction test) for each pair of subgroups.

### 3.9 Control of type I error for multiple looks

The Haybittle–Peto rule with a maximum of three analyses will be used to control the overall type I error to 0.05. The

critical value to be used for primary and secondary outcomes in our study is 1.975.

### 3.10 Tables and figures

Tables will include baseline characteristics of the participants (Table 1), process measures and concomitant treatments (Table 2), outcomes including safety outcomes (Table 3 and Table 4), and subgroup analyses (Table 5). Examples of the format of the tables are available at <<http://www.thegeorgeinstitute.org/research/renal/studies/rct-of-normal-vs.-augmented-level-of-renal-replacement-therapy-in-icu---renal.cfm>>.

Planned figures are:

- A CONSORT diagram illustrating the flow of patients through the study (Figure 1).
- A line graph for mean (95% CI) morning urea concentration by treatment group for the first 14 days.
- A forest plot of odds ratios for death at 90 days for all patients and for the a-priori subgroups described in Section 3.8.
- A Kaplan–Meier curve for survival to 90 days.

### 3.11 Future ancillary analyses

Although the primary analysis is as described above, we plan to use the data obtained from this study to conduct subsequent exploratory analyses. The goal of these post-hoc analyses is to detect specific associations between aspects of the processes of care and outcomes in all patients combined. Such exploratory analyses will be defined and described before execution, after the primary analysis has been completed, and the results of the primary study are published.

### Acknowledgements

The statistical analysis plan was completed on 28 November 2008 and has been approved by the RENAL Study Management Committee.

### Author details

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#### Box 2. RENAL Study Investigators (listed alphabetically)

##### Australian Capital Territory

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##### New South Wales

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Concord Hospital: David Millis

John Hunter Hospital: Peter Harrigan

Liverpool Hospital: Deepak Bhonagiri

Mater Calvary Hospital, Newcastle: Jorge Brieva

Nepean Hospital: Louise Cole

Prince of Wales Hospital: Yahya Shehabi

Royal North Shore Hospital: Simon Finfer

Royal Prince Alfred Hospital: Richard Totaro

St George Hospital: John Myburgh

St Vincentis Hospital: Priya Nair

Westmead Hospital: Ashoke Banerjee

##### New Zealand

Auckland City Hospital/CVICU: Shay McGuinness

Auckland City Hospital/DCCM: Colin McArthur

Christchurch Hospital: Seton Henderson

Whangarei Hospital: Michael Kalkoff

##### Queensland

Mater Adult and Mater Private Hospital: John Morgan

Nambour General Hospital: Peter Garrett

Princess Alexandra Hospital: Chris Joyce

Royal Brisbane Hospital: Jeff Lipman

##### South Australia

Royal Adelaide Hospital: Arthus Flabouris

##### Tasmania

Royal Hobart Hospital: Andrew Turner

##### Victoria

Austin Hospital: Rinaldo Bellomo

Bendigo Hospital: John Edington

Epworth Hospital: Benno Ihle

Frankston Hospital: John Botha

Geelong Hospital: Neil Orford

Monash Medical Centre: Christopher Wright

Royal Melbourne Hospital: Megan Robertson

St Vincentis Hospital Melbourne: Antony Tobin

The Alfred Hospital: Carlos Scheinkestel

Western Hospital: Craig French

##### Western Australia

Fremantle Hospital: David Blythe

Royal Perth Hospital: Geoff Dobb