STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI): A Multi-Centre, Randomized, Controlled Trial

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CONFIDENTIAL

Principal Investigators:

Sean M. Bagshaw, MD MSc FRCPC
Division of Critical Care Medicine, Faculty of Medicine and Dentistry
University of Alberta
Associate Professor, Division of Critical Care Medicine
University of Alberta
2-124E Clinical Sciences Building
8440-112 Street
Edmonton, Alberta
T6G 2B7
Phone: 780-492-3817
Fax: 780-492-1500
Email: bagshaw@ualberta.ca

Ron Wald, MDCM MPH FRCPC
Division of Nephrology, Department of Medicine
St. Michael's Hospital
Assistant Professor, Department of Medicine
University of Toronto
30 Bond Street
Toronto, Ontario
M5B 1W8
Phone: 416-867-3703
Fax: 416-867-3709
Email: waldr@smh.ca

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Protocol Synopsis

Background: Acute kidney injury (AKI) is a common and devastating complication of critical illness. Once AKI is established, treatment is largely supportive and no intervention has been found to restore kidney function or improve overall survival. Renal replacement therapy (RRT), usually in the form of hemodialysis, is frequently needed to manage patients with severe AKI. Such patients have an in-hospital mortality that consistently exceeds 50% with delays in RRT initiation implicated as a possible contributor. A recent meta-analysis suggested that earlier initiation of RRT may improve survival, but this is based on data derived overwhelmingly from observational studies. Our group recently completed a multi-centre pilot randomized controlled trial that confirmed the feasibility of allocating patients to two different strategies of RRT initiation. Patient recruitment and follow-up, as well as patient safety, were successfully demonstrated during the pilot phase of this research program.

Objectives: The objectives of this trial are to determine whether, in critically ill patients with severe AKI, randomization to accelerated initiation of RRT, compared to a conservative strategy consistent with standard care, leads to:

1. *Improved survival* (primary outcome) at 90 days; and
2. *Recovery of kidney function* (*principal* secondary outcome), defined as independence from RRT at 90 days

Study Population: We will enroll 2,866 critically ill patients with severe AKI who do not have an urgent indication for RRT initiation at the time of screening but who have a reasonable likelihood of ultimately requiring RRT. Recruitment will occur at centres in Canada, the USA, Australia, New Zealand, the UK, Austria, and potentially several other countries.

Inclusion criteria (all need to be fulfilled for eligibility):

1- Age ≥ 18 years

2- Admission to an critical care unit (CCU)

3- Evidence of kidney dysfunction [serum creatinine ≥100 μmol/L (women) and ≥ 130 μmol/L (men)]

4- Evidence of severe AKI defined by at least 1 of the following 3 criteria:

- i) ≥ 2-fold increase in serum creatinine from a known pre-morbid baseline or during the current hospitalization; OR
- ii) Achievement of a serum creatinine ≥ 354 μmol/L with evidence of a minimum increase of 27 μmol/L from pre-morbid baseline or during the current hospitalization; OR
- iii) Urine output < 6.0 mL/kg over the preceding 12 hours

Exclusion criteria (any of the following factors will result in ineligibility):

1- Serum potassium > 5.5 mmol/L

2- Serum bicarbonate < 15 mmol/L

3- Presence of a drug overdose that necessitates initiation of RRT

4- Lack of commitment to ongoing life support (including RRT)

5- Any RRT within the previous 2 months (either acute or chronic RRT)

6- Kidney transplant within the past 365 days

7- Known pre-hospitalization advanced chronic kidney disease, defined by an estimated glomerular filtration rate < 20 mL/min/1.73 m^2

8- Presence or clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy or acute interstitial nephritis

9- Clinician(s) caring for patient believe(s) that immediate RRT is absolutely mandated

10- Clinician(s) caring for patient believe(s) that deferral of RRT initiation is mandated

The patient or substitute decision maker will be asked to provide consent within 12 hours of the above criteria being met. Alternatively, in the absence of a substitute decision maker and where approved by the local Ethics Board, enrollment by deferred/delayed consent will need to be documented within 12 hours of the above criteria being met. The patient will be excluded if consent cannot be obtained (or enrollment by deferred/delayed consent cannot be documented) during this time window.

Interventions

Accelerated RRT initiation (experimental arm): A dialysis catheter will be placed and RRT initiated as soon as possible and no more than 12 hours after the patient became fully eligible.

Standard RRT initiation (control arm): In the absence of kidney function recovery, the initiation of RRT will be permitted if one of the following develops: serum potassium ≥ 6.0 mmol/L; pH ≤ 7.20 or serum bicarbonate ≤ 12 mmol/L; evidence of severe respiratory failure, based on a PaO_2/FiO_2 ≤ 200 and clinical perception of volume overload; and/or persistent AKI > 72 hours following the time of randomization. Once a decision is made to start RRT, a dialysis catheter will be placed and RRT initiated as soon as possible.

All aspects of RRT (i.e. RRT modality, dose, anticoagulation) administered to patients in both treatment arms will follow guidelines that reflect local practice and usual standards of care.

Outcomes

Primary outcome:

All-cause mortality at 90 days.

Secondary outcomes:

1 - RRT dependence at 90 days among surviving patients.
2 - Composite of death or RRT dependence at 90 days.
3 - Estimated glomerular filtration rate among patients alive at Day 90.
4 - Albuminuria at Day 90.

5 - Major adverse kidney outcomes, defined as death, RRT dependence or sustained reduction in kidney function (defined as eGFR < 75% baseline eGFR) at 90 days.
6 - Mechanical ventilation-free days through day 28.
7 - Vasoactive therapy-free days through day 28.
8 - ICU-free days through day 28.
9 - Hospitalization-free days through day 90.
10 - Death in ICU, at 28 days, and in-hospital.
11 - EuroQoL EQ-5D-5L (a measure of health-related quality of life and patient utility) at day 90 and at 1 year among survivors.
12 - Health care costs through day 365.
13 – Vital status and RRT dependence at 365 days among survivors.

Implications:

The optimal timing of RRT initiation is an existing knowledge gap and a clear priority for investigation. With the successful completion of the STARRT-AKI pilot trial, the feasibility and relevance of the proposed interventions has been established. It is now time to definitively evaluate whether earlier/pre-emptive/accelerated RRT initiation is associated with enhanced survival as compared to a conservative strategy for initiation of RRT, which is driven by conventional indications and clinician judgment.

SECTION 1. BACKGROUND

1.1 Scope of the clinical problem

In critically ill patients who require support in an intensive care unit (ICU) setting, the development of acute kidney injury (AKI) is common. Recent epidemiologic data show that AKI rates among critically ill patients are increasing and that AKI complicates the ICU course in up to 67% of patients.[1-4] For critically ill patients with more severe forms of AKI, renal replacement therapy (RRT), also known as dialysis, is frequently employed.[5] For these individuals, RRT initiation often results in a considerable escalation in both the complexity and associated costs of care.[6] Moreover, these critically ill patients experience substantial morbidity, including non-recovery of kidney function and RRT dependence,[7-9] and excess mortality, with hospital case-fatality rates commonly exceeding 50%.[5,10]

Many aspects of RRT delivery to critically ill patients with AKI remain uncertain resulting in heterogeneity in the prescription and delivery of acute RRT.[11,12] Life threatening scenarios such as severe hyperkalemia, profound non-lactate-related metabolic acidosis, and severe fluid overload resulting in respiratory failure are complications of AKI that can be readily corrected with RRT. *In such situations, the need to initiate RRT is unequivocal.* However, in the ICU, patients with severe compromise of kidney function without these complications are commonly encountered. ***The optimal time for initiating RRT in patients without a life-threatening complication of AKI is unknown.***

Initiating RRT earlier in critically ill patients with AKI may confer better control of uremia, acid-base homeostasis, electrolyte imbalances, extracellular volume accumulation and systemic inflammation. The earlier initiation of RRT would also prevent the development of a life-threatening complication of AKI such as a hyperkalemia-associated arrhythmia. Intuitively, the earlier initiation of RRT in the absence of life-threatening complications may confer a variety of benefits and is supported by the preponderance of available data, mostly derived from observational studies.[13,14] As a result, this practice has become common and endorsed by key opinion leaders. On the other hand, there is no high quality evidence to support the notion that the initiation of RRT - in the absence of a life-threatening complication of AKI – modifies clinically important outcomes. This problem is compounded by the fact that RRT is associated with potential risks and entails significant costs.[16] Furthermore, most of the observational studies did not consider patients with AKI who did not receive RRT. There is a possibility that with a strategy of supportive management and the introduction of RRT only when a life-threatening complication supervenes, some patients with severe AKI might recover kidney function spontaneously *without ever starting RRT*. As a result, widespread adoption of a clinical strategy of early RRT commencement might expose patients, some needlessly, to the risks of RRT while inflating costs.

As a consequence, there is a critical knowledge gap in evidence to guide the ideal timing and circumstances for initiation of RRT in critically ill patients with AKI. The Acute Kidney Injury Network (AKIN), an international working group comprised of experts from both nephrology and critical care, identified the question, ***"When should RRT be initiated, and does timing affect outcome?"*** as the highest-ranked priority research topic by both nephrologists and critical care experts.[17] Noting the absence of evidence in this area, the recently-released Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice

Guideline for AKI recommended the pursuit of research to ***"Determine [if] early vs late start of RRT….results in improved outcomes (eg, mortality, evolution to chronic kidney disease stage 5) in AKI patients."***[18] The National Institute for Health and Care Excellence (NICE) in the United Kingdom recently issued a statement, as part of its set of Guidelines on AKI noting that ***"A prospective study is needed of adult inpatients with acute kidney injury AKIN stages 2 and 3, who are likely to need renal replacement therapy within a given timeframe (for example, 72 hours), but have no urgent need for therapy."***[19] This is in essence the trial we have planned. In summary, there is international consensus around the necessity to perform a definitive trial to determine whether the earlier initiation of RRT leads to improved patient-relevant outcomes. A trial showing superior survival with accelerated RRT initiation will establish this approach as the standard of care; on the other hand, the absence of superiority of an accelerated RRT strategy will justify a more conservative approach to RRT initiation thereby leading to significant resource savings. **As a result, our proposed trial will have a meaningful clinical impact irrespective of its findings.**

1.2 Study objectives

The principal research questions for the proposed trial are:
In critically ill patients whose course is complicated by the development of AKI, and who do NOT have urgent clinical indications to commence RRT, does the accelerated initiation of RRT, compared with initiation of RRT using standard indications and clinical judgment, lead to

1) ***A lower risk of mortality at 90 days (primary outcome)?***
2) ***A lower likelihood of persistent RRT dependence at 90 days among survivors (principal secondary outcome)?***

This proposed trial is intended to be the definitive guide for clinical practice and address one of the most pressing and controversial questions in the field of Critical Care Nephrology.

1.3 Consensus regarding the need for a trial

The acute delivery of RRT to critically ill patients with AKI is common practice; yet there have been controversies regarding the optimal delivery of RRT for these patients that have been clarified in recently completed randomized trials. These have largely focused on the delivered dose/intensity of RRT,[20-22] RRT modality[23,24] and RRT clearance mode.[25,26] ***However, characterization of the optimal time to initiate RRT, in particular whether earlier initiation translates into improved clinical outcomes, remains unknown, and is a clear priority for higher quality evidence.*** [18]

1.4 Review of the literature on the timing of RRT initiation in AKI

A number of retrospective cohort studies have suggested that earlier RRT initiation may improve outcomes. Gettings et al performed a retrospective single centre study of trauma-related AKI where a serum urea of 21.4 mmol/L at RRT initiation was used as a cut-off to discriminate between early and late RRT.[27] This study found that "early RRT" was initiated nine days earlier than "late RRT", and was associated with a shorter total hospitalization and lower mortality (61% for "early" starters vs 80% for "late" starters). In a multicentre retrospective cohort study, Liu et al found that "early RRT" (initiation when serum urea concentration was < 27.1 mmol/L) was associated with a lower adjusted-risk of death.[28] These studies are at odds with another multicentre observational study of timing of RRT in critically ill patients which found no significant difference in the adjusted odds for mortality when lower serum urea concentration was used as a surrogate for earlier RRT initiation.[29]

Bouman et al randomized 106 predominantly post-cardiac surgical patients with AKI at a single-centre to early (soon after meeting criteria for AKI) or late (following development of a classic indication for RRT) RRT initiation.[30] They found no difference in mortality; however, the trial was underpowered, and may not be generalizable due to unexpectedly high survival and the preponderance of cardiac surgery-associated AKI. A recently published trial of 208 patients with community-acquired AKI was conducted at a single-centre in India.[31] In the earlier RRT arm, RRT commenced once urea exceeded 25 mmol/L or serum creatinine exceeded 619 µmol/L irrespective of other AKI complications. In the usual-start arm, RRT was only initiated in the setting of medically-refractory hyperkalemia, acidosis or volume overload or in the setting of uremic symptoms. No difference in mortality or kidney recovery was observed. Applicability of these findings remains limited due to the young age of the patients (mean 42 y), the spectrum of illnesses associated with AKI (> 50% tropical infections or obstetric complications) and the fact that most patients were not critically ill. Moreover, the trial was inadequately powered to detect a realistic treatment effect for earlier RRT. In summary, the available evidence suggests that there may be clinical benefit to earlier RRT initiation in critically ill patients with AKI; however, clear inferences are limited by the small size of the completed trials, variable definitions for study inclusion and limited generalizability to a broad spectrum of ICU patients.

1.5 Background work by the investigators

The current proposal is the culmination of a multi-pronged research program led by the investigative team.

1.5.1 National survey of current practice

We performed a survey of Canadian nephrologists and intensive care clinicians to better understand their attitudes and behaviors regarding the timing of RRT initiation in patients with AKI. The survey was distributed to members of the Canadian Society of Nephrology and the Canadian Critical Care Society. We asked respondents whether they would consider it ethical to conduct a randomized trial of RRT timing in critically ill patients with AKI where patients would be randomized to either “early” or “standard-of-care” initiation of RRT. Amongst respondents, 94% believed it would be ethical to randomize patients in such a trial, strongly suggesting there is equipoise among Canadian intensivists and nephrologists regarding the issue of timing of RRT initiation.[32] Our findings have been confirmed in two further surveys conducted in the United States and Europe.[33,34]

1.5.2 Cohort studies

In a secondary analysis of the multinational Beginning and Ending Supportive Therapy (BEST) for the Kidney study, we evaluated the timing of initiation of RRT in 1238 critically ill patients with AKI.[29] Timing of RRT was stratified into “early” and “late” using several markers: serum urea (< and ≥ 24.2 mmol/L, respectively), serum creatinine (< and ≥ 309 µmol/L, respectively), urine output, and time from ICU admission to start of RRT. In a multivariate analysis, after adjustment for demographics, baseline kidney function, illness severity, primary diagnosis, and contributing factors for AKI, there was no association between serum urea concentration at RRT initiation and hospital mortality (OR, 1.25; 95% CI, 0.91-1.70; p=0.16). While higher serum creatinine concentration at the time of RRT initiation was associated with significantly lower adjusted-mortality (OR, 0.51; 95% CI, 0.37-0.69; p=0.001), late RRT defined relative to time from ICU admission (≥ 5 days) was associated with higher adjusted-mortality (OR, 1.95;

95% CI, 1.30-2.92; p=0.001). Furthermore, the duration of RRT, the likelihood of RRT dependence at hospital discharge, and hospital length-of-stay were greater when the interval from ICU admission to RRT initiation was prolonged.

To characterize current Canadian practice, we performed a prospective cohort study to describe the characteristics of critically ill patients with AKI at the time of RRT initiation and their association with mortality at six intensive care units in Edmonton and Toronto (n=234).[35] At RRT initiation, median serum creatinine and urea were 331 µmol/L and 22.9 mmol/L, respectively. Oligo-anuria (urine output <400mL/24hr) was present in 32.9% and 92.2% had a positive fluid balance. Notably, only 16.2% had significant hyperkalemia (serum potassium ≥ 5.5 mmol/L) and 33.8% had important metabolic acidosis (serum bicarbonate ≤ 15 mmol/L) at RRT initiation. We found several factors at the time of RRT initiation to be independently associated with hospital mortality including: creatinine < 332 µmol/L (odds ratio 2.8, 1.5-5.4), change in urea from ICU admission > 8.9 mmol/L (OR 1.8, 1.0-3.4), urine output <82 mL/24hr (OR 3.0, 1.4-6.5), fluid balance exceeding 3.0 L/24hr (OR 2.27, 1.2-4.5) on the day prior to RRT initiation, Sequential Organ Failure Assessment score[36] >14 (OR 2.3, 1.3-4.3), and RRT initiation ≥4 days from ICU admission (OR 4.3, 1.9-9.5). While these data provide insight into the clinical, physiologic and laboratory parameters at the time RRT was initiated, there is no information on the factors clinicians used to decide when to initiate RRT. We performed an additional survey to clarify the triggers that clinicians used to start RRT in 119 critically ill patients with AKI from 11 centres across Canada.[37] The most common factors influencing the decision to start RRT were oligoanuria (72%), metabolic acidosis (48%), azotemia (34%), and pulmonary edema (29%). These data confirmed that the decision to initiate RRT is often influenced by numerous clinical factors; 79% of patients had two or more triggers for initiation of RRT. These data provided key insights into the current standard-of-care for RRT initiation in Canada and have been complemented by observations from other parts of the world in order to inform the eligibility criteria for the STARRT-AKI program.[38,39]

1.5.3 Systematic review on the timing of RRT initiation in AKI

We have performed a systematic review and meta-analysis examining timing of RRT initiation in critically ill patients with AKI.[13] We included controlled studies that specifically focused on adult critically ill patients with AKI receiving RRT where timing was evaluated and mortality was reported. We identified 15 unique studies for inclusion (2 randomized trials, 4 prospective cohort studies, and 9 retrospective cohort studies) published between 1999 and 2010. Overall study quality was generally low. In a pooled analysis, early initiation of RRT was associated with a significantly reduced odds of death (OR 0.45; 95% CI, 0.28-0.72) when compared to delayed or late RRT initiation amidst important heterogeneity (I^2 = 78%). We believe that these findings, while limited in inference due to the observed heterogeneity, confirm equipoise for a prospective randomized trial evaluating whether accelerated/early initiation compared to a conservative strategy for RRT initiation in critically ill patients with AKI can impact patient survival and kidney recovery.

1.5.4 Completion of the STARRT-AKI pilot trial confirming the feasibility and safety of the protocol

We completed a CIHR-funded 12-centre RCT that confirmed the feasibility and safety of our protocol.[40,41] We identified 132 individuals who met all the eligibility criteria and enrolled 101 individuals (77%; pre-specified target > 50% for enrollment of eligible patients). The median time from eligibility to initiation of RRT was 7.4 hours in the accelerated arm and 3/48 (6%) participants commenced RRT beyond the specified 12-hour window for that treatment arm. In

the standard arm, 33/52 individuals (63%) commenced RRT, 6 (12%) died without the initiation of RRT while the remaining participants experienced recovery of kidney function and did not commence RRT. Among patients who did commence RRT, the median time from eligibility to RRT initiation was 31.6 hours. No participants in the standard arm commenced RRT within the first 12 hours of study eligibility. Overall, adherence to the study protocol exceeded the pre-specified target of > 90% in each study arm. All patients were followed to Day 90 (pre-specified target > 95%). A careful review of adverse events and severe adverse events did not reveal any tendency to harm in either study arm. An independent Data Safety Monitoring Board oversaw the trial and concluded that there were "…no study-related safety concerns that require report to the site Ethics/Institutional Review Boards or other regulatory authorities."

SECTION 2. TRIAL METHODOLOGY

2.1 Trial design

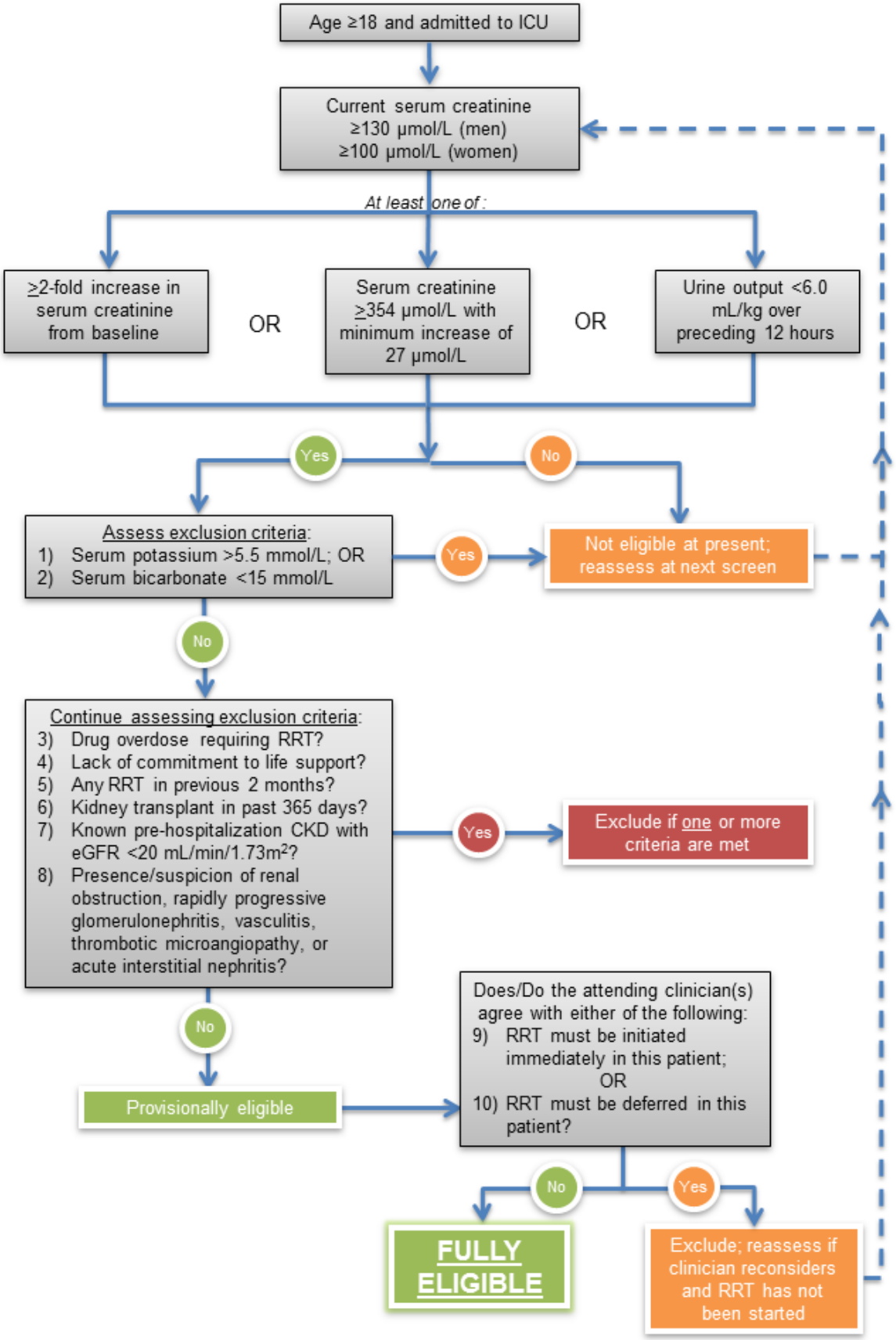
This multicentre, open-label, randomized controlled trial will compare an accelerated (or early/pre-emptive) approach to the initiation of RRT versus a conservative strategy of initiation of RRT as guided by standard indications and clinical judgment in critically ill patients with AKI. Two thousand eight hundred sixty six (2,866) critically ill patients with evidence of severe AKI will be randomized 1:1 to receive accelerated versus standard RRT initiation.

2.2 Eligibility criteria

2.2.1 Screening overview

Research coordinators will screen the ICU population at each of the participating sites. Screening sweeps will occur in the morning and afternoon. Individuals with signs of AKI who are not initially eligible for the trial will be re-screened as several of the conditions for eligibility are dynamic. On a practical level, screening will begin by examination of the patient's bloodwork. To meet preliminary eligibility criteria, sCr must exceed 100 μmol/L in women and 130 μmol/L in men. The coordinator will only continue screening the patient record if this sCr threshold is exceeded. If the other inclusion criteria are met and NONE of the exclusion criteria are met, the patient will be considered provisionally eligible. Once provisionally eligible, the clinicians (Critical Care and/or Nephrology) caring for the patient will be asked if they believe that either the immediate initiation of RRT is mandated or the deferral of RRT is mandated. If the answer is negative to both these questions, the patient will be considered fully eligible and efforts to obtain consent will commence. If a patient's eligibility is excluded by a clinician but RRT has not yet commenced at the subsequent screening round, the patient may be reconsidered for participation in the trial, and the clinician re-approached about the need to initiate/defer RRT, provided the patient still meets the other eligibility criteria.

A suggested approach to identifying eligible patients is found below:



In addition we will request, at sites where this is feasible, permission from Ethics Boards to collect a minimal data set (demographic data, some baseline lab values, receipt of RRT, and outcomes) on those patients who are provisionally or fully eligible at screening, but are excluded from participation due to one of:

a. Clinician(s) belief that either immediate RRT OR deferral of RRT initiation is absolutely mandated (exclusion criteria 9 and 10)

b. Inability to obtain consent within 12 hours of the patient meeting eligibility criteria

The collection of this minimal data set will enable comparisons between patients in the above groups with patients who ultimately participate in order to ensure that there are no fundamental problems with the trial's generalizability.

2.2.2 Inclusion criteria

All of these must be fulfilled at the time of screening assessment:

1- Age ≥ 18 years (Operational definition: Patient's age on the day of eligibility screening.)

2- Admission to a critical care unit (Operational definition: Any unit where there is capability to administer invasive mechanical ventilation.)

3- Evidence of kidney dysfunction (Operational definition: serum creatinine ≥100 µmol/L [women] and ≥ 130 µmol/L [men] based on most recent bloodwork available prior to screening and that has not declined by > 27 µmol/L compared to the highest value recorded in the preceding 48 hours.)

4- Evidence of severe AKI based on at least one of the following three criteria:

i) ≥ 2-fold increase in serum creatinine (sCr) from baseline (Operational definition: The baseline sCr is an *outpatient* reading within 365 days of the current admission date; if multiple pre-hospitalization values are available, the one closest to the date of hospital admission will be used. If an outpatient pre-hospitalization value is not available during the 365 days prior to admission date, the lowest creatinine value obtained during the current hospitalization should be taken as the baseline. This criterion is met if the current sCr is ≥ 100% higher than the baseline value.)

ii) If current serum creatinine is ≥ 354 µmol/L, this must be accompanied by evidence of a minimum increase of 27 µmol/L from the baseline sCr. (Operational definition: If current sCr is ≥ 354 µmol/L and the patient has experienced an increase of 27 µmol/L from the documented baseline, based on the definition delineated in i) for baseline sCr.)

iii) Urine output < 6.0 mL/kg over the preceding 12 hours.

2.2.2.1 Rationale for inclusion criteria

The inclusion criteria are designed to identify a population of critically ill adults with severe AKI who have an increased likelihood of requiring RRT at some point during their hospitalization but who do NOT need immediate RRT at the time of eligibility assessment.

Criterion 3, Evidence of kidney dysfunction: This criterion will be used as an initial screen to identify patients with some degree of kidney dysfunction in whom RRT may be considered if the remainder of the criteria are met. It provides a useful entry point for coordinators to screen patients quickly and only consider individuals further if there is an elevation in sCr.

Criterion 4, Evidence of severe AKI: Determination of severe AKI will be grounded in the staging system outlined in the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines for Acute Kidney injury.[18] This classification system stages AKI into three levels based on the extent of sCr elevation in parallel with the degree and duration of oliguria; patients are classified based on the worst finding (either sCr or oliguria). In order to identify patients with severe AKI in whom RRT may be contemplated, patients must have evidence of at least Stage 2 AKI, which constitutes either a doubling of sCr or urine output < 0.5 mL/kg/hr x 12 hours (adapted to < 6 mL/kg over preceding 12 hours for ease of screening) or if the sCr is above 354 µmol/L at the time of screening, evidence that the sCr rose by at least 27 µmol/L from baseline.

2.2.3 Exclusion criteria

Any one of the criteria below would be grounds for exclusion:

1- Serum potassium concentration > 5.5 mmol/L (Operational definition: Based on last available bloodwork).

2- Serum bicarbonate concentration < 15 mmol/L (Operational definition: Based on last available bloodwork).

3- Presence of a drug overdose that necessitates initiation of RRT. (Operational definition: If noted in the chart or directly from the treating team as the primary reason for administering RRT.)

4- Lack of commitment to provide RRT as part of limitation of ongoing life support. (Operational definition: Critical care team has deemed the patient not to be eligible for escalation of life support, including the initiation of RRT, or substitute decision makers have declined offer of same.)

5- Any RRT within the previous 2 months. (Operational definition: If recorded in the medical chart by any clinician following the patient.)

6- Kidney transplant within the past 365 days. (Operational definition: As reflected in the medical chart.)

7- Known pre-hospitalization advanced chronic kidney disease, defined by an estimated glomerular filtration rate < 20 mL/min/1.73 m^2 in a patient who is not on chronic RRT. (Operational definition: The coordinator will review all documented serum creatinine values

within 365 days prior to the date of admission for the current hospitalization. The value closest to the admission date will be considered as the "baseline" and will be used to calculate the corresponding estimated glomerular filtration rate using an online calculator. A value of < 20 mL/min/1.73 m^2 derived from the CKD-EPI equation[42] will be grounds for exclusion. The serum creatinine, age, sex, and race (Black/non-Black) is entered into a calculator found at: http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr. It is expected that a large number of patients will not have readily available pre-hospitalization sCr data. In the case of a missing pre-hospitalization sCr, this exclusion criterion will be considered to have been NOT met.)

8- Presence or strong clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy (eg, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, scleroderma renal crisis) or acute interstitial nephritis. (Operational definition: If explicitly described in the medical chart or strongly suspected as the cause of AKI by the clinicians following the patient.)

IF THE PATIENT MEETS ALL OF THE ABOVE INCLUSION CRITERIA AND NONE OF EXCLUSIONS 1-8, THEN THE PATIENT IS DEEMED PROVISIONALLY ELIGIBLE AND THE ATTENDING CLINICIANS WILL BE APPROACHED BY THE RESEARCH TEAM TO CONFIRM THEIR COMFORT WITH THE TRIAL ENROLLMENT USING THE TWO EXCLUSION CRITERIA DESCRIBED BELOW

9- Clinician(s) caring for patient believe(s) that immediate renal replacement therapy is absolutely mandated. (Operational definition: The study team will speak to the Critical Care attending physician, and at relevant sites, the Nephrology attending physician caring for the patient and ask if he/she agrees with the statement: "Renal replacement therapy must be initiated immediately in this patient." If at least one of the clinicians answers "Yes", the clinician will be asked to identify the primary reason for mandating the immediate start of RRT.)

10- Clinician(s) caring for patient believe(s) that deferral of renal replacement therapy initiation is mandated. (Operational definition: The study team will speak to the Critical Care and, at relevant sites, the Nephrology attending physician caring for the patient and ask if he/she agrees with the statement: "Renal replacement therapy must be deferred in this patient." If at least one of the clinicians answers "Yes", the clinician will be asked to identify the primary reason for mandating the delay in initiation of RRT.)

2.2.3.1 Rationale for exclusion criteria

Criterion 1: Hyperkalemia may predispose to dangerous cardiac arrhythmias. As a result, randomization of a patient with hyperkalemia to standard RRT initiation may be unethical.

Criterion 2: Severe metabolic acidosis may impair normal cell functions and compromise sensitivity to vasopressor agents in patients who are hemodynamically unstable. As a result, randomization of a patient with significant metabolic acidosis to a strategy of standard RRT initiation may be unethical.

Criterion 3: It is not ethical to withhold RRT in the presence of a dialyzable toxin.

Criterion 4: Severe irreversible acute or chronic illness leading clinicians to curtail or not escalate care is grounds for exclusion as it is unlikely that the timing of RRT initiation will have an impact on clinical outcomes in these individuals.

Criterion 5: The treatment effect of earlier RRT may be reduced by the receipt of any RRT in the preceding 2 months.

Criterion 6: The risk of acute graft rejection is greatest within 1 year following transplant and this condition is addressed primarily with enhanced immunosuppression.

Criterion 7: The prognosis of critically ill patients with severe chronic kidney disease may be disproportionately affected by chronic kidney disease rather than by the acute superimposed deterioration in kidney function (or any intervention for this deterioration) and such patients are routinely excluded from intervention trials in AKI.[20]

Criterion 8: Since the prognosis of these conditions will largely be guided by ancillary therapies (e.g., relief of urinary obstruction, systemic immunosuppression), patients with AKI that is due to causes other than suspected acute tubular necrosis will be excluded.

Criteria 9 and 10: Even after all the above eligibility criteria have been satisfied, it is crucial for the relevant attending clinician(s) to be comfortable with randomization to either group as this reflects clinical equipoise.

Note regarding exclusions 9 and 10: Discussions with the attending physicians following the achievement of provisional eligibility are a crucial part of the enrollment process in this trial. Though patients may meet the study inclusion criteria and have none of exclusions 1-8, we are relying on clinician judgment to tell us whether a patient's condition mandates immediate RRT initiation or alternatively, if a patient's clinical condition is such that he/she is likely to have imminent kidney function recovery. Both such patients should be excluded from this trial.

This approach understandably entails some degree of subjectivity on the part of the attending physicians. The trial will allow clinicians to utilize a variety of clinical tools to make their determination, as no single biomarker has emerged as an adequately robust predictor of AKI progression and the subsequent need for RRT. In patients with oliguric AKI, a patient's response to a furosemide bolus is a frequently-employed prognostic tool of AKI progression in clinical practice; specifically, a limited response in terms of urine output (with varied definitions of what constitutes a "poor" response") might suggest the patient is likely to require RRT or have AKI that will not recover in the near future. This diagnostic strategy, named the "Furosemide Stress Test" has been standardized and evaluated by Chawla and Koyner et al.[43,44] In preliminary studies, they have found that a urine output of < 200 mL in the 2 hours that follow an intravenous furosemide bolus has strong sensitivity and specificity for AKI progression. Though not mandated by the trial, clinicians wishing to risk stratify prospective trial participants using this technique will be asked to follow the method outlined in the published studies (provided in the study Operations Manual). For example, for a provisionally eligible patient who clinicians are reluctant to enroll in STARRT-AKI due to the possibility of imminent renal recovery, a low urine output in response to a furosemide

bolus (ie, a "positive furosemide stress test") might change the physician's impression regarding trial eligibility.

2.3 Trial intervention

2.3.1 Allocation of participants

Participants will be randomized 1:1 to accelerated vs standard initiation of RRT with variable block sizes and stratified by centre using a central randomization system that will be managed at the Applied Health Research Centre.

2.3.2 Accelerated RRT initiation (experimental arm)

A dialysis catheter will be placed and RRT initiated as soon as possible and within 12 hours of eligibility. This 12-hour window includes the time needed to obtain consent or, where permissible, to document enrollment by deferred/delayed consent.

2.3.3 Standard RRT initiation (control arm)

This treatment arm comprises a strategy of conservative management with respect to RRT initiation and RRT will only be initiated in the presence of the criteria below:

a) Persistent severe AKI defined as sCr that remains > 50% of the value recorded at randomization

AND at least one of the following indications for RRT initiation:

a) Serum potassium ≥ 6.0 mmol/L, or
b) pH ≤ 7.20 or serum bicarbonate ≤ 12 mmol/L, or
c) Evidence of severe respiratory failure, based on a PaO_2/FiO_2 ≤ 200 and clinical perception of volume overload, or
d) Persistent severe AKI (sCr remains > 50% the value recorded at randomization) for > 72 hours from randomization

Patients will be evaluated on a daily basis by research staff to ascertain the presence of indications for RRT and provide consistent reminders to clinicians about study-prescribed criteria for RRT initiation. Clinicians will be asked to not initiate RRT unless the above criteria are present. By the same token, the clinician is not obligated to commence RRT even if the above conditions are met. However, the experience from the pilot phase of this program showed that two-thirds of patients in the standard arm commenced RRT in the absence of meeting the above criteria highlighting the challenges of absolutely restricting the application of this therapy in the realities of clinical practice. Thus, RRT may still be commenced in the standard RRT initiation arm anytime at the discretion of the attending clinician(s) based on clinical judgment. The clinician will be asked to specify the primary reason for initiating RRT in the absence of meeting the trial-specified criteria. However, initiation of RRT within 12 hours of eligibility will be considered a protocol violation and the clinician will also be asked to provide the primary reason(s) for RRT commencement. The decision to initiate RRT in the standard

arm of the trial will have to be approved by the **attending physician(s)** involved in the patient's care.

Once a decision is made to start RRT, a dialysis catheter will be placed and RRT initiated as soon as possible. In the standard initiation group, it is expected that a proportion of participants may die before receiving RRT while others may experience recovery of kidney function thus obviating the need for RRT.

2.3.4 RRT delivery in the STARRT-AKI Trial

Other than the study intervention (i.e., differential timing of RRT initiation), all RRT delivered to patients in both treatment arms will follow an identical set of recommended guidelines that is compatible with contemporary clinical practice as described in the study Operations Manual.

2.3.5 Criteria for discontinuation of renal replacement therapy

Once started in either treatment arm, RRT will continue until one of the following circumstances is encountered:

1- Death; or
2- Withdrawal of life support in the context of a change in the goals of care; or
3- Kidney function recovery with no need for continued RRT as per the nephrologist's or critical care physician's judgment. Guidance regarding the presence of renal recovery is found in the Operations Manual. RRT may be reinitiated at any time according to the same principles described in the Operations Manual.

2.4 Frequency and duration of follow-up

Each participant will be followed for up to 90 days following randomization, and where feasible, to one year from randomization using administrative data.

Patients randomized to accelerated RRT initiation: After consent has been obtained from the patient or SDM (or enrollment by deferred/delayed consent documented), patients will be assessed frequently in order to ensure that the randomized intervention is correctly implemented (i.e., within 12 hours of eligibility). Study personnel will provide regular reminders to the clinical team until RRT is started. Even after 12 hours have elapsed, the study team will encourage the initiation of RRT as soon as possible. Reasons for delays will be recorded.

Patients randomized to the standard RRT initiation strategy: Clinical and laboratory data will be reviewed daily for 14 days after randomization and clinicians will be notified if any indications have developed that prompt consideration of RRT initiation based on the criteria listed in Section 2.3.3. The initiation of RRT in a patient allocated to the standard arm must be approved by the attending physicians.

Patients in both arms will receive identical daily follow-up from randomization until Day 14 for assessment of clinical and physiologic data. We will also monitor and collect data on all RRT that is administered during the first 14 days after randomization. Similarly, we will collect data on safety events during this time period. Each participant will be followed to 90 days following

randomization and, where feasible, overall follow-up (using administrative databases and a phone call to ascertain quality of life) will conclude at 365 days following randomization.

2.5 Outcomes

2.5.1 Primary outcome

The primary outcome will be all-cause mortality within 90 days of randomization. We chose this as our primary outcome as it is least susceptible to bias in an unblinded trial, is reliably captured and is of unquestionable clinical relevance. All-cause mortality has also been used as the primary outcome in all major trials involving RRT interventions in the ICU.[20,21,23]

2.5.2 Secondary outcomes

1 - RRT dependence at 90 days among surviving patients.
2 - Composite of death or RRT dependence at 90 days.
3 - Estimated glomerular filtration rate among patients alive at Day 90.
4 - Albuminuria at Day 90.
5 - Major adverse kidney outcomes, defined as death, RRT dependence or sustained reduction in kidney function (defined as eGFR < 75% baseline eGFR) at 90 days.
6 - Mechanical ventilation-free days through day 28.
7 - Vasoactive therapy-free days through day 28.
8- ICU-free days through day 28.
9 - Hospitalization-free days through day 90.
10 - Death in ICU, at 28 days, and in-hospital.
11 - EuroQoL EQ-5D-5L (a measure of health-related quality of life and patient utility) at day 90 and at 1 year among survivors.
12 - Health care costs through day 365.
13 – Vital status and RRT dependence at 365 days among survivors.

2.5.3 Safety events

The following events related, all felt to be clinically significant consequences of the receipt of RRT, will be recorded through Day 14 (specific details on ascertainment of each event are found in the Operations Manual):

1 - RRT-associated hypotension
Defined as: A drop in blood pressure requiring one of: initiation of a vasopressor during RRT session or need to escalate dose of a vasopressor during the RRT session or premature discontinuation of RRT session due to hypotension.

2 - Severe hypophosphatemia
Defined as: Serum phosphorus < 0.5 mmol/L on any bloodwork.

3 - Severe hypokalemia
Defined as: Serum potassium < 3.0 mmol/L on any bloodwork.

4 - Severe hypocalcemia

Defined as: Albumin-adjusted serum calcium < 1.90 mmol/L or ionized calcium < 0.90 mmol/L.

5 - Allergic reaction
Defined as: Clinician suspicion of allergic reaction to one of the components of the RRT apparatus.

6 - Arrhythmia during RRT
Defined as: New atrial (excluding sinus tachycardia or sinus arrhythmia) or ventricular arrhythmia that develops during RRT and was not present prior to initiation of RRT that requires treatment with any medication or cardioversion/defibrillation or decision to stop RRT prematurely as a result of arrhythmia.

7 - Seizure
Defined as: Seizure that develops during RRT session and confirmed by attending clinician.

8 - Major Bleeding
Defined as:
a) Life threatening bleeding and associated hypovolemic shock (e.g., from ruptured abdominal aortic aneurysm or upper or lower gastrointestinal hemorrhage).
b) Life threatening bleeding at a critical site (e.g., intracranial, retroperitoneal, pericardial).
c) Overt, clinically important bleeding associated with one of the following within 24 hours of the bleed: decrease in hemoglobin >20 g/L or transfusion ≥ 2 packed red blood cells.
d) Bleeding requiring an invasive intervention (e.g., re-operation).

2.5.4 Safety events potentially related to the central venous catheter (CVC) used for RRT

The following events related, all felt to be clinically significant consequences of the receipt of the CVC used for RRT, will be recorded through Day 14 (specific details on ascertainment of each event are found in the Operations Manual):

1 - Hemorrhage at the site of CVC insertion
Defined as: Bleeding described by clinician inserting catheter requiring transfusion of ≥ 1 unit(s) of packed red blood cells and/or surgical intervention/repair within 12 hours following insertion.

2 - CVC-associated bloodstream infection
Defined as: Bloodstream infection in 2 blood culture sets (one drawn from dialysis catheter and the other from another site) with no proven alternative source for bloodstream infection as per ICU attending OR culture-positive recovery of the same organism from the dialysis catheter upon removal.

3 - Ultrasonographically-confirmed thrombus attributed to CVC
Defined as: Any confirmed occlusive or non-occlusive thrombus in the vein in which a CVC for RRT was placed (or remains in place) or in the venous system drained by the vein in

which the CVC was placed; further qualified by pulmonary embolism as a result of thrombus.

4 - Pneumothorax (for catheters placed in the internal jugular or subclavian positions)
Defined as: Air in the pleural space on routine chest x-ray that is performed following CVC insertion; further qualified by requirement for chest tube placement.

5 - Hemothorax (for catheters placed in the internal jugular or subclavian positions)
Defined as: Blood in the pleural space following CVC insertion; further qualified by requirement for chest tube placement.

6 - Air embolism

7 - Inadvertent arterial puncture at time of CVC insertion

8 - Other CVC-related safety events

2.6 Safety outcomes

All deaths that occur during the 14-day follow-up period will be reviewed by the local investigators in coordination with attending clinicians in order to determine whether these may be linked to participation in the trial. We will also collect data on safety events with a focus on those related to the administration of RRT and the associated need for vascular access as described above. The local research team will determine whether these events qualify as serious adverse events (see definition below).

2.6.1 Definition of a serious adverse event

The standard definition of a serious adverse event (SAE) includes any adverse event that meets at least one of the following conditions:

- is fatal (results in death)
- is felt to be life-threatening
- requires in-patient hospitalization or prolongation of an existing hospitalization
- results in significant disability or incapacity

For this study, a reportable SAE must meet the definition noted above and also be considered[45]:

i. an atypical event, defined as clinically significant and unexpected in the context of critical illness secondary to AKI, AND;
ii. an event that is at least possibly related to study procedures.

For reportable SAEs that occur from the time of patient consent/enrollment until Day 14, the following reporting procedure applies:

- Report using the Adverse Event Form of the eCRF within 1 business day of becoming aware of the event.
- Document in source records.
- Follow-up of any SAE that is fatal or life threatening should be provided within 7 calendar days.

- Follow-up the outcome of SAEs until clinical recovery is complete and laboratory results have returned to baseline, or until progression has been stabilized. Follow-up will continue for the duration of the patient's study participation.

Local reporting requirements may differ from those of the trial. The local investigator will be responsible for reporting SAEs to their Ethics Board as per institutional requirements.

2.7 Measurement of outcomes

2.7.1 Primary outcome

We will access hospital records (both study hospital and facilities to which patients may be transferred), consult primary care physicians, contact participants/SDMs, and if needed, access death registries to ascertain vital status at 90 days.

2.7.2 Secondary outcomes

1 - RRT dependence will be defined by the receipt of any form of RRT within +/- 14 days of the 90-day time point following randomization.

2 - The composite outcome of death by Day 90 (primary outcome) or RRT dependence at Day 90 (principal secondary outcome).

3 - We will evaluate kidney function in all patients alive at Day 90. Serum creatinine will be drawn at Day 90 (or as close as possible to Day 90) and not beyond 132 days after randomization (i.e., we will accept a serum creatinine value from Day 90 minus 14 days or Day 90 plus 42 days). eGFR will be derived from the CKD-EPI equation and expressed in mL/min/1.73 m^2.[42]

4 - A urine sample will be obtained at Day 90 (or as close as possible to Day 90) and not beyond 132 days after randomization (i.e., Day 90 minus 14 days or Day 90 plus 42 days) for assessment of spot albumin and creatinine concentrations.

5 - Major adverse kidney event (MAKE) by Day 90 (defined as the composite of death, RRT dependence or sustained reduction in kidney function [defined as Day 90 eGFR < 75% baseline eGFR]).

6 - A ventilator-free day will be defined as the receipt of < 2 hours of either invasive or non-invasive ventilation within a 24-hour period.

7 - A vasoactive-free day will be defined as < 2 hours of receipt of any vasoactive therapy provided by continuous infusion within a 24 hour period.

8 - An ICU-free day will be defined as admission to an ICU for < 2 hours within a 24 hours period.

9 - Hospital-free days will be defined as a 24-hour period completely free of an inpatient hospitalization.

10 - Death in ICU, at 28-days and in-hospital will be compared between the groups.

11 - The EuroQol EQ-5D-5L questionnaire will be used to measure health-related quality of life. As a widely accepted measure of patient utility, the EQ-5D-5L can be converted to quality-adjusted life years (QALYs) for use in the economic evaluation.

12 - The economic evaluation will include the cost of the strategy itself (which will be assessed using a micro-costing approach[46]), plus any implications on length of stay, safety events associated with an accelerated or standard initiation strategy, and the costs associated with RRT use after ICU discharge up to 365 days from randomization. To measure these

impacts, we will assess hospital and ICU use, physician claims, and subsequent outpatient claims for RRT for all patients within the trial. Consistent with usual practice within a multicentre clinical trial, valuation of costs will be done for the subset of all patients enrolled within the province of Alberta, Canada (extrapolated based on resource use for all patients in the trial) using administrative costing data available from Alberta Health Services, and from the Alberta Physicians' fee schedule, using methods familiar to study investigators[46].

13 - In jurisdictions where this is feasible, we will access administrative data to ascertain vital status and the need for RRT at Day 365 from randomization. RRT dependence will be defined by the patient having a kidney transplant or the receipt of any form of RRT within +/- 14 days of the 365-day time point following randomization.

2.8 Health resource utilization analysis

Given that a strategy of accelerated RRT initiation is likely to increase short-term resource use, assessing the implications on long-term health outcomes and costs is important. Since we will be assessing survival, RRT dependence, patient utility, and costs, we will be able to conduct a full economic evaluation of accelerated RRT initiation in patients who have AKI.

Consistent with current guidelines, we will use the perspective of the publicly funded health care system. As noted above, we will carefully measure the cost of the intervention, as well as any associated and downstream costs. We will also estimate "time and travel" costs for patients in the trial, based on the subsequent need for RRT therapy.[48]

If RRT dependence at 90 days differs between the two treatment arms, then extrapolation of the benefits and costs beyond the timeframe of the clinical trial will be required to assess the complete economic implications of this strategy. This will be critical to justifying (or not) the use of this strategy to health care payers. To enable this, a decision analytical framework will be developed alongside the data from the clinical trial to model the potential impact of accelerated RRT initiation on long-term outcomes and costs, using a lifetime perspective. Sensitivity analysis will be undertaken to account for uncertainty regarding the long-term estimated costs and effects.

2.9 Sample size justification

We expect a 90-day mortality of 40% in the standard arm. This mortality rate is compatible with 90-day mortality reported in contemporary cohorts of patients with RRT-requiring AKI in Finland and Australia/New Zealand.[4,21] There is no clear guidance on the estimated risk reduction afforded by accelerated RRT so we have selected a relative risk reduction of 15% (absolute risk reduction 6%) as recommended by experts to be an effect magnitude that is minimally important and conceivable with this intervention.[49] With Type I error of 0.05 and power of 0.90, a sample size of 1,359 patients/arm would be required (total 2,718). In order to account for the interim analyses, the required sample size increases to 2,780. After accounting for a combined rate of crossover and dropouts of 3% (as derived from the pilot phase), we will target a total sample size of 2,866.

2.10 Analysis plan

Baseline data will be summarized descriptively. The primary outcome of 90-day mortality will be evaluated using an intent-to-treat approach. A simple comparison of proportions will be performed using a chi-squared test. The risk ratio and relative risk reduction will be estimated with 95% confidence intervals. An adjusted analysis will also be completed using logistic regression and will include the following baseline variables: age, sex, sepsis, receipt of cardiopulmonary bypass and SOFA score.

The principal secondary outcome, the proportion of survivors who are RRT dependent at 90 days, presents challenges as the non-inclusion of participants who died might obviate the inter-group balance afforded by randomization. We will consider two complementary approaches to examine this question. First, we will use the adjusted model for the primary outcome to estimate the probabilities of 90-day survival. We will then use the reciprocals of these as weights in a logistic regression for RRT, resulting in an inverse probability weighted analysis. This is typically called a marginal structural model. The second approach will employ a multinomial regression model to jointly consider the states: dead at 90 days, alive at 90 days receiving RRT and alive at 90 days RRT-free. A similar approach will be used to estimate the probabilities of 365-day survival and to consider the states: dead at 365 days, alive at 365 days receiving RRT and alive at 365 days RRT-free.

Duration of ventilation, vasoactive therapy, ICU stay and hospitalization and albuminuria at 90 days (expressed as the urinary albumin to creatinine ratio in mg/mmol) will be compared by means of a t-test. Finally, eGFR decline of 25%, death in ICU, by 28 days and in-hospital, and ICU readmission and rehospitalization within 90 days will be compared by chi-squared tests.

Interim analyses for efficacy based on the primary outcome will be done when 25, 50 and 75% of planned enrollees have completed 90-day follow-up. Given the risks of false positive results with early stopping for benefit, statistical significance will be declared using small p-values established by O'Brien-Fleming boundaries on the primary outcome (90-day mortality). A detailed monitoring plan will be developed in consultation with the DSMB prior to commencement of recruitment.

We will evaluate the effect of accelerated vs. standard RRT in the following *a priori* defined subgroups: i) patients with sepsis (based on the possibility that earlier RRT, due to more aggressive removal of inflammatory mediators, might have a more prominent effect among patients with sepsis-associated AKI); ii) patients whose baseline eGFR is < 45 mL/min/1.73 m^2 (based on the possible modifying effect of pre-existing chronic kidney disease on mortality and progression to chronic RRT dependence) and iii) region of the world- Canada/US vs Australia/NZ vs Europe (based on possibility that regional RRT and/or critical care practices have a modifying effect on the impact of the intervention on outcomes).

2.11 Planned recruitment rate and methods to ensure enrollment

We anticipate a recruitment rate of 1-2 participants/site/month. Based on a conservative estimate, we should be able to recruit the target population within 3 years. Site coordinators will screen patients in the critical care unit every weekday morning and afternoon and identify eligible patients. An attempt will then be made to obtain consent.

The participating centers have large critical care programs with extensive experience in the administration of RRT to patients with AKI. Each site also has a team of skilled ICU research coordinators who have successfully enrolled patients into numerous multicentre trials, including some in the area of AKI.

We are also proposing several steps to ensure this trial's success including: 1) *Site Education*: Prior to the trial start up at each centre, the principal investigators will visit each site and present rounds to clinicians and nurses on the rationale, design, and logistics of the STARRT-AKI trial. 2) *Monitoring of Recruitment*: The central trial coordinating centre will conduct regular surveillance, monitoring and reporting of recruitment activity at each participating site, and distribute regular newsletters and progress reports. We also propose to hold regularly scheduled investigator and research staff meetings. 3) *Novel consent models:* The need to assure the rapid enrollment of eligible patients is of particular importance in a trial that is testing the value of early/accelerated RRT initiation. The burden of illness in our eligible population is such that in most cases, the substitute decision maker (SDM) will need to be approached for consent. This SDM may often be unavailable at the time the potential participant is found to meet eligibility criteria. In these situations, and where permitted by the Ethics Board, we will try to obtain consent by phone to enable recruitment of patients whose SDMs cannot attend the hospital in-person. At centres where this has been approved by the Ethics Board, if SDMs are not available or readily contactable, eligible patients may be recruited through a process of deferred/delayed consent.

2.12 Co-Enrollment

Patients recruited to STARRT-AKI may also be enrolled in other studies or clinical trials as long as those studies/trials do not interfere with the timing of RRT initiation mandated by the STARRT-AKI protocol. Furthermore, the therapy tested in the other trial must not have a plausible interaction with the timing of RRT initiation. Investigators and coordinators will routinely review trials that are operating in parallel in the study ICUs. The trial Steering Committee will review and approve co-enrollment in other studies on a case-by-case basis.[50]

2.13 Study centres

This will be an international initiative comprising up to 100 centres and in up to 15 countries.

2.14 Mitigation of bias

Institution of a sham/placebo RRT would be ethically and logistically difficult and hence blinding is impractical. However, we will take several steps to mitigate bias. Central computer-based randomization will be concealed. The use of random treatment blocks will prevent investigators and site coordinators from predicting the treatment assignment for the subsequent eligible patient.

To minimize the impact of co-interventions, a major concern when investigators and clinicians are unblinded to the trial-mandated intervention, the protocol calls for all delivered RRT to

follow guidelines that are consistent with contemporary evidence-based practice. As done in a recent RCT, the protocol calls for RRT modality to be modified with the evolving hemodynamic state of the participant,[20] although the balance of evidence at the current time does not suggest the superiority of any RRT modality even in hemodynamically unstable patients.[23,24] Two recently published landmark trials have not demonstrated any benefit of "intensive" or "high dose" RRT in the setting of AKI.[20,21] Our RRT prescription guidelines reflect the range of doses that were administered in these trials but also specify minimum doses for each modality. For patients receiving IHD and SLED, session duration needs to be a minimum of 3 and 8 hours, respectively with a session frequency of at least 3 times/week. The minimum prescribed effluent dose in CRRT is 20 mL/kg/hr (averaged over a 24 hr period). We have also been deliberately liberal with respect to the choice of clearance mode (hemodialysis vs hemofiltration vs hemodiafiltration) given the fact that local practices may vary based on the availability of technology and the opinion of local clinicians. A recent meta-analysis did not demonstrate the superiority of any clearance mode in the setting of AKI.[26] Strict criteria for RRT cessation have been established. Together, these measures will ensure that once RRT is started, patients in both treatment arms receive RRT according to identical principles.

Since the study arm will be apparent to investigators from the outset, the risk of clinician-directed crossover is a concern, with participants being switched to the treatment arm that is perceived to be more "beneficial" or "appropriate". The patient's changing clinical needs must always supersede adherence to the study protocol and some crossovers are thus unavoidable. However, concerns about crossovers are mitigated from our experience in the pilot phase of the trial. Only 3/48 patients assigned to accelerated RRT commenced RRT > 12 hours from eligibility. Importantly, no patients assigned to standard RRT initiated RRT within 12 hours of eligibility and among those patients who did commence RRT, the median time from eligibility to RRT initiation was 31 hours. In this trial, crossovers will be documented and reasons for crossover will be elicited from treating clinicians and reported and reviewed by both the trial Steering Committee and the DSMB.

Most importantly, outcome assessment will not be significantly affected by the lack of blinding, especially the primary outcome of all-cause mortality.

SECTION 3. TRIAL MANAGEMENT

3.1 The Coordinating Centre

The Coordinating and Data Management Centre is the Applied Health Research Centre of the Li Ka Shing Knowledge Institute (www.ahrconline.com) of St. Michael's Hospital in Toronto, Canada. This comprehensive trials unit employs expert project management staff. The Coordinating Centre will be responsible for developing and programming the electronic case report forms, trial procedure manual, data monitoring, regulatory documents, data management and analysis, and providing progress and data reports to the Steering Committee, Data Safety and Monitoring Board, and participating sites. The Applied Health Research Centre staff is highly familiar with the STARRT-AKI protocol as they managed the pilot phase of the trial.

3.2 Role of the site investigators

The site investigators will be responsible for: a) obtaining local institutional review board / research ethics board approval and ensuring the ethical conduct of the trial, b) publicizing the study to all intensivists, nephrologists, trainees, and ICU nurses c) ensuring that eligible patients consenting to the trial are randomized, d) ensuring that all randomized patients are followed according to protocol, and e) ensuring that serious adverse events are promptly transmitted to the Methods Centre and Ethics Board, with follow-up enquiries addressed in a timely manner.

3.3 Role of the local study coordinators

The site study coordinators will be responsible for: a) identification of eligible patients, recruitment and consent; b) providing day-to-day guidance to the ICU team (physicians and nurses) regarding adherence to study protocols, c) providing appropriate follow-up for all study patients, completing the fields in the data forms and ensuring the meticulous and secure storage of information and d) maintaining a screening log of all eligible patients.

3.4 Steering Committee

As co-principal investigators, **Ron Wald** and **Sean Bagshaw** will assume overall responsibility for all operational aspects of the trial, including acquisition and administration of funds, training of research staff, supervision of trial implementation, data interpretation and completion of the final manuscript. Senior investigators with an extensive background in Critical Care Nephrology and clinical trials will oversee the trial in Canada (**Neill Adhikari**[22,25,51] , **Matthew Weir**[52] and **Francois Lamontagne**[53-57]), the United States (**Kathleen Liu**[28,62] and **Paul Palevsky**[20,58-60]), Europe (**Michael Joannidis**[61-63], **Marlies Ostermann**[64-67] **Ville Pettila**[4,68-70], and Alistair Nichol[71-74]) and Australia/New Zealand (**Rinaldo Bellomo**[21,75-77], **Martin Gallagher**[78-81] and **Shay McGuiness**[82,83]). **Braden Manns** is a nephrologist at the University of Calgary and a health economist who has published extensively on the costs of novel therapies in Nephrology, including the application of RRT in the setting of AKI.[16,46,48,84] He will supervise an evaluation of the implications of the treatment strategies on health resource utilization. **Orla Smith,** Research Manager for Critical Care at St. Michael's Hospital, operationalized the screening process and developed data collection tools for this research program.[40,85,86] She will oversee the practical training of research staff. **Kevin Thorpe** is the head of biostatistics at the AHRC and an assistant professor at the Dalla Lana School of Public Health, University of Toronto, with expertise in kidney disease-oriented studies, including prior trials conducted by our group, and an internationally recognized expert in the design and execution of pragmatic trials.[25,87-89] He will generate the randomization protocol, and conduct or oversee all the interim and final analyses as well as any additional analyses requested by the DSMB.

3.5 Data safety and monitoring board

A DSMB will be established, consisting of 5 members with expertise in Nephrology, Critical Care and trial methodology. Members will meet at least every 6 months while the trial is recruiting patients to review all serious adverse events separately and in aggregate. The DSMB Chair will communicate with the principal investigators after each meeting. The DSMB will also review results of the interim analyses described above and make recommendations to the Steering Committee, based on the *a priori* stopping rules. A DSMB charter will be drafted.

3.6 Sub-studies

The Steering Committee will establish a sub-committee to consider potential sub-studies, some of which will require additional funding beyond the core trial funding to accomplish the stated objectives of the trial. Proposed sub-studies may include but are not limited to the following:

1. Long-term survival/renal function (1-5 years)
2. Long-term costs/resource use (1-5 years)
3. Mechanistic/pharmacological substudies
4. Fluid balance substudy
5. Novel kidney damage biomarker substudy
6. Weaning from mechanical ventilation support substudy

3.7 Ethics and consent issues

Ethics Board approval will be secured prior to the commencement of screening activities at each centre. Study coordinators will be responsible for obtaining informed consent from the eligible patient or the substitute decision maker (SDM) if the patient is incapable. If the SDM provides consent but the patient becomes capable prior to the end of the follow-up period, the study coordinator will seek consent directly from the patient, who will have the option of withdrawing from the study. If a SDM is contactable by phone but is not able to come in person to sign the consent form, steps will be taken to obtain phone consent for the study.

At sites where this has been approved by the local Ethics Board, patients who are eligible but incapable of providing consent and for whom an SDM is not available may be enrolled and randomized through a process of deferred/delayed consent. In this circumstance, a dedicated effort will be made to locate a SDM even after recruitment has taken place and the SDM -once found- will be given the option of affirming or withdrawing the patient's participation. In addition, once the participant regains capacity, he/she will be asked to affirm or withdraw consent for the trial.

The time of eligibility will be documented on the study screening log. Consent (or documentation of enrollment in the case of deferred/delayed consent) must be obtained within 12 hours of this time, otherwise the patient's eligibility will have elapsed and the patient will not be included in the trial.

To ensure confidentiality, patients will be identified to the Methods Centre only by their study identification number. The site study coordinator will keep a master list of patient names and identification numbers in a password-protected computer file. At the end of the study, master lists will be destroyed. In accordance with current requirements, we will store data for a minimum of 10 years.

3.8 Publication and authorship policy

Members of the Steering Committee will participate in drafting the manuscript that describes the main findings of the STARRT-AKI trial (i.e., the "principal paper"). All investigators will be asked to review and provide input on the final manuscript and will be invited to serve as co-

authors. It is anticipated that the principal paper's authorship will be attributed collectively to "The STARRT-AKI Investigators".

Authorship on STARRT-AKI publications (principal paper and papers emanating from sub-studies) will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors.[90] These Requirements state "*Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3*."

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