Design and Challenges of the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) Trial: High-Dose versus Standard-Dose Hemofiltration in Acute Renal Failure

The RENAL Study Investigators

Key Words
Intensive care · Acute renal failure · Dialysis · Continuous hemodiafiltration · Renal replacement therapy, continuous · Kidney

Abstract
Background/Aims: The optimal dose of renal replacement therapy (RRT) in acute renal failure (ARF) is uncertain. Methods: The Randomized Evaluation of Normal versus Augmented Level Replacement Therapy Trial tests the hypothesis that higher dose continuous veno-venous hemodiafiltration (CVVHDF) at an effluent rate of 40 ml/kg/h will increase survival compared to CVVHDF at 25 ml/kg/h of effluent dose. Results: This trial is currently randomizing critically ill patients in 35 intensive care units in Australia and New Zealand with a planned sample size of 1,500 patients. This trial will be the largest trial ever conducted on acute blood purification in critically ill patients. Conclusion: A trial of this magnitude and with demanding technical requirements poses design difficulties and challenges in the logistics, conduct, data collection, data analysis and monitoring. Our report will assist in the development of future trials of blood purification in intensive care. This study was registered with ClinicalTrials.gov (NCT00221013).

Introduction
In 2000, the Lancet published a single-center randomized trial suggesting that augmenting the dose of continuous renal replacement therapy (CRRT) in critically ill patients with acute renal failure (ARF) achieved a significant reduction in short-term mortality [1]. Ronco and colleagues randomized 425 ICU patients with severe ARF to receive one of three treatments using the CRRT technique of continuous veno-venous hemofiltration (CVVH): (1) CVVH at 20 ml/kg/h of effluent (low dose); (2) CVVH at 35 ml/kg/h of effluent (higher dose), and (3) CVVH at 45 ml/kg/h of effluent (highest dose). Survival in the low-dose treatment patients was significantly lower than in the higher-dose treatment patients and/or the highest-dose patients.

At the time of designing the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy Trial (the RENAL trial, 2005), additional support for the findings that increasing the dose of renal replacement therapy (RRT) might improve survival had emerged from a number of animal and human studies. Such support included indirect evidence from patients with chronic renal failure [2] and direct evidence from patients with severe ARF [3]. The RENAL study was designed to provide a randomized, controlled trial testing the hypothesis that the higher dose of renal replacement therapy improves outcome in critically ill patients with severe ARF.

1 The names of the RENAL Study Investigators are listed in the Appendix.
failure that, within a defined range, a higher dose of dialysis was associated with increased survival [2]; a retrospective analysis of the outcome of a large cohort of intensive care unit (ICU) patients with severe ARF at the Cleveland Clinic [3] showed that patients treated with a greater dose of dialysis had increased survival; a randomized controlled trial [4] comparing daily to second-daily dialysis demonstrated a survival advantage for the higher-intensity daily dialysis; a randomized controlled trial comparing continuous hemofiltration to peritoneal dialysis in ICU patients showed a survival advantage for the increased-dose regimen delivered with hemofiltration [5]; animal studies of high-volume hemofiltration in experimental sepsis and septic shock [6, 7] demonstrated improvement in hemodynamics with high-dose treatment, and phase I human studies of higher-intensity treatment (60–80 ml/kg/h of effluent) showed similar physiological effects and possible clinical outcome benefits [8, 9].

Whilst these studies collectively made a strong case for delivering higher-dose CRRT, some evidence was available in 2005 that was not supportive. Two recent studies in the chronic renal failure setting cast doubt on the suggestion that survival could be improved by increasing the dose of dialysis. A Mexican group of investigators conducted a multicenter, prospective, randomized controlled trial of the effects of increased peritoneal clearances on mortality in peritoneal dialysis patients [10]. This study demonstrated no clear survival advantage with increased dose. Similarly, a large multicenter randomized controlled trial of hemodialysis performed in the USA [11] found that increasing hemodialysis dose in patients receiving chronic hemodialysis conferred no significant improvement in mortality.

Globally, the higher dose ranges for CRRT dose proposed by Ronco et al. [1] were not embraced [12] in the acute setting for a variety of reasons. First, the study was conducted unblinded at a single center over 5 years. Second, the study population had a low incidence of sepsis, in contrast with international populations where sepsis is the predominant cause of ARF. Third, there were concerns about the additional cost of intensifying therapy (USD 150–200/day). Fourth, there was concern that increasing dialysis dose may lead to large and difficult to assess nutrient losses. Fifth, the study provided limited information on the ancillary care of patients, and finally, the study used an unusual primary outcome measure (survival 15 days after discontinuation of treatment) and provided no evidence of secondary outcome benefits.

Thus, in 2005, there appeared to be a possibility that increasing the dose of acute RRT might significantly increase survival but, as yet, this treatment has not been widely adopted. In response to this uncertainty, we designed, obtained funding for and began to conduct a phase III multicenter, randomized controlled trial comparing CRRT at a dose of 40 ml/kg/h of effluent with CRRT at a dose of 25 ml/kg/h of effluent. The aim of this trial was to provide high-quality evidence about the comparative effects of different levels of CRRT dose in patients with ARF treated in the ICU. This evidence will have direct relevance to decisions about the care of critically ill patients worldwide. If this study shows a benefit similar to the Ronco study, given the current incidence of severe ARF, it may save an estimated 15,000 lives/year worldwide.

Common to other large-scale clinical trials in ICUs and because of the additional issues related to blood purification technology, however, RENAL posed some unique and major challenges. Understanding their nature and how they were addressed may assist with the conduct of similar complex studies in the future. Accordingly, here we describe several important aspects of this study and how we met some of its challenges.

Ensuring an Ethical and Representative Control Treatment

There has been growing concern that investigators must ensure that the control group of any ICU trial will receive a level of care which represents current practice [13]. This is particularly important in the ICU because decisions about trial participation have to be made over a short period of time, the patient is typically unable to consent and the patient’s representative has to act on his/her behalf with limited time to consider the available options. Accordingly, as a prelude to this study, the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG) conducted a survey of CRRT practice in Australian and New Zealand (ANZ) ICUs. This survey included all intended trial hospitals and showed the following findings:

1. More than 98% of ICUs in ANZ treated ARF exclusively with CRRT, not intermittent hemodialysis.
2. Eighty-six percent of units prescribed a ‘fixed’ standard dose of 2 liters/h of effluent or less which was not adjusted for body weight.
3. Continuous veno-venous hemodiafiltration (CVV-HDF) was the most common CRRT technique.
4. The median estimated body weight among ANZ patients receiving CRRT was 80 kg and not 70 kg as usually assumed.

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[...]
Accordingly, the standard dose of dialysis (2 liters/h of effluent) was typically 25 ml/kg/h.

CRRT was associated with significant circuit down times [14] that effectively reduced the mean ‘dose’ of CRRT from the typically ‘prescribed’ dose of 25 ml/kg/h.

Accordingly, the average total daily treatment dose received by most people in ANZ at the time of the survey before the trial was approximately 25 ml/kg/h, a value slightly above the median worldwide [12]. For the RENAL study, this meant that randomizing patients to a control group at a 20 ml/kg/h dose of CRRT (as done in Ronco’s study) would have been unethical. On the other hand, a dose of 25 ml/kg/h of CRRT reasonably represented current practice in ANZ and was ethically justifiable.

**Selecting Study Treatments**

In addition to the survey results, to achieve feasibility, dose separation, clinical relevance and reproducibility, the choice of CRRT for the two arms of the study had to be based on the following principles:

1. The intervention dose should be the average of the two higher-dose treatments found to achieve improved outcomes in the *Lancet* study.
2. The dose difference between the treatment and control arms should be 15 ml/kg/h, the same as in the *Lancet* study.
3. The control arm should deliver a dose which reflected current practice.
4. The technique of CRRT should be the same for both the normal and augmented dose arms of the study.
5. The technique of CRRT should be deliverable using the machines available in ANZ ICUs at the time of inception.

As a result, it was agreed that patients in the control arm should receive CVVHDF at 25 ml/kg/h of effluent flow rate and that the intervention arm should receive CVVHDF with the generation of 40 ml/kg/h of effluent. For both treatments, it was agreed that dialysate flow and post-filter fluid replacement should be delivered in equal amounts (50% dialysate and 50% replacement fluid) in order to comply with the above requirements. The ratio of 1:1 for dialysate and replacement fluid flow represented current practice in ANZ. However, the relatively common practice of delivering replacement fluid in the pre-filter position had to be changed to avoid the solute dilution effect of such an approach. This effect would lead to greater solute dilution (and decreased urea and creatinine clearance) with 40 ml/kg/h of CRRT dose compared to 25 ml/kg/h and would significantly diminish the dose separation between the two treatments. Accordingly, it was agreed that post-filter replacement fluid administration was necessary.

**Other Technical Issues**

CVVHDF is a complex blood purification technique and correct application of this technique required that several technical aspects be dealt with in a way that ensured feasibility, clinical relevance and reproducibility.

**Anticoagulation**

CVVHDF circuits typically require anticoagulation to prevent filter clotting [12]. The method of anticoagulation varies from patient to patient and from institution to institution. To ensure patient safety, feasibility and clinical relevance, it was decided that choice of anticoagulation should be left to the treating clinician and recorded.

**Replacement and Dialysate Fluid Choice**

Replacement and dialysate fluids are produced commercially and come with different buffers (lactate, citrate and bicarbonate). The nature and concentration of the buffer can have profound effects on acid-base balance and, most notably, high doses of lactate-based fluids can induce hyperlactatemia [15]. Using lactate-based fluids in the study would have led to a differential effect on blood lactate between the two study groups and may have generated a major confounder. Accordingly, despite the additional cost, the investigators agreed that all patients should receive CVVHDF using bicarbonate-based fluids with an identical concentration of bicarbonate.

**Weight**

The RENAL investigators decided that patient weight would be measured directly wherever possible. If this was not possible, it was agreed that it should be estimated using a variety of sources of information (medical records, family, height-based assessment) as was done for the *Lancet* study.

**Membranes**

Membranes for CRRT have variable composition (modified cellulose, polyacrylonitrile, polysulfone, polyamide). These different compositions can produce quite different blood-membrane interactions and biological...
consequences. Accordingly, it was necessary to ensure that all patients were treated with the same membrane. We conducted a survey and found that the AN69 (polyacrylonitrile) membrane was used by 180% of study centers and that 70% of centers used the Prisma CRRT machine. These factors made it necessary to mandate the use of AN69 membrane in both groups.

Machines
As different units used different machines and as there was no reason to believe that machine choice would affect clearance in any specific way, different ICUs were allowed to use whatever CRRT machines were available to them, as long as they could deliver the trial therapy.

Blood Flow
It was agreed that target blood flow should be set at >150 ml/min. Blood flows of at least 150 ml/min were needed to ensure adequate small solute equilibration in the high-dose group. In addition, because replacement fluid was delivered post-filter, it was necessary to ensure sufficient blood flows to avoid marked hemoconcentration in the high-dose group. Such hemoconcentration would be expected to decrease filter life and possibly increase ‘down time’ for the high-dose circuits. This phenomenon could, in turn, decrease clearances in a way that reduced the differences in study treatments. It was felt that this approach to blood flow would minimize this possible bias.

Dialysis Catheters
Differences in patient size and associated risk of central venous catheter insertion require clinical judgment; thus decisions regarding the choice of catheter size (11.5 Fr or above) and access site were left to the discretion of the treating clinicians.

Ancillary Care
As this was a study of acute RRT, there was no intention of regulating other practices not related to RRT per se. However, an investigator brochure was issued to highlight important aspects of general patient care related to the two different doses. These aspects included antibiotic dose adjustments and nutritional adjustments that might derive from amino acid losses, phosphate losses, vitamin losses and trace element losses.

Ensuring a Representative Study Population
The RENAL study inclusion and exclusion criteria had to fulfill the following requirements: simplicity, clinical relevance and applicability to the majority of patients currently receiving CRRT in ANZ. As such, patients were excluded from the study if they were treated with CRRT for reasons other than ARF (overdose of drugs, temperature control, adjuvant treatment of sepsis); were less than 18 years old, were about to die, were already receiving dialysis for end-stage renal failure, or were unable to receive the protocol as planned or had been previously treated with acute dialysis. These issues were summarized in three principles of inclusion:

1. The treating clinician should believe that the patient requires CRRT for ARF.
2. The patient should fulfill at least one of several criteria for initiating acute CRRT (table 1).
3. The clinician should be uncertain about the balance of benefits and risks likely to be conferred by treatment with higher intensity or lower intensity CRRT. This ‘uncertainty principle’ has been used to guide patient inclusion in many other large trials in seriously ill patients [16].

We excluded the following patients: (1) age <18 years; (2) imminent (<24 h) death; (3) strong likelihood that the study protocol could not be delivered; (4) previous CRRT or dialysis during this hospital admission; (5) end-stage renal failure (patient receives chronic dialysis), and (6) the patient’s body weight is <60 or >110 kg (technology limit).

The weight upper limit was later altered to 120 kg (by formal trial amendment) as technology to deliver a higher dose in such patients became widely available in ANZ. The choice of a lower weight limit was dictated by the need to ensure that no patient would receive <1.5 liters/h of effluent, the lowest level delivered in ANZ ICUs prior to the trial.

Ensuring Appropriate Sample Size and Power
The treatment effect observed in the Lancet study was a reduction in mortality from 59 to 42% (29% relative re-
duction and 17% absolute reduction in mortality). We assumed a conservative 90-day mortality rate of 60% in our control group [17]. We also assumed a conservative estimate for the relative reduction in mortality in patients which was half that reported in the Lancet study (i.e. 14.5%) and a parallel absolute reduction in mortality of 8.5%. Based on these figures, we calculated that a study of 1,500 patients would have a 90% power of detecting an 8.5% absolute reduction from a 90-day mortality of 60% in the control group to 51.5% in the intervention group ($\alpha < 0.05$). Such a difference is clinically significant (number needed to treat $= 12$) and would likely lead to a wide-spread change in the practice of CRRT around the world. As the additional cost of the extra fluid needed is easily calculated and the average duration of therapy is approximately 5 days, this treatment would be highly cost effective at USD 12,000/life saved.

**Blinding**

To ensure patient safety, fluid removal and fluid replacement during CRRT must be closely monitored and the results known to the clinical staff treating the patients. As patient safety was considered paramount, it was not possible to design a study that would blind clinical staff to treatment allocation. It was considered that bias would be minimized by ensuring adequate concealment of treatment allocation prior to central randomization and by the use of robust, objective outcome measures such as all-cause, 90-day mortality. As the primary outcome was death, which is 100% verifiable, it was also not considered to be subject to ascertainment bias.

**Randomization and Allocation of Treatment**

Subjects had a 50% chance of being allocated to either the normal or augmented dose treatment group. The George Institute for International Health managed the web-based randomization via a secure password-protected, encrypted, web-based interface. The sequence was concealed until treatment was assigned. This system was available 24 h/day and 7 days/week.

**Duration of Treatment**

An important decision was related to the cessation of study treatment. The guiding principles were to ensure that standard practice should be altered as little as possible and that the study treatment should be given for as long as possible within such constraints. Accordingly, study treatment should continue until one of the following events applied: (1) death; (2) discharge from ICU; (3) the clinician considered that CRRT could be ceased and the patient had a spontaneous urinary output of at least 400 ml over the preceding 24 h, and (4) in the absence of criteria 1, 2, or 3, until at least 1 week had passed from randomization and the patient no longer required endotracheal intubation and/or vasopressor support.

Patients withdrawn from the randomized treatment for any reason were to be followed up according to the study follow-up schedule and analyzed according to the intention-to-treat principle. Once the study treatment ceased, further renal replacement was prescribed at the discretion of the clinical staff managing the patient. If the patients return to CRRT within 90 days after randomization, if clinically appropriate, they will return to treat-

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**Table 2. Major items for data collection during the RENAL trial**

<table>
<thead>
<tr>
<th>At baseline and before randomization</th>
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<tr>
<td>Patient identifiers</td>
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<tr>
<td>Key clinical characteristics</td>
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<tr>
<td>Inclusion and exclusion criteria</td>
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<tr>
<td>APACHE III and SAPS II or III? scores (intensive care, severity of illness scores)</td>
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<tr>
<td>Previous history of renal dysfunction</td>
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<tr>
<td>Pretreatment urea, creatinine, electrolytes and acid-base variables</td>
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<tr>
<td>Timing of start of CRRT</td>
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<tr>
<td>Urine volume</td>
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<td>Body weight</td>
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<tr>
<th>During follow-up in the intensive care unit</th>
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<tbody>
<tr>
<td>Daily urea, creatinine</td>
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<tr>
<td>Daily morning electrolytes and acid-base variables</td>
</tr>
<tr>
<td>Daily fluid balance</td>
</tr>
<tr>
<td>Daily nutritional intake</td>
</tr>
<tr>
<td>Type of machine used</td>
</tr>
<tr>
<td>Type and site of vascular access</td>
</tr>
<tr>
<td>Anticoagulation mode and dose</td>
</tr>
<tr>
<td>Filter life</td>
</tr>
<tr>
<td>Time spent off filtration daily</td>
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<tr>
<td>Complications of CRRT</td>
</tr>
<tr>
<td>Need for inotropic/vasopressor agents and/or positive pressure ventilation</td>
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<tr>
<td>Deaths and nonfatal serious adverse events</td>
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<tr>
<th>After live discharge from the intensive care unit</th>
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<tr>
<td>Vital status at ICU and hospital discharge</td>
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<tr>
<td>Vital status 28 and 90 days after randomization (for all patients who die during follow-up, information about the cause of death will be sought from collaborating centers)</td>
</tr>
</tbody>
</table>

Data on the use and duration of intermittent dialysis
ment with the previously assigned dose. RRT required after ICU discharge would be prescribed at the discretion of the clinical staff managing the patient and the type of dialysis, its frequency, duration and timing of cessation would be recorded.

Study Outcomes

The primary study outcome was set as all-cause mortality 90 days after randomization. Every randomized patient was to be followed up until either death or 90 days after randomization as recommended by the UK Medical Research Council International Working Party for Clinical Trials in Patients with Sepsis and Septic Shock [1]. Recent data indicate that mortality for patients with ARF reaches a plateau at between 60 and 90 days [17]. Secondary outcomes are presented in Table 3.

Adverse Events

The ICU environment poses major challenges to the identification of relevant adverse events as major derangements of physiology and clinical condition are daily occurrences. As the treatments under investigation are well-established as are their side effects, investigators were directed to report those adverse events they felt were potentially related to trial treatment.

Data Collection and Follow-Up

Streamlined data collection instruments and procedures were developed to minimize the work for collaborating centers. Data collection was restricted primarily to those variables necessary to define patient characteristics at baseline, the incidence and severity of biochemical abnormalities related to renal function, the timing of treatment initiation, the daily monitoring of biochemical and acid-base control, nutritional intake, fluid balance, post-CRRRT trial RRT (hemo- or peritoneal dialysis) and documentation of deaths and other serious adverse events during follow-up (Table 2).

Data Quality Assurance

Investigators agreed that an independent, trained and qualified representative of the George Institute for International Health would monitor the conduct of the study by visiting the sites. During the visits, information would be verified against source documents.

Informed Consent

Obtaining written and informed consent from patients the ICU is complicated because Intensive Care patients are often unconscious, sedated, intubated or too ill to understand information relating to clinical trial participation. The Declaration of Helsinki recognizes that some clinical research will involve patients who are physically incapable of giving informed consent (Principle 26, World Medical Association Declaration of Helsinki, 2000). For critically ill patients who were not able to provide consent, an explanatory statement was to be provided to their legal surrogate at the earliest opportunity, with additional consent from the necessary authorities (civil and administrative tribunals) as required by state or territory legislation or obtained from a legal surrogate when allowed by such legislation in ANZ. According to legislation, it was agreed that the participant information sheet would be provided to the patient when and if they regained legal capacity and were able to make an informed decision concerning continued participation in the study. Unless specifically prohibited by the patient or their legal surrogate, follow-up data was to be collected to day 90.

Analysis of Results

Analyses will be performed by independent statisticians on an intention-to-treat basis. Accordingly, at interim and final analysis, the baseline variables will be

Table 3. Secondary outcomes (all to be determined at 90 days and in relation to the index ICU admission)

<table>
<thead>
<tr>
<th>Outcome</th>
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<tbody>
<tr>
<td>Death in the intensive care unit</td>
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<tr>
<td>Death within 28 days of randomization</td>
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<tr>
<td>Death prior to hospital discharge</td>
</tr>
<tr>
<td>ICU-free days</td>
</tr>
<tr>
<td>Hospital-free days</td>
</tr>
<tr>
<td>Mechanical ventilation-free days</td>
</tr>
<tr>
<td>Vasopressor drug-free days</td>
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<tr>
<td>CRRRT-free days</td>
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<tr>
<td>RRT-free days</td>
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<tr>
<td>Dialysis-independent survival at 90 days</td>
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Table 2. Baseline characteristics (all to be determined at baseline)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>70/30</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>20</td>
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</table>

Design and Challenges of the RENAL Trial

summarized using descriptive statistics (means, standard deviations for continuous variables, frequencies and percentages for categorical endpoints). Mortality outcomes will be compared across treatment arms using a χ² test or a Fisher exact test as appropriate. Survival times at days 28 or 90 will be assessed by means of the log-rank test and presented as Kaplan-Meier survival curves. A measure of effect with its 95% confidence interval will also be reported; relative risk/hazard ratio or difference in means/proportions will be reported as appropriate.

Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee, comprising experts in clinical trials, biostatistics, nephrology and intensive care, was established. The committee was located in the United Kingdom and was charged with reviewing unblinded data on patient characteristics, treatment compliance and study outcomes at regular intervals during the study, monitoring total mortality and serious adverse events, and making recommendations based on other outcomes such as cause-specific death or serious nonfatal adverse events.

Organization and Collaboration

The study is being conducted under the auspices of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and the George Institute for International Health (GI), University of Sydney. It is overseen by a study management committee comprising principal and associate investigators. The coordinating and administrative center for the project is the

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Fig. 1. RENAL trial recruitment.
The ANZICS CTG and the George Institute have demonstrated ability to conduct such large-scale, multicenter clinical trials [18, 19].

**Patient Recruitment**

The trial has been recruiting from all centers since early 2006. Site investigators have now randomized more than 900 patients and recruitment is proceeding at close to the predicted rate (fig. 1). On current randomization rates, it is expected that recruitment will be completed by early October 2008.

**Outcomes and Significance**

This study will provide high-quality evidence about the comparative effects of different targets for CRRT dose in patients with ARF treated in the Australian and New Zealand intensive care setting. This evidence will have direct relevance to decisions about the care of critically ill patients admitted to ICUs. If the study confirms the treatment effect reported in the *Lancet* study, augmented dose CRRT should become the standard of treatment in Australia, New Zealand and worldwide.

**The Context**

This study must be seen within the broader issues surrounding RRT. They include choice of therapy and dose [20–23], the epidemiology of dose selection [23, 24], the best approach to dose calculation [24–28] and the debate concerning dose selection and modality selection [29, 30]. Finally, it must be seen in relation to the recent release of the results of the VA/NIH ARF trial [31]. Although a detailed discussion of these various aspects of RRT and the controversies that surround them is beyond the scope of this paper, we contend that, especially in view of the limitations of the VA/NIH ARF trial (late intervention, limited dose separation between high-dose IHD and low-dose CRRT, multiple modalities being applied to each patient, randomization after a period of up to 24 h of uncontrolled RRT in 64% of patients, high rate of non-recovery), the RENAL study will have significant and pivotal value of the intensive care and nephrology communities.

**Conclusion**

We have designed and are conducting a multicenter, randomized controlled trial of augmented dose RRT. Strong supportive evidence suggests this will reduce mortality, however, such therapy has not been widely adopted. We have addressed a variety of ethical, organizational, logistic and technical issues. If proven to decrease mortality, the proposed therapy would be highly cost-effective. This study is of great clinical and scientific importance and has the potential to save 15,000 lives per year worldwide.

**Acknowledgements**

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**Appendix**

The RENAL study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and George Institute for International Health.


*Site Investigators and Research Coordinators* (in alphabetical order)

**Australian Capital Territory**
Canberra Hospital: Jelena Gissane, Katya Malchukova, Imogen Mitchell and Jamie Rans

**New South Wales**
Blacktown Hospital: Asif Raza and Sara Treena
Concord Hospital: David Millis and Jeff Tan
John Hunter Hospital: Elise Crowfoot and Peter Harrigan
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References


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Nepean Hospital: Louise Cole, Rebecca Gresham, Maria Nikas and Leonie Weisbrrodt
Prince of Wales Hospital: Frances Bass, Michelle Campbell and Yahya Shehabi
Royal North Shore Hospital: Susan Ankers, Simon Finfer, Anne O’Connor and Julie Potter
Royal Prince Alfred Hospital: Dorriyln Rajbhandari and Richard Totaro
St. George Hospital: Alina Jovanovska, Francesca Munster and John Myburgh
St. Vincent’s Hospital: Jeff Breeding, Claire Burns and Priya Nair
Westmead Hospital: Ashoke Banerjee, Caroline Pfeffercorn and Anne Ritchie

New Zealand
Auckland City Hospital/CVICU: Michelle Eckleston, Shay McGuinness and Rachael Parke
Auckland City Hospital/DCCM: Jeanette Bell, Colin McArthur and Lynette Newby
Christchurch Hospital: Seton Henderson and Jan Mehtrens
Whangarei Hospital: Michael Kalkoff and Cathy West

Queensland
Mater Adult and Mater Private Hospital: John Morgan, Lorraine Rudder and Joanne Sutton
Nambour General Hospital: Peter Garrett, Nicole Groves and Jennifer Palmer
Princess Alexandra Hospital: Jean Helyar, Chris Joyce and Benjamin Mackie
Royal Brisbane Hospital: Claire Bertenshaw, Renae Deans, Cheryl Fourie, Melissa Lassig-Smith and Jeff Lipman

South Australia
Royal Adelaide Hospital: Jason Edwards, Arthus Flabouris, Stephanie O’Connor and Justine Rivett

Tasmania
Royal Hobart Hospital: Andrew Turner, Tanya Field and Kathryn Marsden

Victoria
Austin Hospital: Rinaldo Bellomo, Donna Goldsmith and Kim O’Sullivan
Bendigo Hospital: Catherine Boschert, John Edington and Julie Smith
Epworth Hospital: Michael Graan, Samuel Ho and Benno Ihle
Frankston Hospital: John Botha, Nina Fowler, Jodi Mclnness and Naomi Pratt
Geelong Hospital: Tania Elderkin and Neil Orford
Monash Medical Centre: Sue Burton, Carly Culhane, Pauline Galt, Rebecca Rutzou and Christopher Wright
Royal Melbourne: Deborah Barge, Tanja Caf, Belinda Howe, Patzy Low and Megan Roberston
St. Vincent’s Hospital Melbourne: Nicole Groves, Jennifer Holmes, Roger Smith and Antony Tobin
The Alfred Hospital: Rachael Nevill, Carlos Scheinkestel and Vicki White
Western Hospital: Craig French, Lorraine Little and Heike Raunow

Western Australia
Fremantle Hospital: David Blythe and Anna Palermo
Royal Perth Hospital: Melanie Boardman, Jenny Chamberlain, Geoff Dobb, Andree Gould, Geraldine McEntaggart, Samantha Perryman and Linda Thomas

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