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

Statistical Analysis Plan
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CONFIDENTIAL

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Statistical analysis plan for the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial

The optimal time for renal replacement therapy (RRT) initiation in critically ill patients with acute kidney injury (AKI) is uncertain and presents a dilemma for clinicians. [1] Numerous observational studies that have described an association between the timing of RRT initiation and outcomes have been susceptible to bias and unmeasured confounding, [2-4] while recent randomised controlled trials [5-7] have disparate findings.

The Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial will be the largest trial to date to evaluate the timing of RRT initiation among critically ill patients with AKI. In this article we describe the pre-specified statistical analysis plan (SAP) for the STARRT-AKI trial finalised before the completion of targeted recruitment and locking of the trial database for analysis, in accordance with consensus recommendations.8

Trial design

The STARRT-AKI is a multinational, randomised, open-label, controlled trial of critically ill patients with severe AKI that is designed to compare the clinical and cost-effectiveness of a pre-emptive (accelerated) strategy of RRT initiation versus a strategy of watchful waiting and RRT initiation guided by
AKI-related indications and clinician judgment (standard). [9] The protocol was finalised on 5 October 201 5, without intervening amendments. [10]

The primary hypothesis is that a strategy of accelerated RRT initiation will reduce 90-day all-cause mortality, compared with a strategy of standard RRT initiation, among critically ill patients with severe AKI.

Trial sites

The STARRT-AKI trial will recruit a minimum of 2866 patients across an estimated 1 70 sites in 1 5 countries.

Patient population Adult critically ill patients with severe AKI are eligible for enrolment.

Inclusion criteria

All the inclusion criteria below must be fulfilled: ● age 18 years or over on the day of eligibility screening; ● admission to an intensive care unit (ICU); ● evidence of kidney dysfunction (serum creatinine, ≥1 00 grnol/L for women and 1 30 gmol/L for men, based on last blood work available before screening); and ● evidence of severe AKI based on at least one of the following three criteria.

- ▸ twofold increase in serum creatinine from baseline; or ▸ current serum creatinine is 354 grnol/L or more, with a minimum increase of 27 urnol/L from the baseline serum creatinine; or ▸ urine output is less than 6 ml/kg in the prior 1 2 hours.

Exclusion criteria

The exclusion criteria are the following (none may be present): ● potassium at time of screening greater than 5.5 mmol/L; ● bicarbonate at time of screening less than 1 5 mmol/L; ● presence of a drug overdose or dialysable toxin that necessitates RRT; ● lack of commitment to provide RRT as part of philosophy of care;
• receipt of any RRT in the preceding 2 months; ■ kidney transplant within the past 365 days; ● known advanced chronic kidney disease (CKD), defined by estimated glomerular filtration rate (eGFR) of less than 20 mL/min/1 .73 rn ^{2} • ● presence or clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy or acute interstitial nephritis; ● the clinicians caring for the patient believe that immediate RRT is mandated. After fulfilling the above inclusion/exclusion criteria, the study team will speak to

the ICU and/or nephrology attending physician and ask if they agree with the statement: " RRT must be initiated immediately in this patient' If the answer is "Yes", the patient will be excluded but may be rescreened for eligibility; and ● the clinicians caring for the patient believe that deferral of RRT is mandated. After fulfilling the above inclusion/ exclusion criteria, the study team will speak to the ICU and/or nephrology attending physician and ask if they agree with the statement: "RRT must be deferred in this patient' If the answer is "Yes", the patient will be excluded but may be rescreened for eligibility.

Randomisation, treatment allocation and blinding

Intervention

Patients enrolled in the STARRT-AKI trial will be randomly allocated to receive either accelerated (early) initiation of RRT, defined as start of RRT within 1 2 hours of fulfilling eligibility, or standard (delayed) initiation of RRT, whereby

RRT initiation is discouraged unless one or more clinical criteria for RRT develop and/or the attending physician determines that deferral of RRT is no longer in the patient's best interest. Eligible patients will be allocated 1 :1 by randomised permuted blocks (of variable size) and stratified by site, using a dedicated web-based platform.

Primary outcome

The primary outcome is all-cause mortality 90 days after randomisation.

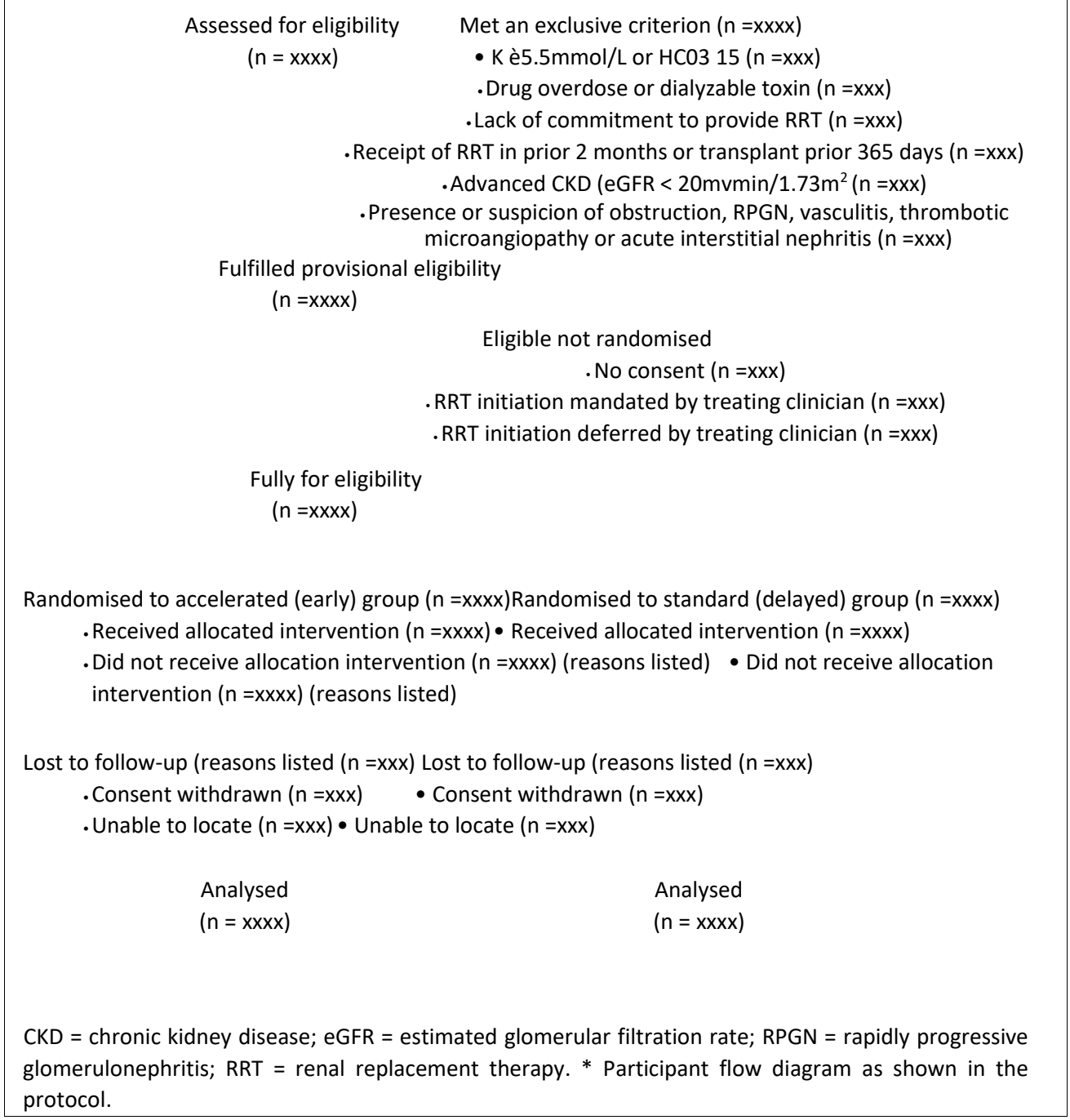
Secondary outcomes

The secondary outcomes are:

- RRT dependence at 90 days after randomisation among surviving patients;
- composite of death and/or RRT dependence at 90 days after randomisation; ● composite of major adverse kidney events, defined as death, RRT dependence or sustained reduction in kidney function (defined as eGFR < 75% baseline eGFR) at 90 days after randomisation,. 1 1 ● eGFR among surviving patients at 90 days after randomisation; ● albuminuria among surviving patients at 90 days after randomisation; ● death in the ICU, at 28 days after randomisation, and inhospital;
- RRT-free days to 90 days after randomisation; ● ventilator-free days and vasoactive therapy-free days to 28 days after randomisation; ● length of ICU stay and ICU-free days to 28 days after randomisation, ● length of hospitalisation and hospitalisation-free days to 90 days after randomisation; and ● health-related quality of life, using the EuroQoL EQ5D-5L scale, among surviving patients at 90 days after randomisation. 1 2

RRT-free days, ventilator-free days and vasoactive therapy-free days will be defined as the number of days alive and without receiving interventional support (RRT, mechanical ventilation or vasoactive therapy) through 28 days (for ventilator-free and vasoactive-free days) or 90 days (for RRT-free days) after randomisation. Patients who die within 28 or 90 days will be assigned a value of zero days, [5] as previously described for ventilator-free days. [13]

Figure 1. Participant flow diagram*



CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RPGN = rapidly progressive glomerulonephritis; RRT = renal replacement therapy. * Participant flow diagram as shown in the protocol.

ICU free-days and hospitalisation-free days will be defined as the number of days alive and not admitted to the ICU to 28 days after randomisation, or the number of days alive and not admitted to hospital through 90 days after randomisation; patients who die will be assigned a value of zero days.

Safety outcomes

The safety outcomes are:

- adverse events within 14 days after randomisation; and
- serious adverse events after randomisation.

Sample size

The STARRT-AKI trial population will include a minimum of 2866 patients, in order to have at least 90% power to detect a 15% relative reduction (6% absolute risk reduction) in the risk of death, assuming an estimated baseline 90-day all-cause mortality of 40%. The baseline mortality rate was based on the available published literature and data from our pilot trial. [1415] A 1 5% relative risk reduction required a total sample of 271 8 (1359 patients per arm); however, to account for the three planned interim analyses and an estimated combined rate of crossover, dropout and loss to follow-up of 3%, the total sample size was increased to include a minimum of 2866 patients. Following the planned third interim analysis, performed when 75% of recruitment had been achieved (24 April 2019), the Data Safety Monitoring Board (DSMB) supported the extension of recruitment to achieve a sample size of a minimum of 3000 patients.

Statistical analysis

Analysis principles

Analysis will be performed on an intention-to-treat (ITT) basis. ● All tests will be two-sided and the overall type I error probability for the primary outcome will not exceed 5% (u = 0.05) over the three interim analyses by employing an O'Brien—Fleming stopping boundary. This approach gives P values thresholds for stopping at each of the interim analyses of 0.00001473, 0.003045 and 0.0183, respectively, and a required significance level of 0.044 at the final analysis. [16] The primary outcome will be analysed independently by two statisticians. For secondary analyses and endpoints, P values will be reported, but since these are best viewed as exploratory, formal hypothesis testing (ie, for rejection of null hypotheses) will be avoided. ● This SAP and the main STARRT-AKI trial manuscript will only include analyses up to 90 days after randomisation. ● The analysis of one-year outcomes (eg, mortality, dialysis dependence, health-related quality of life) and health economic outcomes will be reported separately and the analytic approach to these outcomes will not be covered in this SAP.

- Pre-specified subgroup analyses will be performed irrespective of the result for the primary outcome.
- Secondary outcome analyses will be performed irrespective of the result for the primary outcome and will be considered exploratory.
- The secondary analyses will not be adjusted for multiple testing; however, the results of all statistical testing will be reported according to the American Statistical Association guidelines to provide the necessary context for interpretation. [17]
- All estimates of treatment effect will be accompanied by 95% confidence intervals (C l).
- All analyses will be performed using the R software package (R Core Team, 2008; www.R-project.org).

Interim analyses and the Data Safety Monitoring Board

An independent DSMB will review unblinded data to examine recruitment rate, patient characteristics, randomisation compliance, treatment compliance, completeness of data, outcomes and adverse events on three occasions (following the completion of 90-day follow-up for the 71 6th, 1432nd and 21 50th patient, respectively). The DSMB charter is available at: https://www.ualberta.ca/critical-care/research/ current-research/starrtaki/documents.10

Analysed datasets

All main analyses will be performed on the ITT population dataset. For these analyses, all patients will be analysed according to the group to which they were randomised; however, any randomised patient found to have not fulfilled eligibility criteria based on data available at the time of initial assessment Cie, randomised in

error) will be excluded following independent adjudication by two investigators who will be blinded to outcomes. [18]

Trial profile

The flow of patients through the trial will be shown in a Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 1). [19] The figure will provide a summary of the number of patients screened, the number of patients who fulfilled eligibility, the number of patients who were excluded and the reason(s) for exclusion.

Patient characteristics and baseline comparisons ● A description of baseline characteristics will be presented by treatment allocation, as outlined in the proposed Table 1 ● Categorical variables will be summarised with frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available.

- Continuous variables will be summarised as means with standard deviation (SD) or medians with the interquartile range (IQR) (QI and Q3).
- Baseline measures for all patients will be tabulated for the following variables: ▸ sociodemographics; ▸ admission characteristics; ▸ pre-existing comorbidities; ▸ primary diagnostic category; ▸ vital signs at the time of randomisation; ▸ laboratory data at the time of randomisation; ▸ baseline kidney function; ▸ severity of illness at the time of randomisation; and ▸ organ support (eg, mechanical ventilation, vasopressor therapy) at the time of randomisation.

The information on the proposed additional figures and supplementary tables and figures is included in the online Appendix (available at cicm.org.au/Resources/ Publications/Journal).

Analysis of adherence to timelines for randomisation and renal replacement therapy initiation

Compliance with randomisation will be reported and defined as the proportion of all enrolled patients who are randomised within 12 hours of fulfilling eligibility. Compliance with treatment allocation will also be reported overall and separately for both the accelerated and standard groups. In the accelerated group, compliance will be defined as the proportion of patients initiating RRT within 1 2 hours of meeting all eligibility criteria. In the standard group, compliance will be defined as the proportion of patients who initiated RRT more than 12 hours from the time of eligibility or who did not receive RRT at any time during the follow-up period.

Protocol deviations

Protocol deviations will be summarised as the number of deviations by type (eg, randomisation of ineligible patient, failure to adhere to randomisation timeline, failure to adhere to allocated intervention). All deviations will be listed and will be adjudicated by the principal investigators

Table 1. Baseline characteristics by treatment allocation*

Characteristic	Accelerated strategy (N = xxxx)	Standard strategy (N = xxxx)
Age (years), mean (SD)	xx.x ± x.x	xx.x ± x.x
Female sex, n (^{0}/0)	xxxx (xx.x%)	xxxx (xx.x%)
Weight (kg), mean (SD)	xx.x ± x.x	xx.x ± x.x
Coexisting conditions, n (^{0}/0)		
Hypertension	xxxx (xx.x%)	xxxx (xx.x%)
Diabetes mellitus	xxxx (xx.x%)	xxxx (xx.x%)
Heart failure	xxxx (xx.x%)	xxxx (xx.x%)
Coronary artery disease	xxxx (xx.x%)	xxxx (xx.x%)
Liver disease	xxxx (xx.x%)	xxxx (xx.x%)
Metastatic cancer	xxxx (xx.x%)	xxxx (xx.x%)
Hematologic malignancy	xxxx (xx.x%)	xxxx (xx.x%)
AIDS	xxxx (xx.x%)	xxxx (xx.x%)
SAPS II score at enrolment, ^{t} mean (SD)	xx.x ± x.x	xx.x ± x.x
SOFA score at enrolment, ^{t} mean (SD)	xx.x ± x.x	xx.x ± x.x
Admission type, n (^{0}/0)		
Scheduled surgery	(xx.x%)	xxxx (xx.x%)
Unscheduled surgery	(xx.x%)	xxxx (xx.x%)
Medical	xxxx (xx.x%)	xxxx (xx.x%)
Hospital-acquired risk factors for AKI in preceding 7 days, n (^{0}/0)		
Cardiopulmonary bypass	xxxx (xx.x%)	xxxx (xx.x%)
Aortic aneurysm repair	xxxx (xx.x%)	xxxx (xx.x%)
Other vascular surgery	XXXX (xx.x%)	xxxx (xx.x%)
Major trauma	xxxx (xx.x%)	xxxx (xx.x%)
Obstetric complications	xxxx (xx.x%)	xxxx (xx.x%)
Radiocontrast exposure	XXXX (xx.x%)	xxxx (xx.x%)
Receipt of aminoglycosides	xxxx (xx.x%)	xxxx (xx.x%)
Receipt of amphotericin B	xxxx (xx.x%)	xxxx (xx.x%)
Sepsis, n (^{0}/0)	xxxx (xx.x%)	xxxx (xx.x%)
Septic shock, n (^{0}/0)	xxxx (xx.x%)	xxxx (xx.x%)
Physiological support, n (^{0}/0)		
Mechanical ventilation	xxxx (xx.x%)	xxxx (xx.x%)
Vasoactive support	xxxx (xx.x%)	xxxx (xx.x%)

Serum creatinine, baseline (mg/dL), mean (SD) xxx.x ± x.x xxx.x ± x.x eGFR (ml-/min/l .73m ^{2}), mean (SD) xxx.x ± x.x xxx.x ± x.x		
Serum creatinine, randomisation (mg/dL), mean (SD)	xxx.x ± x.x	± X.X
Patients with oliguria or anuria, n (^{o}/0)	xxx (xx.x%)	xxx (xx.x%)
Urine output (ml-]24 h), mean (SD)	xx.x ± x.x	xx.x ± x.x
Blood urea nitrogen (mg/dL), mean (SD)	xx.x ± x.x	xx.x ± x.x
Serum potassium (mmol/L), mean (SD)	x.x ± x.x	x.x ± x.x
Serum bicarbonate (mmol/L), mean (SD)	xx.x ± x.x	xx.x ± x.x

xx.x ± x.x xx.x ± x.x

AIDS = acquired immunodeficiency syndrome; AKI = acute kidney injury; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; eGFR = estimated glomerular filtration rate. * Plus—minus values will be expressed as mean ± standard deviation (SD) (where the distribution of the data are not normal, median [interquartile range] will be reported instead of mean ± SD). t Scores on the SAPS Il range from 0 to 163, with higher scores indicating more severe disease and a higher risk of death. Scores on the SOFA score range from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.

to classify as to whether they were potentially avoidable, with disagreements resolved by discussion. Analysis of the primary outcome

Principal analysis

The number and percentage of deaths through 90 days after randomisation will be reported for each treatment group. The primary effect estimate will be the relative risk of 90-day mortality, reported with 95% Cl. The absolute risk difference and 95% Cl will also be reported. Deaths up to 90 days after randomisation will be compared between the treatment groups using test. Additionally, the odds ratio (OR) (95% Cl) will also be determined, primarily to permit comparisons between the primary unadjusted analysis and the various secondary pre-specified adjusted analyses of 90day mortality (Table 2).

Adjusted sensitivity analysis

Death at 90 days will also be analysed, adjusting for baseline characteristics (eg, age, sex, baseline eGFR, Simplified Acute Physiology Score [SAPS] Il score at randomisation, surgical status, and presence of sepsis). Continuous variables (eg, age, eGFR and SAPS Il score) will be modelled using restricted cubic splines with four knots to accommodate the possibility of non-linear relationships with the log odds of death. The OR and 95% Cl will be determined first, primarily to permit comparisons between the unadjusted analysis and the secondary adjusted analyses of 90-day mortality. The adjusted treatment effect will be reported as the adjusted OR (95% CD. Should the adjusted OR be materially different from the unadjusted OR, a second adjusted model will be fit that employs the log link to provide adjusted estimates of the risk ratio. An additional sensitivity analysis will include site as a random effect in a generalised linear mixed model to assess if the variance component is important and affects inference.

Treatment of missing data

If more than 5% of patients from the ITT population are excluded from the adjusted analysis of the primary outcome due to missing data for baseline covariates, missing data will be imputed using fully conditional specification [20] The imputation model will include all covariates required for the adjusted analysis as well as other baseline variables deemed related to the variables for which imputations are required. The multiple imputation will then be performed via chained equations to obtain ten imputed datasets. The adjusted analysis will be performed on the imputed datasets with the results appropriately pooled.

Evaluation of heterogeneity in treatment effect Death at 90 days will also be analysed across baseline predicted risk of death using the SAPS Il score [21] This analysis
will be assessed by adding an interaction between treatment and SAPS Il in the fully adjusted model described earlier.

Subgroup analyses

We will evaluate the effect of allocated treatment on the primary outcome across the following a priori defined subgroups by means of interaction terms in the adjusted model and displayed in a forest plot: ● patient sex; ● baseline eGFR, ● baseline SAPS Il score; ● primary reason for ICU admission surgical versus medical; ● sepsis; and ● geographic region (eg, North America, Europe, Australia/ New Zealand, Asia/South America etc).

Exploratory analyses of the primary outcome We will further evaluate the primary outcome with the following exploratory analyses:

- We will examine the effect of the allocated treatment on the primary endpoint in a per-protocol population, defined by omitting patients with a protocol violation due to crossover to the opposite allocated treatment to which they were randomised.

- We will examine the effect of the treatment on the primary endpoint in a modified ITT (mITT) population. The mITT population will be defined as an "as treated" population, whereby patients with a protocol violation will be analysed in the treatment arm that reflects the RRT initiation strategy that was received.
- To further inform the interpretability of the main primary analysis, we will examine the utility of a Bayesian analysis approach, across a range of plausible reference and data-driven priors, to provide estimates of the posterior probability of any mortality benefit (using both relative risk and absolute risk reduction), of an accelerated compared with standard strategy for RRT initiation in critically ill patients with severe AKI [22]

These proposed exploratory analyses may be reported after the publication of the main trial findings.

Additional analyses of mortality

The analysis of all-cause mortality described in the main analysis will be replicated to compare the proportion of patients who died in the ICU, before hospital discharge, and at 28 days after randomisation, respectively. No additional adjusted or subgroup analyses will be performed on these endpoints.

We will perform an analysis of time to death. This analysis will be censored at 90 days after randomisation or on the date the patient was last known to be alive, whichever occurs earlier. A Kaplan—Meier survival curve stratified by randomised group will be used to describe survival rates. Differences in survival will be tested using a log-rank test.

Table 2. Primary and secondary outcomes

	Accelerated strategy (N = xxxx)	Standard strategy (N = xxxx)	Estimate (95% CI)	
Primary outcome, n (^{0}/0)			Relative risk (95% CI)	Mortality
at 90 days xxxx (xx.x%) xxxx (xx.x%) XX (xx—xx) x.xx				
Secondary outcomes, n (^{0}/0)			Relative risk (95% a)	
RRT dependence at 90 days	xx (xx.x%)	XX (xx.x%)	xx (xx—xx)	x.xx
Death or RRT dependence at 90 days	XX (xx.x%)	xx (xx.x%)	XX (xx—xx)	x.xx
MAKE at 90-days	xx (xx.x%)	xx (xx.x%)	xx (xx—xx)	x.xx
ICU mortality	xx (xx.x%)	xx (xx.x%)	xx (xx—xx)	x.xx
28-day mortality	xx (xx.x%)	xx (xx.x%)	xx (xx—xx)	x.xx
Hospital mortality xx (xx.x%) XX (xx.x%) xx (xx—xx) x.xx Serum creatinine at 90 days (mg/dL) xx (xx.x%) XX (xx.x%) x.xx eGFR (ml]min/l .73m^2 at 90 days), mean (SD) xxx.x ± x.x xxx.x ± x.x x.xx				
Health services use			Mean difference (95% co	
Received any RRT, n (^{0}/0)	xxxx (xx.x%)	xxxx (xx.x%)	XX (xx—xx)	x.xx
RRT-free days through 90 days, median (IQR)	xx (xx—xx)	XX (xx—xx)	xx (xx—xx)	x.xx
Initial modality CRRT, n (^{0}/0)	xxxx (xx.x%)	xxxx (xx.x%)	XX (xx—xx)	x.xx
CRRT treatment days, median (IQR)	xx (xx—xx)	XX (xx—xx)	xx (xx—xx)	x.xx
Initial modality IHD, n (^{0}/0) xxxx (xx.x%) xxxx (xx.x%) xx (xx—xx) x.xx IRRT treatment days, median (IQR) XX (xx—xx) xx (xx—xx) XX (xx—xx) x.xx				
ICU length of stay, median (IQR)				
Survivors XX (xx—xx) xx (xx—xx) XX (xx—xx) x.xx Non-survivors XX (xx—xx) XX (xx—xx) XX (xx—xx) x.xx				
Hospital length of stay, median (IQR)				
Survivors	XX (xx—xx)	XX (xx—xx)	xx (xx—xx)	x.xx
Non-survivors	xx (xx-xx)	xx (xx—xx)	XX (xx—xx)	x.xx
Ventilator-free days through 28 days, median (IQR)	XX (xx—xx)	xx (xx—xx)	xx (xx—xx)	x.xx
Vasoactive agent-free days through 28 days, median (IQR)	XX (xx—xx)	xx (xx—xx)	xx (xx—xx)	x.xx
ICU-free days through 28 days, median (IQR)	xx (xx-xx)	XX (xx—xx)	XX (xx—xx)	x.xx
Hospitalisation-free days through 90 days, median	XX (xx—xx)	xx (xx—xx)	xx (xx—xx)	x.xx

(IQR)				
Rehospitalisation through 90 days, n (^{0}/0)	xx (xx.x%)	xx (xx.x%)	XX (xx—xx)	x.xx
Health-related quality of life (EQ-5D-5L), n (^{0}/0)			Mean difference (95% CD	
EQ-VAS	XX (xx.x%)	xx (xx.x%)	XX (xx—xx)	x.xx
Mobility	xx (xx.x%)	xx (xx.x%)	XX (xx—xx)	x.xx
Self-care	xx (xx.x%)	XX (xx.x%)	xx (xx—xx)	x.xx
Usual activities	xx (xx.x%)	xx (xx.x%)	XX (xx—xx)	X.XX
Pain/discomfort	XX (xx.x%)	XX (xx.x%)	xx (xx—xx)	x.xx
Anxiety/depression	xx (xx.x%)	XX (xx.x%)	XX (xx—xx)	x.xx
Clinical Frailty Scale score > 4	xx (xx.x%)	xx (xx.x%)	XX (xx—xx)	x.xx

CRRT = continuous renal replacement therapy; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQoL EQ-5D-5L scale; EQ-VAS = EuroQol Visual Analogue Scale; ICU = intensive care unit; Il-ID = intermittent haemodialysis; IQR = interquartile range; IRRT = intermittent renal replacement therapy; MAKE = major adverse kidney events; RRT = renal replacement therapy; SD = standard deviation.

Table 3. Adverse events and serious adverse events

Event	Accelerated strategy (N = xxxx)	Standard strategy (N = xxxx)
Adverse events, n (^{0}/0)	xxxx (xx.x%)	xxxx (xx.x%)
RRT-associated, n (^{0}/0)		
Hypotension	xxxx (xx.x%)	xxxx (xx.x%)
Arrhythmia	xxxx (xx.x%)	xxxx (xx.x%)
Seizure	xxxx (xx.x%)	xxxx (xx.x%)
Bleeding xxxx (xx.x%) xxxx (xx.x%) Allergic reaction xxxx (xx.x%) xxxx (xx.x%) Hypophosphatemia (< 0.5 mmol/L) xxxx (xx.x%) xxxx (xx.x%)		
Hypokalaemia (< 3.0 mmol/L)	xxxx (xx.x%)	XXXX (xx.x%)
Hypocalcaemia (ionised calcium < 0.90 mmol/L)	xxxx (xx.x%)	xxxx (xx.x%)
Dialysis catheter-associated, n (^{0}/0)		
Pneumothorax/haemothorax	xxxx (xx.x%)	xxxx (xx.x%)
Bleeding	xxxx (xx.x%)	xxxx (xx.x%)
Thrombus (ultrasound-confirmed)	xxxx (xx.x%)	xxxx (xx.x%)
Arterial puncture	xxxx (xx.x%)	xxxx (xx.x%)
Bloodstream infection	xxxx (xx.x%)	xxxx (xx.x%)
Other	xxxx (xx.x%)	xxxx (xx.x%)
Serious adverse events, n (^{0}/0)	xxxx (xx.x%)	xxxx (xx.x%)

RRT = renal replacement therapy.

We will categorise the cause of death and the distribution will be compared between treatment allocation using a test.

Analysis of other secondary outcomes

Other secondary outcomes include RRT dependence among surviving patients, a composite of death and RRT dependence and major adverse kidney events, all at 90 days after randomisation (Table 2). These unadjusted outcomes will be analysed using relative risk (95% C I) and absolute risk difference (95% C I) and compared using a test.

The proportion of survivors who are RRT-dependent at 90 days requires special consideration, as the non-inclusion of participants who died might obviate the intergroup balance afforded by randomisation. We will undertake two complementary approaches. First, we will develop a model for the primary outcome to estimate the probabilities of 90-day survival.

We will then use the reciprocals of these probabilities as weights in a logistic regression for RRT dependence, resulting in an inverse probability weighted analysis. The second approach will employ a multinomial regression model to jointly consider the following states: dead at 90 days, alive at 90 days receiving RRT, and alive at 90 days free of RRT. In addition, time-to-event models that incorporate competing risks or multiple outcomes will be considered.

Days alive and free of outcome will be calculated for treatment with RRT through 90 days, vasoactive therapy through 28 days, mechanical ventilation through 28 days, ICU stay through 28 days, and hospital stay from randomisation through 90 days (Table 2). These will be summarised by treatment allocation using means (SDS) or medians (IQRs). Differences will be explored using linear regression and presented as a mean difference (95% CI).

We will obtain a measure of health-related quality of life at 90 days using the EuroQoL EQ-5D-5L scale to enable a cost-effectiveness analysis of the two approaches to RRT initiation [12] This health economic evaluation will be reported after the publication of the main trial findings.

Analyses of adverse events and serious adverse events

The number and percentage of adverse events and serious adverse events occurring between randomisation and 14 days will be reported for the treatment arm (Table 3).

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