Guy's and St Thomas' NHS
NHS Foundation Trust

STARRT AKI

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

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CONTENT

Study Synopsis

Title	**STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI): A Multi-Centre, Randomized, Controlled Trial**
Protocol Short Title/Acronym	STARRT-AKI
Protocol Version number and Date	Version 3 (27 December 2019)
IRAS	191390
Study Phase if not mentioned in title	Randomized controlled trial
Is the study a Pilot?	No
Study Hypothesis	In critically ill patients with severe acute kidney injury (AKI), randomization to accelerated initiation of renal replacement therapy (RRT), compared to a conservative strategy consistent with standard care, leads to: 1. improved survival at 90 days; and 2. better recovery of kidney function, defined as independence from dialysis at 90 days.
Study Duration	3 years
Methodology	Randomized controlled trial
Sponsor name	University of Toronto, Toronto, Canada
UK Legal representative	Guy's & St Thomas NHS Foundation Hospital London
UK Chief Investigator	Dr Marlies Ostermann
REC number	
Medical condition or disease under investigation	Acute kidney injury (AKI)
Purpose of clinical trial	The objectives of this trial are to determine whether, in critically ill patients with severe AKI, randomization to accelerated initiation of renal replacement therapy (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 dialysis at 90 days
Primary objective	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 improved survival at 90 days.
Secondary objectives	1. 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 better recovery of kidney function defined as independence from dialysis at 90 days and is cost-effective.

	2. To determine the long-term outcome of patients who meet the eligibility criteria but are not randomized and treated according to clinician judgement only.
Number of Subjects/Patients	Worldwide: 2,866 patients In UK, including England, Scotland, Wales and Northern Ireland: approximately 580 patients (randomized and non-randomized patients)
Trial Design	Randomized controlled non-blinded study followed by observational phase
Endpoints	Primary outcome: All-cause mortality at 90 days
Main Inclusion Criteria	1. Age ≥ 18 years 2. Admission to an intensive care unit (ICU) 3. Evidence of kidney dysfunction [serum creatinine ≥100 µmol/L in women and ≥ 130 µmol/L in 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 result obtained during the current hospitalization; OR ii) Achievement of a serum creatinine > 354 µmol/L with evidence of either a minimum increase of 27 µmol/L or an increase of 50% from pre-morbid baseline or result obtained during the current hospitalization; OR iii) Urine output <6.0 mL/kg over the preceding 12 hours
Statistical Methodology and Analysis	Baseline data will be summarized descriptively. The primary outcome of 90-day mortality will be evaluated using an intention-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. Interim analyses for efficacy based on the primary outcome will be done when 25, 50 and 75% of planned enrollees of the total study 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). In UK, we will also undertake a cost-utility analysis of early RRT

	compared to usual care base on the trial data and applying a 1-year time and longer-term horizon through data linkage with routine NHS healthcare databases and registries.

Glossary of Terms and Abbreviations

AE	Adverse Event
AKI	Acute kidney injury
AR	Adverse Reaction
CEAC	Cost-Effectiveness Acceptability Curve
CHI	Community Health Index Number
CI	Chief Investigator
CKD	Chronic kidney disease
CRF	Case Report Form
CTU	Clinical Trials Unit
CVC	Central venous catheter
DoH HIB	Department of Health Hospital Information Branch
DSMB	Data Safety Monitoring Board
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation.
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
ISF	Investigator site file
Main REC	Main Research Ethics Committee
MAKE	Major adverse kidney event
NISRA	Northern Ireland Statistics and Research Agency
NRS	National Records for Scotland
NHS R&D	National Health Service Research & Development
ONS	Office for National Statistics
PI	Principle Investigator
QA	Quality Assurance
QALY	Quality Adjusted Life-Year
QC	Quality Control

Participant	An individual who takes part in a clinical trial
PEDW	Patient Episode Database for Wales
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RMP	Registered Medical Practitioner
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SICSAG	Scottish Intensive Care Society Audit Group
SMR	Scottish Morbidity Records
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

Introduction

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.[1-3] For critically ill patients with more severe forms of AKI, renal replacement therapy (RRT), also known as dialysis, is frequently employed.[4] For these individuals, RRT initiation often results in a considerable escalation in both the complexity and associated costs of care.[5] Moreover, these critically ill patients experience substantial morbidity, including non-recovery of kidney function and dialysis dependence,[6-8] and excess mortality, with hospital case-fatality rates commonly exceeding 50%.[4,9]

Many aspects of RRT delivery to critically ill patients with AKI remain uncertain resulting in heterogeneity in the prescription and delivery of acute RRT.[10,11] 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.[12,13] As a result, this practice has become common and endorsed by key opinion leaders.[14] 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.[15] 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.[16] 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."[17] The National Institute for Health and Care Excellence (NICE) in the United Kingdom recently developed an

AKI guideline.[18] They identified 5 areas of highest priority for future research. The document states **"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."**[18]

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, this proposed trial will have a meaningful clinical impact irrespective of its findings.**

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,[19-21] RRT modality[22,23] and RRT clearance mode.[24,25] 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.[16,26]

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 the median serum urea (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 similarly designed multicentre retrospective cohort study, Liu et al also found that "early RRT" (initiation when [urea] <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]

Small single centre controlled trials in cardiac surgery patients have further suggested that earlier RRT, most often defined as initiation within 8 hours of surgery, can reduce morbidity and improve survival.[30,31] 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.[32] 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.[33] In the earlier RRT arm, RRT commenced once urea exceeded 23 mmol/L or serum creatinine exceeded 618 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 years), 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.

Background work by the investigators

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

i) National survey of current practice

Canadian nephrologists and intensive care clinicians were invited to participate in a survey to better understand their attitudes and behaviors regarding the timing of RRT initiation in patients with AKI. Participants were asked 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.[34] The findings have been confirmed in two further surveys conducted in the United States and Europe.[35,36]

ii) Cohort studies

In a secondary analysis of the multinational Beginning and Ending Supportive Therapy (BEST) for the Kidney study, the timing of initiation of RRT in 1238 critically ill patients with AKI was evaluated.[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 and hospitalization, and the rate of RRT dependence at hospital discharge, were greater when the interval from ICU admission to RRT initiation was prolonged.

A prospective cohort study was conducted in six intensive care units in Edmonton and Toronto (n=234) to explore the characteristics of critically ill patients with AKI at the time of RRT initiation and their association with mortality. At RRT initiation, serum creatinine and urea were 331 (225-446) µmol/L and 22.9 (13.9-32.9) mmol/L, respectively. Oligo-anuria (<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. The factors at the time of RRT initiation which were independently associated with hospital mortality included creatinine < 332 µmol/L, change in urea from ICU admission >8.9 mmol/L, urine output <82 mL/24hr, fluid balance exceeding 3.0 L/24hr on the day prior to RRT initiation, Sequential Organ Failure Assessment score[37] >14, and RRT initiation ≥4 days from ICU admission.

Another study was undertaking in 1847 patients who had received RRT for AKI in 21 ICUs in Germany and UK.[37] It showed that the number of associated organ failure, pre-existing chronic comorbidities, oligo-anuria and severity of acidosis at time of initiation of RRT were associated with an increased risk of dying.

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.

An additional survey was conducted to clarify the triggers that clinicians used to start RRT in 119 critically ill patients with AKI from 11 centres across Canada.[34] The most common factors influencing the decision to start RRT were oligo-anuria (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 and have been complemented by observations from other parts of the world in order to inform the eligibility criteria for the STARRT-AKI program.[39]

iii) Systematic review on the timing of RRT initiation in AKI

Bagshaw et al performed a systematic review and meta-analysis examining timing of RRT initiation in critically ill patients with AKI.[12] They included controlled studies that specifically focused on adult critically ill patients with AKI receiving RRT where timing was evaluated and mortality was reported. They 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%). 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.

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

Bagshaw and Wald completed a 12-centre RCT that confirmed the feasibility and safety of this protocol.[40] 132 individuals were identified who met all the eligibility criteria. 101 individuals were enrolled (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, 39/52 individuals (75%) commenced RRT or died without the initiation of RRT, while the remaining patients 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."

2 Trial Objectives, Design and Statistics

2.1. Trial Objectives

The **primary objective** of this trial is 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 improved survival at 90 days.

S**econdary 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 better recovery of kidney function defined as independence from dialysis at 90 days and long-term up to 5 years, better general health and is cost-effective.
Another secondary objective is to determine the long-term outcome of patients who meet the eligibility criteria but are not randomized and treated according to clinician judgement only (ie. observational phase).

Primary outcome:

- all-cause mortality at 90 days

Secondary outcomes:

Kidney specific outcomes:

- Dialysis dependence at 90 days among surviving patients;
- Composite of death or dialysis dependence at 90 days
- Estimated glomerular filtration rate among patients alive at Day 90 after randomization
- Albuminuria at Day 90
- Major adverse kidney event (MAKE), defined as death, dialysis dependence or sustained reduction in kidney function (defined as eGFR < 75% baseline eGFR) at 90 days
- Dialysis dependence at 1 year and long-term up to 5 years

Patient-centered outcomes:

- Mortality at 28 days, ICU discharge, hospital discharge, 1 year and long-term up to 5 years after randomization
- Health-related quality of life (EQ-5D-5L) (a measure of health-related quality of life) at day 90, 6 months and 1 year among survivors
- Vital status and dialysis dependence at 365 days among survivors
- Change in organ dysfunction, as defined by the SOFA score, in the 7 days after randomization.

Resource utilization outcomes:

- Mechanical ventilation-free days through day 28
- Vasoactive therapy-free days through day 28

- ICU-free days through day 28
- Hospitalization-free days through day 90
- Utilisation of primary care at 90 days, 6 months and 1 year
- Utilisation of health care services in the NHS at 90 days, 6 months and 1 year

Economic evaluation

- Cost-utility over one year and long-term up to 5 years

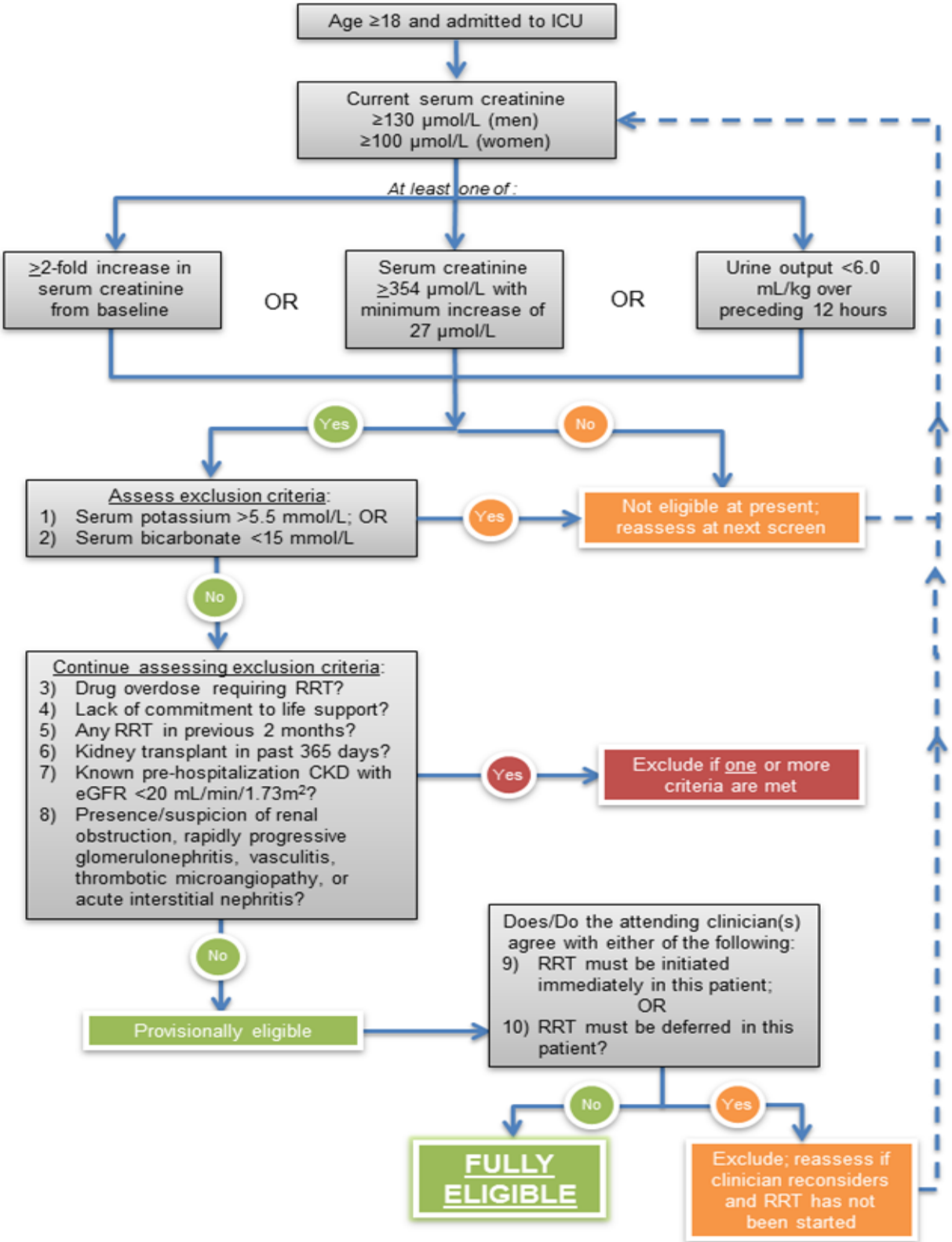
2.2 Trial Design & Flowchart

Trial design

This multi-centre, unblinded, 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. Worldwide, 2,866 critically ill patients with evidence of severe AKI will be randomized 1:1 to receive accelerated versus standard RRT initiation. In the UK, including England, Scotland, Wales and Northern Ireland, approximately 580 patients will be enrolled.

After completion of the randomized study, we will continue the observational phase of the study to determine the long-term outcome of patients who meet the eligibility criteria and are treated according to clinician judgement.

2.3 Trial Flowchart



2.4 Trial Statistics

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.[20,47] 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.[48] 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. In the UK, including England, Scotland, Wales and Northern Ireland, we plan to recruit approximately 580 patients (ie. approximately 20% of total enrolment target consisting of randomized and non-randomized patients).

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 Sequential Organ Failure Assessment (SOFA) score.

The principal secondary outcome, the proportion of survivors who are dialysis 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 dialysis, 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 dialysis and alive at 90 days dialysis-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 dialysis and alive at 365 days dialysis-free.

The SOFA scores over the first seven days will be analyzed using a linear mixed effect model to compare these over time. If there is significant early mortality, a joint longitudinal-survival model will be considered. Duration of ventilation, vasoactive therapy, ICU stay and hospitalization 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 of the whole study 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); and ii) patients whose baseline eGFR < 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).

The economic analysis will determine the cost-utility of early RRT from a UK health and social care perspective over a time horizon of one year and patients' lifetimes. Data on secondary care will be taken from national databases and registries, including Hospital Episode Statistics (HES) records for each patient. Data on primary care and productivity will be collected from patients at 90, 180 and 270 days and 1 year using a bespoke questionnaire. Mean incremental costs of early RRT will be determined over one year after application of appropriate unit costs (e.g. NHS reference costs) to resource use. Quality Adjusted Life-Years (QALYs) will be calculated for each patient using linear interpolation of quality of life data measured using the EQ-5D-5L at 90 and 365 days. Missing data will be imputed using Multiple Imputation if assumptions that the data are Missing at Random are plausible. Incremental costs and QALYs will be estimated after adjustment for age, sex and SOFA score; uncertainty will be quantified using bootstrapping. As outlined in the statistical plan of the international trial, we will evaluate the effect of accelerated vs. standard RRT in the following *a priori* defined subgroups: i) patients with sepsis and ii) patients whose baseline eGFR <45 mL/min/1.73 m^2. Cost-effectiveness will be reported as the Incremental Cost-Effectiveness Ratio (ICER) and the Cost-Effectiveness Acceptability Curve. Sensitivity analysis will include productivity costs.

A Markov model will be built to extrapolate costs and QALYs over the lifetime of patients. Resource use and mortality outcomes at one year will be supplemented with longer-term follow-up of patient records in national healthcare databases and registries, including HES, the Scottish Morbidity Records and the UK Renal Registry. The structure of the model will be determined following a conceptual modelling phase, but is likely to include health states representing renal replacement and kidney transplantation. The model will be fully probabilistic to allow generation of results in the form of a CEAC and ICER. Structural uncertainty arising from the extrapolation of time to event data to parameterize the model will be explored with sensitivity analysis. Analysis according to pre-defined subgroups will be undertaken. Sensitivity analysis will include productivity costs.

3. Sample Size, Selection and Withdrawal of Subjects

3.1 Sample size

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** patients across all centres worldwide. In the UK, we plan to recruit approximately 580 patients (ie approximately 20% of total enrolment target consisting of randomized and non-randomized patients).

3.2 Inclusion criteria (all of these must to be fulfilled at the time of screening assessment)**:**

1. Age ≥18 years on the day of eligibility screening

2. Admission to a critical care unit defined as a unit where there is capability to administer invasive mechanical ventilation

3. Evidence of kidney dysfunction [ie. serum creatinine ≥100 µmol/L (women) and ≥ 130 µmol/L (men) based on most recent blood results available prior to screening and that has not declined by >25 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 a 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 but 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

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.

3.3 Exclusion criteria (any one of the criteria below would be grounds for exclusion)**:**

1. Lack of commitment to provide RRT as part of limitation of ongoing life support.

2. Presence of a drug overdose that necessitates initiation of RRT.

3. Any RRT within the previous 2 months.

4. Kidney transplant within the past 365 days.

5. 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 dialysis.

6. Presence or 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.

7. Likelihood that an absolute indication for RRT will arise in the subsequent 24 hours based on the most recent blood work for the following parameters: serum K >5.5

8. Likelihood that an absolute indication for RRT will arise in the subsequent 24 hours based on the most recent blood work for the following parameters: serum bicarbonate <15 mmol/L.

Exclusion criteria 7 and 8 are dynamic, and if corrected, patient may be reconsidered.

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 and/or 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 the answer is “Yes”, the clinician will be asked to identify the primary reason for mandating the start RRT immediately)

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/or 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 the answer is “Yes”, the clinician will be asked to identify the primary reason for mandating the delay in initiation of RRT.)

3.4 Criteria for Premature Withdrawal

A patient will be withdrawn from the study if the patient or personal consultee withdraws their consent. The data will be included in the analysis unless the patient or personal consultee explicitly requests for the data not be included.

4. Study procedures

4.1 Screening Procedures

Research coordinators will screen the relevant ICU patients at each of the participating sites during weekdays and at weekends if possible. Individuals with signs of AKI who are not initially eligible for the trial will be re-screened as several of the conditions for eligibility proved to be dynamic during the pilot phase. On a practical level, screening will begin by examination of the

patient's blood results. To meet preliminary eligibility criteria, sCr must exceed 100 µmol/L in women and 130 µmol/L in men. The coordinator will only screen the chart further if this sCr threshold is exceeded. If the other inclusion criteria are met and NONE of exclusion criteria 1-7 are met, the patient will be considered provisionally eligible. Once provisionally eligible, the clinicians 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 is considered fully eligible and efforts to obtain consent 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.

4.2 Consent and Enrolment Procedures

Critically ill patients in the Intensive Care Unit suffering from AKI often have impaired capacity. Consent procedures will be according to current legislation in the specific regions / nations.

In England and Wales, there will be three routes by which a patient may be enrolled in the study.

i) Patient with capacity:

- The patient will be provided with a written 'Patient Information Sheet'.
- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- If the patient chooses to be enrolled in the study they will sign a 'Patient Consent Form'.
- The patient may withdraw consent at any stage (as explicitly stated in the 'Patient Information Sheet').

ii) Patient without capacity, when a Personal Consultee is immediately available:

- When a patient does not have capacity the research team will attempt to identify a personal consultee [in accordance with section 32 of the Mental Capacity Act (England)]
- The personal consultee will be provided with a written 'Personal Consultee Information Sheet'.
- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- The personal consultee will be asked to use their knowledge of the patient's beliefs to advise the research team as to whether or not they feel the patient would chose to enrol in the study.
- When the personal consultee feels the patient would have chosen to enrol in the study they will be asked to sign a Personal Consultee Declaration Form'.
- If the Personal Consultee is unable to come to the hospital, we plan to contact them by phone. We will provide information about the study and email or fax the "Personal Consultee Information Sheet" and answer any questions. If the personal consultee feels the patient would have chosen to enrol in the study, we will email or fax a 'Personal Consultee Declaration Form' and ask them to sign and send it back to us.
- The personal consultee may withdraw the patient at any stage (as explicitly stated in the 'Personal Consultee Information Sheet').
- In the event that the patient regains capacity, the research team will speak to the patient at the earliest opportunity and ask the patient to provide retrospective consent; if the

patient chooses to continue to be part of the study they will sign a 'Consent Form to continue'; if the patient gives consent to continue, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.
- In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the final analysis.

iii) Patient without capacity, when a Personal Consultee is not immediately available and no appropriate person is identified:

- When a patient does not have capacity and the research team are unable to identify or contact an appropriate personal consultee we will contact a Nominated Consultee.
- The nominated consultee will be a Consultant Intensivist who understands the patient's medical problems and renal replacement therapy and has been informed about the study. The nominated Consultee may be the Consultant who is caring for the patient or a Consultant who is not directly involved in the clinical care of the patient. All Consultants who agree to act as nominated consultees will be listed in the site file.
- The nominated consultee will not be a member of the study team and will have no connection to the research, to the funder or to the Research Ethics Committee.
- The nominated consultee will be provided with a 'Nominated Consultee Information Sheet' and a member of the research team with relevant GCP training will provide verbal information and answer any questions.
- When the nominated consultee feels the patient would have chosen to enrol in the study they will be asked to sign a 'Nominated Consultee Declaration Form'.
- The nominated consultee may request at any stage that the patient is withdrawn (as explicitly stated in the 'Nominated Consultee Information Sheet').

- In the event that the patient regains capacity, the research team will speak to the patient at the earliest opportunity and inform them about the study and who has acted as personal consultee or nominated consultee. The patient will be fully informed about the study and be given an information sheet. When all questions are answered, the patient will be asked to provide retrospective consent; if the patient chooses to continue to be part of the study they will sign a 'Consent Form to continue'; if the patient gives consent to continue, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.
- In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the analysis.

In Scotland, a patient may be enrolled in the study via any of the following routes:

i) Patient with capacity:

- The patient will be provided with a written 'Patient Information Sheet'.
- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- If the patient chooses to be enrolled in the study they will sign a 'Patient Consent Form'.
- The patient may withdraw consent at any stage (as explicitly stated in the 'Patient Information Sheet').

ii) Patient without capacity, when a legal representative is immediately available:

- When a patient does not have capacity the research team will attempt to identify a legal representative [in accordance with the 'Adults with Incapacity (Scotland) Act 2000' (Scotland)]
- The legal representative will be provided with a written 'Legal Representative Information Sheet'.
- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- The legal representative will be asked to use their knowledge of the patient's beliefs to advise the research team as to whether or not they feel the patient would chose to enrol in the study.
- When the legal representative feels the patient would have chosen to enrol in the study they will be asked to sign a consent form on behalf of the incapacitated adult.
- If the legal representative is unable to come to the hospital, we plan to contact them by phone. We will provide information about the study and email or fax the "Legal Representative Information Sheet" and answer any questions. If the legal representative feels the patient would have chosen to enrol in the study, we will email or fax a 'consent form and ask them to give consent on behalf of the incapacitated adult and send the form back to us.
- The legal representative may withdraw the patient at any stage (as explicitly stated in the 'Legal Representative Information Sheet').
- In the event that the patient regains capacity, the research team will speak to the patient at the earliest opportunity and ask the patient to provide retrospective consent; if the patient chooses to continue to be part of the study they will sign a 'Consent Form to continue'; if the patient gives consent to continue, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.
- In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the final analysis.

iii) Patient without capacity, when a Legal Representative is not immediately available and no appropriate person is identified:

- When a patient does not have capacity and the research team are unable to identify or contact an appropriate legal representative, the procedures as outlined in the Scottish Adults with Incapacity Act will apply.

In Northern Ireland, a patient may be enrolled in the study via any of the following routes:

i) Patient with capacity:

- The patient will be provided with a written 'Patient Information Sheet'.
- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- If the patient chooses to be enrolled in the study they will sign a 'Patient Consent Form'.
- The patient may withdraw consent at any stage (as explicitly stated in the 'Patient Information Sheet').

ii) Patient without capacity, when a Responsible Person is immediately available:

- When a patient does not have capacity the research team will attempt to identify a responsible person (personal consultee) [in accordance with Mental Capacity Act (NI 2016)]
- The responsible person will be provided with a written 'Responsible Person Information Sheet'.
- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- The responsible person will be asked to use their knowledge of the patient's beliefs to advise the research team as to whether or not they feel the patient would chose to enrol in the study.
- When the responsible person feels the patient would have chosen to enrol in the study they will be asked to sign a 'Responsible Person Declaration Form'.
- If the Responsible Person is unable to come to the hospital, we plan to contact them by phone. We will provide information about the study and email or fax the "Responsible Person Information Sheet" and answer any questions. If the responsible person feels the patient would have chosen to enrol in the study, we will email or fax a 'Responsible Person Declaration Form' and ask them to sign and send it back to us.
- The responsible person may withdraw the patient at any stage (as explicitly stated in the 'Responsible Person Information Sheet').
- In the event that the patient regains capacity, the research team will speak to the patient at the earliest opportunity and ask the patient to provide retrospective consent; if the patient chooses to continue to be part of the study they will sign a 'Consent Form to continue'; if the patient gives consent to continue, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.
- In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the final analysis.

iii) Patient without capacity, when a Responsible Person is not immediately available:

- When a patient does not have capacity and the research team are unable to identify or contact a responsible person, we will contact a Registered Medical Practitioner.
- The Registered Medical Practitioner will be a Consultant Intensivist who understands the patient's medical problems and renal replacement therapy and has been informed about the study. The Registered Medical Practitioner may be the Consultant who is caring for the patient or a Consultant who is not directly involved in the clinical care of the patient. All Consultants who agree to act as Registered Medical Practitioner will be listed in the site file.
- The Registered Medical Practitioner will not be a member of the study team and will have no connection to the research, to the funder or to the Research Ethics Committee.
- The Registered Medical Practitioner will be provided with a 'Registered Medical Practitioner Information Sheet' and a member of the research team with relevant GCP training will provide verbal information and answer any questions.
- When the Registered Medical Practitioner feels the patient would have chosen to enrol in the study they will be asked to sign a 'Registered Medical Practitioner Declaration Form'.

- The Registered Medical Practitioner may request at any stage that the patient is withdrawn (as explicitly stated in the 'Registered Medical Practitioner Information Sheet').
- In the event that the patient regains capacity, the research team will speak to the patient at the earliest opportunity and inform them about the study and who has acted as responsible person or Registered Medical Practitioner. The patient will be fully informed about the study and be given an information sheet. When all questions are answered, the patient will be asked to provide retrospective consent; if the patient chooses to continue to be part of the study they will sign a 'Consent Form to continue'; if the patient gives consent to continue, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.
- In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the analysis.

Consent will only be taken by a member of the research team who is not directly involved in the patient's medical care to mitigate against undue persuasion.

Acute kidney injury is a medical emergency. It is hoped that patients or their personal consultees will not need longer than 2 hours to make a decision regarding participation in the study. However, if patients or their personal consultees need longer to make an informed decision, this will be supported and they will be given more time.

4.3 Randomisation Procedure for the randomized controlled trial

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.

Once the patient has been successfully randomised onto the study, the enrolment of this patient must be documented within an enrolment log.

4.4 Schedule of Treatment during the randomized controlled trial

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.

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. 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.

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.

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 referred to in this protocol.

Treatment during the observational phase

Patients recruited to the observational phase of the study will be treated according to the decisions of the clinical team. There will be no change of treatment.

4.5 Follow up Procedures

Each participant will be followed for up to one year from recruitment. We will seek permission from participants to harvest routinely available data beyond the 1-year follow-up on kidney function from the UK Renal Registry and Scottish Renal Registry, and on secondary health care use as recorded in routine healthcare databases and registries.

Patients randomized to accelerated RRT initiation: After consent has been obtained from the patient or personal consultee (or enrollment by deferred/delayed consent documented), patients will be assessed hourly 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. This will ensure that all RRT administered in the study is compatible with the guidelines outlined in the Operations Manual. Similarly, we will collect data on safety outcomes during this interval.

We will collect outcome at 90 days, 6 months and one year following randomization. Patients will be invited to complete a validated health questionnaire (EuroQol Group EQ-5D-5L) at 90 days, 6 months and 1 year. They will also be invited to complete a bespoke questionnaire on resource use at 90 days, 6 months and 1 year. We will collect creatinine results taken by the clinical teams for clinical reasons either within 14 days before day 90 or 42 days after day 90. There will be no additional blood or urine sampling outside routine clinical care.

Patients who met the eligibility criteria but were not randomized will also be invited to complete a validated health questionnaire and bespoke questionnaire on resource use at 90 days, 6 months and one year. One year after randomization, we will record survival status and whether patients require long-term RRT. In addition, we will seek their consent for data linkage with routinely available databases.
In case patients meet the eligibility criteria for the observational study but do not have capacity to consent, a personal consultee or a professional consultee will be approached as outlined in section 4.2. Consent to continue will be sought from the patient as soon as they regain capacity to consent. If they agree to continue participation, they will be invited to complete a validated health questionnaire and bespoke questionnaire on resource use at 90 days, 6 months and one year. One year after randomization, we will record survival status and whether patients require long-term RRT. In addition, we will seek their consent for data linkage with routinely available databases.

Routinely collected longer-term morbidity and mortality data on patients following enrolment will be harvested from official NHS bodies and national healthcare databases and registries, including Health Episodes Statistics (HES), Civil Registration Data, Intensive Care National

Audit & Research Centre (ICNARC), Scottish Intensive Care Society Audit Group (SICSAG), UK Renal Registry, Scottish Renal Registry, Information Services Division of NHS Scotland, Scottish Morbidity Records held by Information Services Division of NHS Scotland, National Records for Scotland (NRS), and Patient Episode Database for Wales (PEDW), Department of Health Hospital Information Branch (DoH HIB) and Northern Ireland Statistics and Research Agency (NISRA). (see section 12. Additional information about data harvesting from other healthcare databases and NHS bodies)

4.6 End of Study Definition

The international randomized controlled study will end after 2866 patients have been enrolled and the last patient has completed their one-year follow up.
In the UK, the study will end after 580 patients have been recruited and the last patient has completed their one-year follow-up.

5 Laboratories

5.1 Tissue sample transfer
No samples will be transferred.

6. Assessment of Safety

6.1 Safety outcomes
i) 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 or any other intervention to stabilize blood pressure.

ii) Severe hypophosphataemia
Defined as: serum phosphorus <0.5 mmol/L on any bloodwork

iii) Severe hypokalaemia
Defined as: serum potassium <3.0 mmol/L on any bloodwork

iv) Severe hypocalcaemia
Defined as: albumin-adjusted serum calcium <1.90 mmol/L or ionized calcium <0.90 mmol/L

v) Allergic reaction
Defined as: clinician suspicion of allergic reaction to one of the components of the dialysis apparatus

vi) 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

vii) Seizure
Defined as: seizure that develops during RRT session and confirmed by attending clinician

viii) 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)

ix) Safety events potentially related to the central venous catheter (CVC) used for RRT:
a. 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.

b. 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.

c. Ultrasonographically-confirmed thrombus attributed to CVC
Defined as: any confirmed occlusive or non-occlusive thrombus in the vein in which a CVC 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.

d. 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.

e. 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.

f. Air embolism

g. Inadvertent arterial puncture at time of CVC insertion

h. Other CVC-related safety events
Serious adverse events (SAE) will be identified by daily review of the medical notes of an enrolled patient. If the SAE is related (that is, it resulted from administration of any of the research procedures), to the study procedures or is an unexpected occurrence (that is, the type of event is not listed in the protocol as an expected occurrence) then it must be reported immediately upon knowledge of the event to R&D and always within 24 hours. For all other adverse events, these must be reported to GSTT when copied into the Annual Progress Report. For multi-site trials where GSTT is the Sponsor, Principal Investigators at all sites must report all SAEs to the Chief Investigator first where possible. The Chief Investigator is then responsible for reporting events to R&D.

The definition of “serious” may be defined differently within the protocol and it is the responsibility of the research team to adhere to the protocol definition in terms of SAE reporting. Additionally the protocol and other documentation may identify SAEs that do not need immediate reporting and SAEs falling under these categories should be recorded and reported according to the protocol. If an SAE occurs that does not require immediate reporting, this SAE should be reported in the Annual Progress Report and copied to R&D. All adverse events that are to be reported to R&D Directorate must be signed and dated and completed by the Investigator.

6.2 Ethics Reporting

Reports of related and unexpected SAEs will be submitted to the Main REC within 15 days of the Chief Investigator becoming aware of the event, using the NRES template. The form will be completed in typescript and signed by the chief investigator. The Coordinator of the main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt will be sent to the R&D Directorate. For multi-site studies, only safety reports will be sent to the main REC.

7. Trial Management Group and Trial Steering Committee

Trial Management Group

A Trial management Group (TMG) will be established and chaired by the UK CI. It will have representatives from the Clinical Trials Unit (CTU) and co-investigators, and will meet face to face or by teleconference on a monthly basis and will communicate between times via telephone and email as needed.
Meetings will be formally minuted and a list of actions recorded and stored in the Trial Master File (TMF). All the day-to-day activity will be managed by the Trial Manager / Co-ordinators.

Trial Steering Committee

International Trial

Senior investigators with an extensive background in Critical Care Nephrology and clinical trials will oversee the trial in Canada (Neill Adhikari[21,24,49] , Matthew Weir[50] and Francois Lamontagne[51-55]), the United States (Kathleen Liu[28,62] and Paul Palevsky[19,60-62]), Europe (Michael Joannidis[63-65], Danny McAuley, Marlies Ostermann[66-69] and Ville Pettila[47,70-72]) and Australia/New Zealand (Rinaldo Bellomo[20,73-75], Martin Gallagher[76-79] and Shay McGuiness[80,81]).

Dr 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.[15,44,46,82-84] He will supervise an evaluation of the implications of the treatment strategies on health resource utilization.

UK trial

A UK Trial Steering Committee (TSC) will provide oversight to the conduct of the study on behalf of the Funder and Sponsor. An independent Chair will lead the TSC with at least 75% independent membership. Membership and roles of the TSC will be listed in the TSC Charter.

The TSC will incorporate patient/public representatives. The TSC will meet at least annually and observers may be invited and be in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the CTU.

8. Data safety and monitoring board

A DSMB has been established for the main trial. It consists of 5 members in total: 4 international experts in AKI and clinical trial design, and a senior biostatistician. Members 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 communicates with the principal investigators after each meeting. The DSMB also reviews 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.

The DSMB of the international trial will also act as DSMB of the UK trial and review the UK data separately. They will communicate with the UK Chief Investigator and the TSC and make recommendations for the conduct of the trial in the UK.

9. Ethics & Regulatory Approvals

The trial has been approved by a NRES approved Research Ethics Committee (REC) and the Health Research Authority. Any amendments to the protocol, information sheets or consent forms will be submitted to the REC and HRA for formal approval.

10. Data Handling

10.1 Confidentiality

The collection, storage and transfer of data will follow the principles of the current General Data Protection Regulation.
The University of Toronto is the sponsor for this study. Guy's & St Thomas' Hospital London is acting as their legal representative in the UK. At all participating sites in the UK, the research teams will collect data as per approved study protocol, including the name, date of birth, NHS number (or equivalent). The name, date of birth and NHS number (or equivalent) will be required to allow access to data held on routine NHS healthcare databases.

All enrolled patients will have their hospital identification number and name recorded on a master list which will be held in a locked office in the Intensive Care Department. Only members of the study team will have access to the master list.

Data from the randomisation phase will be sent to the University Toronto in Canada. The data sent to the research team at the University Toronto will be fully anonymised and will not include any identifiable information. Only password-protected NHS or university computers will be used to store or transfer any anonymised data. In Toronto, the data will be stored on an electronic database at St Michael's Hospital, University of Toronto. The data system includes a robust security protection and is fully compliant with international privacy and confidentiality requirements. There are also special systems in place to prevent data loss.

Only in exceptional circumstances will identifiable information be transferred from the research sites to the Lead site Guy's & St Thomas' Hospital London. When considering this option, the following criteria need to be met:

Participants who consented to receiving follow up questionnaires have not returned one or several questionnaires
AND they are still alive
AND they have not indicated that they would like to withdraw from the study
AND there is insufficient research capacity at the research site to follow up
AND the information will only be used to contact the participant related to collection of follow up data.

In these situations, the research staff at the individual site may transfer the participants' contact details to the Chief Investigator at Guy's & St Thomas' Hospital London using a secure nhs email address.

Data of patients recruited to the observational phase will be sent to Guy's & St Thomas' Hospital for analysis. At Guy's & St Thomas' Hospital and King's College London, data will be kept for up to 15 years after the study has finished. The main reason is that during the analysis, data queries may come up which may need access to the original data.

The Chief Investigator will act as 'Custodian' for all data collected.

No patient identifiable details will be included in the published study reports.
Information provided to General Practitioners:

- We plan to inform the patient's general practitioner of the patient's enrollment and the fact that the research team may contact them at a later stage to collect routinely information on kidney function (as described in the relevant patient, personal consultee and nominated consultee information sheets, as well as in the relevant consent and declaration forms).
- Patients, their personal consultees and nominated consultees have the option of opting-out of having the patient's general practitioner informed of their enrolment in the study.

10.2 Case Report Form

Please see the supplementary Case Report Form (CRF) template. The CRF is completed by the study team.

10.3 Record Retention and Archiving:

- During the course of research, all records are the responsibility of the Chief Investigator.
- When the research trial is complete the records will be kept and all data will be stored securely on password protected NHS or University computers for a further 15 years.

10.4 Compliance:

- The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

10.5 Clinical Governance Issues

The study may be selected for audit by any method listed below:

- The project may be identified via the risk assessment process.
- An individual investigator or department may request an audit.
- A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
- Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
- Projects may be randomly selected for audit by an external organisation.
- Internal audits will be conducted by a sponsor's representative

10.6 Non-Compliance

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

11. Finance and Publication Policy

11.1 Finance

Funding has been secured in open competition:

UK trial

The UK study is being funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (NIHR HTA 17 42 74). The NIHR and HTA had no involvement in the protocol or design of the study.

International trial

The International trial is funded by a joint funding stream between the Canadian Institutes of Health Research (CIHR) and Baxter.

11.2 Publication 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. 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*."

12. Additional information about data harvesting from other healthcare databases and NHS bodies

A. England

In England, data will be collected from the following healthcare databases:

a) **NHS Digital** stores and analyses information from healthcare organisations in England and Wales. The research team will apply to NHS Digital for data from **HES** (Hospital Episode Statistics) and **Civil Registration Data**.

b) Hospital Episode Statistics (HES) – The NHS collects Hospital Episode Statistics information on all hospital admissions / attendances, including when, why and for how long they happen.

c) **Civil Registration Data** – When someone dies in England, this is recorded in civil registration data, including date and cause of death. The Office for National Statistics (ONS) can make these data available for research through NHS Digital. As part of this study, we will apply to ONS and then send NHS Digital enough information to be able to identify people in this study (study number, NHS number, date of birth and gender). If someone has died they will send back identifiable information (study number) along with the data and cause of death. This reduces the chances of us sending mail, messages or calls to patients who are no longer alive, which might upset relatives or friends.

d) Intensive Care National Audit & Research Centre (ICNARC) - The NHS routinely collects data on all patients admitted to an intensive care unit in the NHS to help hospitals to improve the quality of intensive care. The data are collected by ICNARC.

e) UK Renal Registry – All kidney units in the UK send information about their patients to the UK Renal Registry, including information about end-stage renal failure, dialysis and transplantation.

B. Sites in Scotland

In Scotland, data will be collected from the following organisations:

a**) The Information Services Division (ISD) of NHS Scotland** collects, stores and analyses healthcare information about people living in Scotland. The research team will apply to the ISD for routinely collected data on their databases, including the **Scottish Morbidity Records (SMR)**.

b) **National Records for Scotland (NRS)** – When someone dies in Scotland, this is recorded in civil registration data. The National Records for Scotland can make these data available for research.

c) Scottish Intensive Care Society Audit Group (SICSAG) - The NHS in Scotland routinely collects data on all patients admitted to an intensive care unit in Scotland to help hospitals to improve the quality of intensive care. The data are collected by SICSAG.

d) Scottish Renal Registry and UK Renal Registry – All kidney units in Scotland send information about their patients to the Scottish Renal Registry and UK Renal Registry.

C. Sites in Wales

In Wales, data will be collected from the following organisations:

a) **Patient Episode Database for Wales (PEDW)** – The NHS in Wales collects information on all hospital admissions/ attendances, including when, why and for how long they happen. This is known as Patient Episode Database for Wales and is managed by an organisation called the **NHS Wales Informatics Service**. As part of this study, the research team will send PEDW enough information to be able to identify people in this study (study number, NHS number, date of birth and gender) and if someone has been admitted to / attended hospital they will send back identifiable information (study number) along with details of the hospital admission / attendance. By collecting information from PEDW, we can tell what happens to a participant's health during the study. For example, if someone is admitted to hospital this will be recorded. By doing this, it means that we can use the information the NHS already collects rather than do regular extra study visits. This is particularly important for people with other health problems as treatment already takes up a lot of time.

b**) Civil Registration Data** – When someone dies in Wales, this is recorded in civil registration data. The Office for National Statistics (ONS) can make these data available for research through NHS Digital. As part of this study, we will apply to ONS and then send NHS Digital enough information to be able to identify people in this study (study number, NHS number, date of birth and gender). If someone has died they will send back identifiable information (study number) along with the data and cause of death. This reduces the chances of us sending mail, messages or calls to patients who are no longer alive, which might upset relatives or friends.

c) Intensive Care National Audit & Research Centre (ICNARC) - The NHS routinely collects data on all patients admitted to an intensive care unit in the NHS to help hospitals to improve the quality of intensive care. The data are collected by ICNARC.

d) UK Renal Registry – All kidney units in the UK send information about their patients to the UK Renal Registry.

D. Sites in Northern Ireland

In Northern Ireland, data will be collected from the following organisations:

a**) Department of Health Hospital Information Branch (DoH HIB)** collects, stores and analyses information from healthcare organisations in Northern Ireland. The research teams will apply to the DoH for access to routinely recorded data including data held at the Office for National Statistics (ONS). This reduces the chances of us sending mail, messages or calls to patients who are no longer alive, which might upset relatives or friends.

b) **Northern Ireland Statistics and Research Agency (NISRA)** – When someone dies in Northern Ireland, this is recorded in civil registration data. The NISRA can make these data available for research.

c) Intensive Care National Audit & Research Centre (ICNARC) - The NHS routinely collects data on all patients admitted to an intensive care unit in the NHS to help hospitals to improve the quality of intensive care. The data are collected by ICNARC.

e) UK Renal Registry – All kidney units in the UK send information about their patients to the UK Renal Registry, including information about end-stage renal failure, dialysis and transplantation.

13. References

1. Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2008;23:1203-10.
2. Cook D, McDonald E, Smith O, et al. Co-enrollment of critically ill patients into multiple studies: patterns, predictors and consequences. Critical care 2013;17:R1.
3. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Critical care 2006;10:R73.
4. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. Jama 2005;294:813-8.
5. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. Journal of the American Society of Nephrology : JASN 2005;16:3365-70.
6. Ahlstrom A, Tallgren M, Peltonen S, Rasanen P, Pettila V. Survival and quality of life of patients requiring acute renal replacement therapy. Intensive care medicine 2005;31:1222-8.
7. Bagshaw SM, Mortis G, Godinez-Luna T, Doig CJ, Laupland KB. Renal recovery after severe acute renal failure. Int J Artif Organs 2006;29:1023-30.
8. Wald R, Quinn RR, Luo J, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. Jama 2009;302:1179-85.
9. Bagshaw SM, Laupland KB, Doig CJ, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005;9:R700-9.
10. Ricci Z, Ronco C, D'Amico G, et al. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2006;21:690-6.
11. Overberger P, Pesacreta M, Palevsky PM. Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. Clinical journal of the American Society of Nephrology : CJASN 2007;2:623-30.
12. Karvellas CJ, Farhat MR, Sajjad I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Critical care 2011;15:R72.
13. Vaara ST, Reinikainen M, Wald R, Bagshaw SM, Pettila V, Group FS. Timing of RRT based on the presence of conventional indications. Clinical journal of the American Society of Nephrology : CJASN 2014;9:1577-85.
14. Kellum JA, Bellomo R, Ronco C. Kidney attack. Jama 2012;307:2265-6.
15. Klarenbach S, Manns B, Pannu N, Clement FM, Wiebe N, Tonelli M. Economic evaluation of continuous renal replacement therapy in acute renal failure. Int J Technol Assess Health Care 2009;25:331-8.
16. Kellum JA, Mehta RL, Levin A, et al. Development of a clinical research agenda for acute kidney injury using an international, interdisciplinary, three-step modified Delphi process. Clinical journal of the American Society of Nephrology : CJASN 2008;3:887-94.
17. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney international 2012;2:1-138.
18. Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy2013.

19. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. The New England journal of medicine 2008;359:7-20.
20. Investigators RRTS, Bellomo R, Cass A, et al. Intensity of continuous renal-replacement therapy in critically ill patients. The New England journal of medicine 2009;361:1627-38.
21. Van Wert R, Friedrich JO, Scales DC, Wald R, Adhikari NK. High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis. Critical care medicine 2010;38:1360-9.
22. Vinsonneau C, Camus C, Combes A, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet 2006;368:379-85.
23. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Critical care medicine 2008;36:610-7.
24. Wald R, Friedrich JO, Bagshaw SM, et al. Optimal Mode of clearance in critically ill patients with Acute Kidney Injury (OMAKI) - a pilot randomized controlled trial of hemofiltration versus hemodialysis: a Canadian Critical Care Trials Group project. Critical care 2012;16:R205.
25. Friedrich JO, Wald R, Bagshaw SM, Burns KE, Adhikari NK. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. Critical care 2012;16:R146.
26. Dennen P, Douglas IS, Anderson R. Acute kidney injury in the intensive care unit: an update and primer for the intensivist. Critical care medicine;38:261-75.
27. Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. Intensive care medicine 1999;25:805-13.
28. Liu KD, Himmelfarb J, Paganini E, et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clinical journal of the American Society of Nephrology : CJASN 2006;1:915-9.
29. Bagshaw SM, Uchino S, Bellomo R, et al. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. Journal of critical care 2009;24:129-40.
30. Durmaz I, Yagdi T, Calkavur T, et al. Prophylactic dialysis in patients with renal dysfunction undergoing on-pump coronary artery bypass surgery. The Annals of thoracic surgery 2003;75:859-64.
31. Demirkilic U, Kuralay E, Yenicesu M, et al. Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg 2004;19:17-20.
32. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Critical care medicine 2002;30:2205-11.
33. Jamale TE, Hase NK, Kulkarni M, et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. American journal of kidney diseases : the official journal of the National Kidney Foundation 2013;62:1116-21.
34. Clark E, Wald R, Levin A, et al. Timing the initiation of renal replacement therapy for acute kidney injury in Canadian intensive care units: a multicentre observational study. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2012;59:861-70.
35. Thakar CV, Rousseau J, Leonard AC. Timing of dialysis initiation in AKI in ICU: international survey. Critical care 2012;16:R237.
36. Legrand M, Darmon M, Joannidis M, Payen D. Management of renal replacement therapy in ICU patients: an international survey. Intensive care medicine 2013;39:101-8.

37. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. Jama 2001;286:1754-8.
38. Ostermann M, Chang RW. Correlation between parameters at initiation of renal replacement therapy and outcome in patients with acute kidney injury. Critical care 2009;13:R175.
39. Jun M, Bellomo R, Cass A, et al. Timing of renal replacement therapy and patient outcomes in the randomized evaluation of normal versus augmented level of replacement therapy study. Critical care medicine 2014;42:1756-65.
40. Smith OM, Wald R, Adhikari NK, et al. Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI): study protocol for a randomized controlled trial. Trials 2013;14:320.
41. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine 2009;150:604-12.
42. Koyner JL, Davison DL, Brasha-Mitchell E, et al. Furosemide Stress Test and Biomarkers for the Prediction of AKI Severity. Journal of the American Society of Nephrology : JASN 2015.
43. Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Critical care 2013;17:R207.
44. Manns B, Doig CJ, Lee H, et al. Cost of acute renal failure requiring dialysis in the intensive care unit: clinical and resource implications of renal recovery. Critical care medicine 2003;31:449-55.
45. Guildelines for the economic evaluation of health technologies: Canada 2006.
46. Klarenbach S, Tonelli M, Pauly R, et al. Economic Evaluation of Frequent Home Nocturnal Hemodialysis Based on a Randomized Controlled Trial. Journal of the American Society of Nephrology : JASN 2013.
47. Nisula S, Kaukonen KM, Vaara ST, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive care medicine 2013;39:420-8.
48. Faubel S. Have we reached the limit of mortality benefit with our approach to renal replacement therapy in acute kidney injury? American journal of kidney diseases : the official journal of the National Kidney Foundation 2013;62:1030-3.
49. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Annals of internal medicine 2005;142:510-24.
50. Weir MA, Beyea MM, Gomes T, et al. Orlistat and acute kidney injury: an analysis of 953 patients. Arch Intern Med 2011
171:703-4.
51. Lamontagne F, Clement C, Fletcher T, Jacob ST, Fischer WA, 2nd, Fowler RA. Doing today's work superbly well--treating Ebola with current tools. The New England journal of medicine 2014;371:1565-6.
52. Lamontagne F, McIntyre L, Dodek P, et al. Nonleg venous thrombosis in critically ill adults: a nested prospective cohort study. JAMA internal medicine 2014;174:689-96.
53. Lamontagne F, Brower R, Meade M. Corticosteroid therapy in acute respiratory distress syndrome. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2013;185:216-21.
54. Lamontagne F, Cook DJ, Adhikari NK, et al. Vasopressor administration and sepsis: a survey of Canadian intensivists. Journal of critical care 2011;26:532 e1-7.
55. Lamontagne F, Briel M, Duffett M, et al. Systematic review of reviews including animal studies addressing therapeutic interventions for sepsis. Critical care medicine 2010;38:2401-8.

56. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney international 2011;79:1361-9.
57. Chawla LS, Kellum JA, Ronco C. Permissive hypofiltration. Critical care 2012;16:317.
58. Chawla LS, Amdur RL, Shaw AD, Faselis C, Palant CE, Kimmel PL. Association between AKI and Long-Term Renal and Cardiovascular Outcomes in United States Veterans. Clinical journal of the American Society of Nephrology : CJASN 2013.
59. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. The New England journal of medicine 2014;371:58-66.
60. Demirjian S, Chertow GM, Zhang JH, et al. Model to predict mortality in critically ill adults with acute kidney injury. Clinical journal of the American Society of Nephrology : CJASN 2011;6:2114-20.
61. Palevsky PM, Molitoris BA, Okusa MD, et al. Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. Clinical journal of the American Society of Nephrology : CJASN 2012;7:844-50.
62. Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. American journal of kidney diseases : the official journal of the National Kidney Foundation 2013;61:649-72.
63. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive care medicine 2009;35:1692-702.
64. Joannidis M, Druml W, Forni LG, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit. Expert opinion of the Working Group for Nephrology, ESICM. Intensive care medicine 2010;36:392-411.
65. Joannidis M, Forni LG. Renal replacement therapy: to treat, or not to treat, that is the question. Critical care 2013;17:125.
66. Ostermann M, Chang RW. Intensity of continuous renal-replacement therapy. The New England journal of medicine 2010;362:466; author reply 7-8.
67. Ostermann M, Dickie H, Barrett NA. Renal replacement therapy in critically ill patients with acute kidney injury--when to start. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2012;27:2242-8.
68. Ostermann M, Dickie H, Tovey L, Treacher D. Management of sodium disorders during continuous haemofiltration. Critical care 2010;14:418.
69. Ostermann M, Dickie H, Tovey L, Treacher D. Heparin algorithm for anticoagulation during continuous renal replacement therapy. Critical care 2010;14:419.
70. Nisula S, Vaara ST, Kaukonen KM, et al. Six-month survival and quality of life of intensive care patients with acute kidney injury. Critical care 2013;17:R250.
71. Vaara ST, Pettila V, Reinikainen M, Kaukonen KM, Finnish Intensive Care C. Population-based incidence, mortality and quality of life in critically ill patients treated with renal replacement therapy: a nationwide retrospective cohort study in Finnish intensive care units. Critical care 2012;16:R13.
72. Vaara ST, Reinikainen M, Kaukonen KM, Pettila V, Finnish Intensive Care C. Association of ICU size and annual case volume of renal replacement therapy patients with mortality. Acta Anaesthesiol Scand 2012;56:1175-82.
73. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative w. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical care 2004;8:R204-12.
74. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet 2012;380:756-66.

75. Yunos NM, Bellomo R, Bailey M. Chloride-restrictive fluid administration and incidence of acute kidney injury--reply. Jama 2013;309:543-4.
76. Gallagher M, Cass A, Bellomo R, et al. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS medicine 2014;11:e1001601.
77. Investigators RRTS, Bellomo R, Cass A, et al. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. Critical care medicine 2012;40:1753-60.
78. Gallagher MP, Cass A, Craig JC. Applying evidence into routine clinical care at a unit level: the exemplar of renal anaemia management. Nephrology 2010;15:429-33.
79. Gallagher MP, Kelly PJ, Jardine M, et al. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. Journal of the American Society of Nephrology : JASN 2010;21:852-8.
80. McGuinness SP, Parke RL, Bellomo R, Van Haren FM, Bailey M. Sodium bicarbonate infusion to reduce cardiac surgery-associated acute kidney injury: a phase II multicenter double-blind randomized controlled trial. Critical care medicine 2013;41:1599-607.
81. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. The New England journal of medicine 2012;367:1901-11.
82. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M. Renal replacement therapy in patients with acute renal failure: a systematic review. Jama 2008;299:793-805.
83. James MT, Ghali WA, Tonelli M, et al. Acute kidney injury following coronary angiography is associated with a long-term decline in kidney function. Kidney international.
84. Conly J, Clement F, Tonelli M, et al. Cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2011;183:E1180-8.
85. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. Jama 2009;302:1872-9.
86. Scales DC, Smith OM, Pinto R, et al. Patients' preferences for enrolment into critical-care trials. Intensive care medicine 2009;35:1703-12.
87. Quinn RR, Thorpe KE, Bargman JM. The higher risk of death on peritoneal dialysis in the United States is not explained by background general population mortality: the CANUSA study revisited. Clin Nephrol;73:286-93.
88. Steinhart B, Thorpe KE, Bayoumi AM, Moe G, Januzzi JL, Jr., Mazer CD. Improving the diagnosis of acute heart failure using a validated prediction model. Journal of the American College of Cardiology 2009;54:1515-21.

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	Report to sponsor within 24 hours of learning of the event Report to the MREC within 15 days of learning of the event	SAE report form for non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the sponsor and MREC immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual progress report form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of study declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the research	No standard format However, the following Information should be included: Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor