Renal Enhanced Support by Preventing Excessive fluid with Conservative fluid Therapy in AKI

Research Protocol

Version 1.4

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# 1. Abbreviations

|  |  |
| --- | --- |
| AE | Adverse event |
| AKI | Acute kidney injury |
| AR | Adverse reaction |
| ANZIC RC | Australian and New Zealand Intensive Care Research Centre |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| ARDS | Acute respiratory distress syndrome |
| CRF | Case report form |
| CRRT | Continuous renal replacement therapy |
| CFP | Conservative fluid protocol |
| FB | Fluid balance |
| GCP | Good clinical practice |
| HRC | Health Research Council |
| HREC | Human Research Ethics Committee |
| ICU | Intensive care unit  |
| NHMRC | National Health and Medical Research Council |
| NUF | Net ultrafiltration |
| RCT | Randomised controlled trial |
| RESPECT | Renal Enhanced Support by Preventing Excessive fluid with Conservative fluid Therapy in AKI |
| RRT | Renal replacement therapy |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction |
| SOFA | Sequential Organ Failure Assessment |
| SUSAR | Suspected unexpected serious adverse reaction |
| TGA | Therapeutic Goods Administration |

# 2. Synopsis

### Title

Renal Enhanced Support by Preventing Excessive fluid with Conservative fluid Therapy in acute kidney injury

### Short Title

The RESPECT trial

### Background

Acute kidney injury (AKI) in the critically ill is common and associated with significant morbidity and mortality. The current management of AKI is supportive, with optimization of fluid status considered a key component. Traditionally, fluid therapy has been used to prevent and treat AKI, however, the value of this practice is uncertain. Fluid administration in critically ill individuals with or without AKI, does not universally improve renal function or urine output. Furthermore, a positive fluid balance has consistently been associated with an increased mortality in the intensive care unit. Emerging evidence has demonstrated that conservative fluid therapy in critically ill population is safe and has suggested a positive impact on renal function.

### Aim

To primary aim of this study is to determine the clinical impact of a conservative fluid protocol administered to critically ill patients with acute kidney injury who are deemed to be adequately fluid resuscitated

### Design

The study will be a multi-centre, electronic medical record-embedded, phase IIb/III randomised clinical trial.

### Setting

Intensive care units (ICUs) in Australia

### Population

Inclusion Criteria: Adult patient, admitted to the intensive care unit, less than 72 hours from admission; Acute kidney injury, as defined by stage 1 or greater KDIGO criteria; Deemed to be adequately fluid resuscitated as per treating clinician’s assessment; Patient to remain in ICU until the day after tomorrow.

Exclusion Criteria: Maintenance fluid deemed necessary, such as diabetic ketoacidosis, severe burns; Requirement for RRT, such as dialysable toxin; Commencement of RRT for AKI is likely in the next 6 hours; Chronic hemodialysis or peritoneal dialysis; Acute renal transplant; Presence or strong suspicion of post-renal obstruction; Severe hyponatremia (Na <125mmol/L) or hypernatremia (Na >155mmol/L); Need for extracorporeal membrane oxygenation; Previous enrolment in this study; Pregnant or lactating; Patients who are not to receive full active treatment

### Intervention

Conservative fluid protocol, involving avoidance of intravenous maintenance fluid, early administration of diuretic therapy, high caloric enteral nutrition where able, and concentrated medications when feasible.

### Outcomes

The primary feasibility outcome is fluid balance rom randomisation to 72 hours. The primary clinical outcome is peak serum creatinine from randomisation to day seven, or discharge from ICU. Secondary outcomes relate to feasibility, clinical efficacy and safety of the intervention.

### Sample Size

293 patients (147 in each arm)

### Study Period

Two years

### Registration

ANZCTR: In Progress.

Unique Trial Number (UTN): U1111-1271-6538.

# 3. Study Administration Structure

## 3.1 Coordinating Centre

### 3.1.1 Responsibilities

* Overall management of the trial including assistance with human research ethics committee (HREC) applications
* Contract management between parties as required
* Protocol design
* Database design and management
* Randomisation
* Coordination and monitoring of data entry and feedback of data enquiries
* Serious adverse event notification
* Data analysis and collaboration on publications
* Respond to general queries, including information about current recruitment status

## 3.2 Management Committee

### 3.2.1 Responsibilities

* Overseeing all aspects of the study management including:
* Liaison with coordinating centre staff and trial management centre staff
* Ensuring fiscal responsibilities are maintained
* Development and approval of final protocol and trial materials
* Development and approval of data collection tools and methods
* General trial management issues

### 3.2.2 Members

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Prof | Rinaldo | Bellomo | Co-DirectorDirector of ICU Research | ANZIC-RC, Monash UniversityAustin Health  |
| Dr | Kyle | White | Intensivist | Princess Alexandra Hospital |
| Prof | Kevin | Laupland | IntensivistDirector of Research | Royal Brisbane and Women’s Hospital |
| Dr | Siva | Senthuran | Intensivist | The Townsville General Hospital |
| Dr  | Peter | Garrett | IntensivistDirector of Research | Sunshine Coast University Hospital |
| Dr | James | McCullough | Intensivist | Gold Coast University Hospital |
| Dr | Emily | See  | Intensive Care Fellow | Austin Health |
| A/Prof | Kiran | Shekar | IntensivistDirector of Research | The Prince Charles Hospital |
| A/Prof | Peter | Kruger | Intensivist | Princess Alexandra Hospital |

##

## 3.3 Contact Details

### 3.3.1 Coordinating Centre

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### 3.3.2 Coordinating Investigator

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### 3.3.3 Chief Investigator and Chair Management Committee

Dr Kyle White

Staff Specialist

Intensive Care Unit

Princess Alexandra Hospital

Woolloongabba, Queensland

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## 3.4 Clinical Centres

### 3.4.1 Responsibilities

* Overall management of study at own site in line with the study protocol
* Patient follow up
* Data collection and data transfer
* Management of data queries
* Liaison with local HREC
* Adherence to local HREC guidelines and reporting requirements
* Respond to scientific queries

### 3.4.2 Site principal investigators

|  |  |
| --- | --- |
| Professor Rinaldo Bellomo | Intensive Care Unit, Austin Hospital, Heidelberg, Victoria |
| Doctor Kyle White | Intensive Care Unit, Princess Alexandra Hospital, Woolloongabba, Queensland |
| Professor Kevin Laupland | Intensive Care Unit, The Royal Brisbane & Women’s Hospital, Herston, Queensland |
| Dr Siva Senthuran | Intensive Care Unit, The Townsville General Hospital, Townsville, Queensland |
| Dr Peter Garrett | Intensive Care Unit, Sunshine Coast University Hospital, Birtinya, Queensland |
| Dr James McCullough | Intensive Care Unit, Gold Coast University Hospital, Southport, Queensland |
| A/Prof Peter Kruger | Intensive Care Unit, Princess Alexandra Hospital, Woolloongabba, Queensland |

# 4. Background

## 4.1 Acute Kidney Injury in the Critically Ill Population

Acute kidney injury is common in the critically ill population (1, 2) and is associated with significant morbidity and mortality (2-4). Individuals who develop an AKI in the intensive care unit (ICU) have a high mortality, the magnitude of which increases with severity of AKI (2). The current management of AKI is predominantly supportive, such as treatment of underlying cause, avoiding nephrotoxins, and ensuring appropriate fluid balance (5-7).

## 4.2 Fluid Therapy and Acute Kidney Injury

Conventional management for AKI is the administration of fluid to improve renal perfusion though increasing blood pressure and cardiac output (8). There is uncertainty surrounding the administration of fluid therapy in the critically ill population with acute kidney injury (8, 9). Hypovolaemia and sepsis are two of the most common causes of AKI in the critically ill population (10-12). Prompt fluid resuscitation and restoration of circulating volume may reduce the incidence or severity of AKI associated with these conditions (10).

AKI is not universally responsive to fluid therapy (13). In the critically ill population, low urine output is one of the most common indications for fluid bolus (12) and patients with severe sepsis who received a fluid bolus triggered by oliguria do not have an alteration in their urine output (14). Furthermore, in the CLASSIC trial, no difference in urine output was detected with a higher fluid balance (15).

In the absence of hypovolaemia, further administration of fluid to patients with AKI may not provide any benefit and in fact may lead to harm (16, 17). Fluid therapy leading to positive fluid balance may propagate AKI (18) and increase risk of mortality (19, 20). Observational data has suggested that an increasing positive fluid balance may lead to AKI by an increasing central venous pressure in ICU patients (21). Furthermore, increased fluid administration in AKI has been associated with impaired renal recovery (16).

## 4.3 Fluid Overload and Critically Ill

Independent of the presence of an acute kidney injury there is evidence of an association between positive fluid balance and adverse patient outcomes in the critically ill population (22-25). Admittedly, there is no prospective controlled trial in critically ill patients that demonstrates a reduction in overall fluid balance is associated with an improvement in a patient-centred outcome. However, there is evidence that fluid restrictive strategies in critically ill populations is safe with trials involving general ICU patients (26), patients with ARDS (27), or sepsis (15, 28). The evidence of safety is contrasted by a recent trial in patients undergoing major abdominal surgery, which demonstrated a restrictive fluid strategy for 24 hours postoperatively compared to usual was associated with an increased risk of acute kidney injury with no difference in mortality (29).

## 4.4 Reducing Fluid Balance in Acute Kidney Injury

Two recent trials have explored the impact of manipulating fluid balance in critically ill patients.

The REVERSE-AKI pilot trial compared usual care to restrictive fluid therapy in 100 euvolemic, critically ill adults with acute kidney injury (30). The authors demonstrated the feasibility of a restrictive fluid therapy protocol by producing a statistically and clinically significant difference in fluid balance at 72 hours. Furthermore, the restrictive fluid therapy protocol did not produce a signal of harm and adjusted analysis suggested an association with less renal replacement therapy in the restrictive fluid arm.

The IRIHS trial, compared regularly administered and titrated frusemide to no diuresis in the absence of acute pulmonary oedema or heart failure in mechanically ventilated patients (31). The intervention group had a statistically significant lower weight at extubation, with no difference in mechanical ventilation duration. Importantly, the investigators examined the presence of AKI and its deterioration over time. The intervention group had a statistically significant lower risk of renal function deterioration when compared to the control group.

## 4.5 Further Research

Fluid therapy has been identified by a panel of international experts as an important research topic regarding the management of critically ill patients with AKI (32). The REVERSE-AKI trial is the first clinical trial to prove the feasibility and safety a restrictive fluid protocol, albeit in a small cohort of patients. Furthermore, the IRIHS trial provides further evidence of safety when manipulating the fluid balance state of critically ill adults with AKI. Overall, the current literature supports the concept that limiting fluid administration to critically ill patients is safe and may result in an improvement in patient centered outcomes. We plan on conducting a pilot, randomized clinical trial in Australia to further investigation this important research topic.

# 5. Objectives

## 5.1 Aim

The primary aim of the study is to determine the clinical impact of a conservative fluid protocol administered to critically ill patients with acute kidney injury who are deemed to be adequately fluid resuscitated.

## 5.2 Hypothesis

We hypothesize that a conservative fluid protocol will improve renal recovery and reduce renal replacement dependence when compared to usual care.

# 6. Study Outcome Measures

## 6.1 Primary Outcomes

### 6.1.1 Primary Feasibility Outcome

Fluid balance from randomisation to 72 hours

### 6.1.2 Primary Clinical Outcome

Peak serum creatinine from randomisation to day seven, or discharge from ICU

## 6.2 Secondary Outcomes

### 6.2.1 Secondary Feasibility outcomes

* Fluid balance at 72 hours
* Fluid balance at ICU discharge
* Monthly recruitment rate
* Compliance with conservative fluid protocol
* Effective application of the eligibility criteria across multiple study centres
* Degree of separation in fluid balance between two groups

### 6.2.2 Serum Creatinine Secondary Outcomes

* Delta serum creatinine, difference between randomisation creatinine
	+ highest creatinine
	+ median creatinine
* Time-weighted serum creatinine from randomisation to day 7, or ICU discharge

### 6.2.3 Patient-centred outcomes

* Duration acute kidney injury
* Severity of acute kidney injury
* Duration of mechanical ventilation
* Need for renal replacement therapy (RRT)
* Duration of RRT
* 90-day dependence on RRT
* ICU length of stay
* Hospital length of stay
* ICU mortality
* Hospital mortality
* 30-day mortality
* 90-day mortality

### 6.2.3 Safety outcomes

* Hyponatraemia
* Hypernatraemia
* Hypokalaemia
* Hyperkalaemia
* Cardiac arrhythmia

# 7. Overall Study Design

## 7.1 Study design

The study will be a multi-centre, electronic medical record-embedded, phase IIb/III randomised clinical trial.

### 7.1.1 Phase IIb

The phase IIb portion of the clinical trial will assess the feasibility of the study protocol to produce separation of the two groups. This feasibility assessment will be assessed at a predefined recruitment target and will represent a hurdle to progress with phase III portion of the clinical trial. Furthermore, if separation of groups occurs, the initial phase IIb portion of the clinical trial will provide further information on effect size and allow adaption of recruitment target to ensure an appropriately powered trial.

### 7.1.2 Phase III

The phase III portion of the trial will only occur if the feasibility hurdle is met. This portion of the trial will assess the impact of the intervention on a clinically meaningful outcome.

## 7.2 Study Population

Critically ill adults admitted to the intensive care unit (ICU) with acute kidney injury.

## 7.3 Inclusion Criteria

* Adult patient, age >=18
* Admitted to the intensive care unit for less than 72 hours
* Acute kidney injury defined by any of the following:
	+ >= 1.5 times baseline creatinine (assume normal if baseline unknown)

OR

* + >= 27 umol/L (0.3mg/dL) absolute increase in creatinine

OR

* + < 0.5ml/kg/hr urine output for at least 6 hours
* Deemed to be adequately fluid resuscitated as per treating clinician’s assessment
* Patient to remain in ICU until the day after tomorrow

## 7.4 Exclusion Criteria

* Maintenance fluid deemed necessary (e.g. for diabetic ketoacidosis or severe burns)
* Requirement for RRT, such as dialysable toxin
* Commencement of RRT for AKI is likely in the next 6 hours
* Chronic haemodialysis or peritoneal dialysis
* Acute renal transplant
* Presence or strong suspicion of post-renal obstruction
* Severe hyponatremia (Na <125mmol/L) or hypernatremia (Na >155mmol/L)
* Need for extracorporeal membrane oxygenation
* Previous enrolment in this study
* Pregnant or lactating
* Patients who are not to receive full active treatment

|  |
| --- |
| Figure 1. Screening, Enrolment & Randomisation |
|  |

## 7.5 Co-enrolment in other ICU trials

In accordance with the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG) policy, we will seek agreement from other trials regarding inclusion or exclusion for co-enrolment of patients participating in this study.

# 8. Study Procedures

## 8.1 Intervention

The trial intervention will be a conservative fluid protocol (CFP), which will empower treating clinician to achieve daily negative fluid balances after randomisation. The CFP will consist of bundle of therapies targeting fluid input and fluid output to guide the treating team to achieve targets.

### 8.1.1 Conservative Fluid Protocol

Aim

* Achieve a daily negative daily fluid balance (FB)

Methods

* Implementation of conservative fluid protocol interventions
* Recommend formal twice-daily assessment of fluid balance

Interventions

1. No maintenance intravenous (IV) fluids
	1. IV fluids no greater than 10ml/hr
	2. IV fluids for medications permitted, see below
	3. Exception when unable to provide fluid via enteral or parenteral nutrition
2. Early commencement of diuretic therapy if unable to achieve negative fluid balance
	1. Commence when fluid balance goals not met
	2. Choice of drug as per treating clinician
	3. Dose escalation if not meeting FB goals
3. Concentrated enteral nutrition when feasible
	1. Parenteral nutrition allowed, as per treating clinician
4. Concentrated antibiotics and medications when feasible

### 8.1.2 Fluid boluses

A change in clinical state, or unexpected deterioration, is not uncommon in critically ill patients, therefore, there is a requirement for the trial intervention to accommodate fluid boluses.

In the presence of clinician determined intravascular hypovolaemia, fluid boluses can be given in the intervention when one of following five clinical signs are present:

* Heart rate > 90 bpm
* SBP < 100 mmHg
* MAP < 75 mmHg
* CVP < 10 mmHg
* PAWP < 12mmHg

## 8.2 Control

Usual care will be provided to the control group as per unit policies and guidelines. The treating clinician will be responsible for all decisions regarding intravenous fluid, diuretics, nutrition and fluid balance management. There will be no fluid balance target provided to control group.

## 8.3 Renal Replacement Therapy

The study protocol does not impact the decision to commence RRT. Commencement of RRT and all related fluid balance management decision will be at the discretion of the treating clinician.

## 8.4 Screening Log

The screening log is designed to monitor patient recruitment at each participating site. It will be maintained by the local research coordinator to document patients evaluated for enrolment. The log will provide a record of all patients assessed for eligibility for the study. Research coordinators will review potentially eligible patients at the first available opportunity after admission to ICU. Only eligible patients who meet exclusion criteria or are not recruited will be added to the log and the criteria that excluded them. The log will be used to assess patient recruitment targets.

|  |
| --- |
| Figure 2. Conservative Fluid Protocol |
|  |

## 8.5 Randomization

Eligible patients will be randomised as soon as possible after fulfilling the criteria for enrolment. A permuted block randomisation with stratification by study site will be used. Patients will be allocated in a 1:1 ratio to either Conservative Fluid Protocol (CFP) or Standard Care Group. A centralised web-based system (REDCap) will be employed, allowing 24-hour enrolment and random allocation. The random allocation sequence will be generated using a computer software program by the coordinating centre and embedded into the REDCap system. Site investigators, site research coordinators, or study participants do not have access to the allocation sequence throughout the trial. A senior statistician does not have access to the treatment allocation throughout the trial.

## 8.6 Blinding

The trial will be conducted as an open-label study. All site personnel will be aware of treatment allocation.

## 8.7 Duration of Study Treatment

The study treatment will continue for seven days after randomisation or discharge from the intensive care unit. If the patient is readmitted to the ICU within the seven days, the intervention should be reapplied.

## 8.8 Concomitant Treatment

Outside of the intervention and control procedures, all patients enrolled in this study will be managed as per standard care. The ICU team will have full and independent control of patient management, which will not be affected by participation in the study.

# 9. Ethics

## 9.1 Guiding Principles

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008, 2013 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments, and he NHMRC National Statement on Ethical Conduct in Research Involving Humans 2007 (Updated 2018).

## 9.2 Ethical Considerations

### 9.2.1 Consent

The major ethical issue associated with this study is related to the recruitment of participants who are dependent on medical care and in need of immediate intervention for the management of the life-threatening condition. The process for obtaining consent will be according to the following hierarchy:

* Where possible, and as authorised by local jurisdictions, consent will be obtained from the participant or the participant’s legally authorized substitute decision maker (SDM).
* Where it is not possible or practicable for the SDM to consider the study and give consent within an appropriate timeframe, the patient may be enrolled without prior consent, provided the procedure is in accord with the requirements of applicable legislation.

Where appropriate, the patient and SDM, will be informed of the study and will be able to withdraw consent for ongoing participation at any time.

### 9.2.2 Confidentiality of patient data

After enrolment, patients will be allocated a unique study number. The site research coordinator will compile an enrolment log including the patient’s name, date of birth, hospital identification number, unique study number and date and time of enrolment.

Subsequent data will be identified by the unique study number only. The enrolment log and study data will be kept separately. Study data will be entered into a centralised web-based system (REDCap) which will be password protected managed by the coordinating research centre. No identifying data will be entered.

Similarly, hard copies of the enrolment log will be stored separately in the locked office of the principal investigator or research coordinator. Only the research team will have access to this information, and they will not disclose this information to any other person or entity. When archiving, the study site investigators will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The investigator will maintain the confidentiality of all study documentation and take measures to prevent the accidental or premature destruction of these documents. The investigator will retain the study documents at least 15 years after the completion or discontinuation of the study. The investigator must notify the study management committee prior to destroying any essential study documents following the study completion or discontinuation.

If any investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the coordinating centre or another investigator. The coordinating centre must be notified of and agree to the change. All associated documentation must also be updated.

### 9.2.3 Ethics Committee Approval

Each participating site will submit this protocol, and any other relevant study documentation to the responsible local or national constituted HREC (or equivalent). Approval of the protocol and related documents will be obtained prior to the start of the study at each site. It is the principal investigator’s responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the HREC (or equivalent) as required by that committee.

# 10. Data Management

## 10.1 Data collection methods

Data for this study will be extracted from the electronic health record, ANZICS Adult Patient Database, National Death Index, and Australia and New Zealand Dialysis and Transplant Registry. Only data collected as part of routine care will be utilised for this study. For the primary analysis, randomised patients will be followed until death or 90 days post-randomisation, whichever occurs first. A secondary analysis using the National Death Index and Australia and New Zealand Dialysis and Transplant Registry will follow patients for 1 year. Study day 1 commences on randomisation and concludes at the expiry of the calendar day.

Data collection will be restricted primarily to those variables necessary to define clinical patient characteristics including baseline demographics, primary diagnoses, physiological parameters, diagnostic interventions, therapeutic interventions and documentation of deaths and other serious adverse events.

## 10.2 Data variables

* Patient Characteristics
	+ Sex
	+ Age
	+ Weight
	+ Height
	+ Co-morbidities (as per ANZICS CORE)
		- Diabetes mellitus
		- Hypertension
		- Congestive heart failure
		- Chronic obstructive airways disease
		- Chronic liver disease
		- Malignancy
		- Chronic renal failure
	+ Baseline serum creatinine level and eGFR
		- defined as most recent value measured between 7 and 365 days prior to ICU admission
* Diagnosis
	+ ICU Diagnosis
	+ Primary Hospital Diagnosis
	+ Secondary Hospital Diagnosis
	+ Hospital Admission Source
	+ ICU Admission Source
* Daily ICU Fluid Balance Data (Randomisation to Day 7)
	+ Daily fluid balance
	+ Daily fluid input total
		- crystalloid
		- colloid
		- oral
		- enteral nutrition
		- parenteral nutrition
		- packed red blood cells (PRBC)
		- fresh frozen plasma or cryoprecipitate
		- pooled platelets
		- other
	+ Daily fluid output total
		- urine
		- drain
		- gastrointestinal
		- ICC
	+ Daily diuretic dose
		- Daily frusemide dose
		- Daily spironolactone dose
		- Daily thiazide dose
		- Daily acetazolamide dose
		- Daily bumetanide dose
* Other Daily ICU Data (Randomisation to Day 7)
	+ SOFA score
	+ APACHE III score
	+ Daily weights
	+ GCS (highest and lowest)
	+ Serum creatinine (highest and lowest)
	+ Serum urea (highest and lowest)
	+ pH (highest and lowest)
	+ Serum potassium (highest and lowest)
	+ Serum bicarbonate (highest and lowest)
	+ Base excess (highest and lowest)
	+ Lactate (highest and lowest)
	+ Serum bilirubin (highest and lowest)
	+ Serum platelets (highest and lowest)
	+ Serum ALT (highest and lowest)
	+ Serum white cell count (highest and lowest)
	+ Serum haemoglobin (highest and lowest)
	+ PaO2 / FiO2 ratio (highest and lowest)
	+ Ventilatory support required (yes / no)
	+ Maximum type of ventilatory support required (MV, NIV)
	+ Mechanical circulatory support required (yes / no)
	+ Maximum type of circulatory support required (IABP)
	+ Vasopressor support required (yes / no)
	+ Vasopressor Noradrenaline Equivalent
	+ Vasoactive Inotrope Score
	+ Renal replacement therapy required (yes/no)
* Administrative Data
	+ Hospital admission date and time
	+ ICU admission date and time
	+ ICU discharge date and time
	+ Hospital discharge date and time
* Outcomes
	+ Hospital LOS (days)
	+ ICU LOS (days)
	+ Duration of mechanical ventilation (hours), includes all occurrences of MV
		- Date and time of commencement of mechanical ventilation
		- Date and time of cessation of mechanical ventilation
	+ Duration of renal replacement therapy (hours)
		- Date and time of commencement of RRT
		- Date and time of cessation of RRT
	+ RRT-dependence on ICU discharge
	+ RRT-dependence at 90-days
	+ RRT-dependence at 1-year
	+ ICU mortality
	+ Hospital mortality
	+ 28-day mortality
	+ 90-day mortality
	+ 1-year mortality

## 10.3 Data management

Data management will be coordinated by the coordinating research centre and will include programming (online study database design) and data management support (including data monitoring, database questions, technical issues, data queries, query resolution).

## 10.4 Data quality and monitoring

Several procedures to ensure data quality and protocol standardisation will help to minimise bias and to optimise data quality. These include:

* A site initiation teleconference conducted before site activation to ensure consistency in procedures
* A detailed data dictionary will define the data to be collected
* The coordinating centre will perform timely validation of entered data, queries and corrections

The study will be monitored by quality control reviews of protocol compliance, data queries, safety reporting and protocol deviations. On-site monitoring will only be performed on a case by case basis if quality control issues are flagged by electronic review of data. Medical records, any other relevant source documents and the site investigator files must be made available to the monitoring representative for these monitoring visits during the study and at the completion of the study as needed.

## 10.5 Protocol Deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

Given that the investigator is responsible for patient safety and care he/she may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to trial patients without prior HREC approval. The implemented deviation or change must be reported in a protocol deviation form. The deviation must be reported via the study website by the principal investigator. Protocol deviation summaries will be reported in accordance with the requirements of the approving HREC; a serious breach will be reported ASAP.

# 11. Statistical Considerations

## 11.1 Power calculation and sample size

No previous data for the calculation of the sample size is available. In the absence of accurate, current data, the estimate of the standard deviation was based on a previous study in a similar population (30). Considering a standard deviation on the primary feasibility outcome of 2850 litres, an expected difference of 1000 litres, a power of 80%, a two-sided alpha of 0.05, and an inflation of 15% due to the possibility of using rank-sum tests, 293 patients (147 in each arm) are needed. The estimation of the standard deviation will be updated from the pooled SD from the first 50 patients, and a blinded sample size recalculation is planned.

## 11.2 Analysis of Results

A senior statistician at Queensland University of Technology will perform data analysis on an intention-to-treat basis. Summary statistics will be used to describe the clinical data and presented as mean ± SD, median with interquartile range (IQR) or percentages as appropriate. Chi-squared analysis with Fisher’s exact test (when appropriate), and Student’s t-test (Mann Whitney U test for non-normal distributions) will be used to compare data between the active treatment group and the control group with statistical significance declared for probability values of 0.05 or less. Analysis of the outcome of excluded patients (e.g. due to other trials) will be performed in accordance with the CONSORT guidelines. A complete and finalised statistical analysis plan will be prepared and made available before the recruitment.

# 12. Safety Monitoring and Reporting

## 12.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC), consisting of experts in intensive care, clinical research and biostatistics will be established before patient enrolment and will review all trial protocols. The role of the DMC will be to provide study oversight to ensure that the rights and safety of patients involved in the study are protected by reviewing reported Adverse Events and making recommendations to the Management Committee (MC). Intensive care patients experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. Intensive care patients will frequently develop life-threatening organ failure(s) unrelated to study interventions and despite optimal management. Therefore, consistent with established practice in academic ICU trials, events that are part of the natural history of the primary disease process or expected complications of critical illness will not be reported as serious adverse events in this study. All adverse events which are considered to be potentially causally related to the study intervention or are otherwise of concern in the investigator’s judgement will be reported. There are no planned interim analyses for this feasibility trial.

## 12.2 Adverse event (AE) / Adverse Reaction (AR)

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with this treatment. It is recognised that the patient population with critical illness will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying illness and the impact of standard therapies. These will not necessarily constitute an adverse event unless they are considered to be of concern or related to the study or the intervention in the investigator's clinical judgement. In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported, e.g. renal failure rather than hyperkalaemia, and agitation rather than self-extubation.

An adverse reaction is defined as any untoward and unintended response to an investigational medicinal product or procedure. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product will qualify as adverse reactions.

## 12.3 Serious adverse events (SAE) / Serious adverse reactions (SAR)

A serious adverse event (SAE) or serious adverse reaction is defined as any adverse event/reaction that:

* Results in death
* Is life-threatening
* Requires hospitalisation or prolongation of current hospitalisation
* Results in persistent or significant disability or incapacity

Death is an expected outcome among patients with AKI, therefore, death will not be considered a serious adverse event. Standard care of patients with AKI includes a host of complications that fit the definition of an SAE. Medical and scientific judgement will be exercised by the site principal investigator in deciding whether an adverse event/ reaction will be classified as serious in other situations to avoid over-reporting.

## 12.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reaction (SUSAR) is defined as being an adverse reaction that is both serious and unexpected.

## 12.5 Reporting AEs, SAEs and SUSARs

Adverse events/reactions and serious adverse events/reactions will be recorded on a separate case report form. SAEs and SUSARs should be reported to the coordinating centre within 24 hours of study staff becoming aware of the event.

Minimum information on the report form will include:

* Patient initials and study number
* Nature of the event
* Commencement and cessation of the event
* An investigator’s opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitively related).
* Whether treatment was required for the event and what treatment was administered.

The coordinating centre staff will be responsible for following-up all events to ensure all details are available. The coordinating centre is also responsible for reporting directly to HRECs and investigators, who forward any relevant information to their institution. It is the responsibility of each principal investigator to inform the local or lead HREC of all SUSAR events which occur at their hospital, in accordance with local requirements. Copies of any reporting and correspondence to and from the local HREC should also be sent to the coordinating centre.

## 12.6 Contact phone numbers for SAE advice

Chief Investigation (Dr Kyle White): +61430392529

Coordinating Research Center: +61730761777

# 13. Funding

Funding will be sought to compensate individual centres for the cost of conducting the trial.

# 14. Publication Policy

The study will be conducted in the name of the management committee. The principal publication from the study will be in the name of the management committee with full credit assigned to all collaborating investigators, research coordinators and institutions. Where an individuals’ name is required for publication it will be that of the writing committee, with the chair of the writing committee listed first and subsequent authors listed alphabetically. Funding bodies will be acknowledged in the publication.

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# 16. Appendix

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| Appendix 1 – Conversion to Noradrenaline Equivalent  |
| Drug | Dose | Noradrenaline Equivalent |
| Adrenaline | 0.1 ug/kg/min | 0.1 ug/kg/min |
| Noradrenaline | 0.1 ug/kg/min | 0.1 ug/kg/min |
| Dopamine | 15 ug/kg/min | 0.1 ug/kg/min |
| Phenylephrine | 1.0 ug/kg/min | 0.1 ug/kg/min |
| Vasopressin | 0.04 units/min | 0.1 ug/kg/min |

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| Appendix 2 – Vasoactive Inotrope Score  |
| Drug | Units | Modifier |
| Dopamine | ug/kg/min | 1 |
| Dobutamine | ug/kg/min | 1 |
| Noradrenaline | ug/kg/min | 100 |
| Adrenaline | ug/kg/min | 100 |
| Milrinone | ug/kg/min | 10 |
| Vasopressin | units/kg/min | 10000 |