Data Creation Plan for Secondary Analyses

Name and Number of Study	Factors associated with renal replacement therapy initiation among critically ill adult patients with acute kidney injury
Principal Investigator(s)	Neill Adhikari, Federico Angriman, Ron Wald, Sean Bagshaw
DCP Update History	Version 1 (August 20, 2020) Version 2 (January 21, 2021) Version 3 (February 12, 2021) Version 4 (April 20, 2021)
Short Description of Research Question	1. What are the associated factors with renal replacement therapy (RRT) initiation among critically ill adult patients with acute kidney injury? 2. Does a higher baseline risk of renal replacement therapy initiation among critically ill adult patients with acute kidney injury modify the effect of accelerated initiation of RRT?
List of Datasets Used	STARRT-AKI trial
Time of Data Extraction	TBD

Defining the Cohort	
Cohort	STARRT-AKI mITT population (n=1462 in the standard of care arm for aim 1, 2927 in the full study cohort for aim 2)
Exclusion Criteria	No additional exclusion criteria
Size of Cohort	2927 patients

Time Frame Definitions	
Accrual Start/End Dates	Randomization; death or end of follow-up (90 days)

Max Follow-up Date	90 days

Variable Definitions	
Main Exposure or Risk Factor	**Aim 1.** A priori considered factors, potentially associated with the timing of renal replacement initiation, will be: A) Hospital or intensive care unit site B) Baseline risk factors (serum creatinine, pre-hospitalization urine/albumin (or protein) concentration; hypertension; diabetes mellitus; heart failure; coronary heart disease; liver disease). C) Recent risk factors (cardiopulmonary bypass; Aortic repair; vascular surgery; initial trauma; intravenous contrast; use of aminoglycosides or amphotericin) D) Severity of critical illness (SAPS II; SOFA score; fluid balance pre-randomization; oliguria/anuria; PF ratio) E) Baseline physiologic parameters (including pH; Na; bicarbonate; K; Phosphate; creatinine; hemoglobin; platelet count; vasopressor requirements) **Aim 2.** Accelerated vs. standard RRT initiation; effect modifier will be the baseline risk of RRT initiation as defined in aim 2.
Baseline Characteristics (Table 1 data)	See Table 1
Covariates **(To Inform Model Development)**	See analysis plan below; for aim 1 we will include all a-priori candidate factors. For aim 2, we will not include any covariates in the model with the exception of the exposure and the effect modifier.
Outcome(s) Definitions	**Aim 1.** The main outcome of interest will be the initiation of renal replacement therapy within those patients randomized to the standard of care arm. **Aim 2.** Death from any cause at day 90.

Outline of Analysis Plan	
Primary Outcome Variables	**Aim 1.** Initiation of renal replacement therapy (form 10)
Secondary Outcome Variables	**Aim 2.** 90-day all-cause mortality (primary outcome in original trial)
Detailed Analysis Plan	**Aim 1a.** Associated factors with RRT initiation among patients randomized to standard of care 1. Cohort restricted to those allocated to standard of care arm (n=1462) 2. Compare characteristics at baseline of patients who were and were not started on RRT after randomization (with p values) 3. The multivariable model will be a logistic regression model

	4. Start with a “full-sink” model (i.e., with all a-priori considered factors, as shown above, forced into the model) 5. Predictor selection performed using LASSO. Tuning model: choosing best lambda using Brier score, by 10-fold cross-validation. 6. Refit model with best chosen lambda. 7. We discussed potential validation mechanisms (reporting Brier score, AUC, calibration in the large plot) including: a. Split set (random vs. by time of enrollment) b. Nested cross-validation c. External validation using alternative cohort Potential secondary analysis: we discussed fitting a mixed effects logistic regression with random intercept for site (or country) as a way of capturing variability in RRT initiation; reporting median ORs alongside 95% confidence intervals. **Aim 2.** Modification of the effect of accelerated RRT initiation by baseline risk 1. Include entire study cohort (n=2927) 2. Estimate probability of RRT initiation for the entire study sample based on final multivariable logistic model. 3. Multivariable logistic regression, where outcome is death at 90 days and the model includes the original allocation (accelerated RRT vs. standard of care), the risk of RRT initiation as estimated in point 2, and their interaction
Proposed Tables and Figures	See below.

Mock tables and figure legends

Figure 1. Flow chart of included patients.

Table 1. Baseline characteristics of included patients

Characteristic	Overall sample (N = 1462)	Started renal replacement therapy (N = 903)	Not started renal replacement therapy (N = 559)	p value[1]
Age – yr				
Female sex – no. (%)				
Weight – Kg				
Serum creatinine – mg/dl				
Estimated glomerular filtration rate – ml/min/1.73 m^2				
Preexisting conditions – no. (%)				
Chronic kidney disease				
Hypertension				
Diabetes mellitus				
Heart failure				
Coronary artery disease				
Liver disease				
Metastatic cancer				
Hematologic cancer				
HIV infection or AIDS				
Admission category – no. (%)				
Scheduled surgery				
Unscheduled surgery				
Medical				
Hospital acquired risk factor for acute kidney injury in previous week – no. (%)				
Cardiopulmonary bypass				
Aortic aneurysm repair				
Vascular surgery				
Major trauma				
Intravenous contrast material				
Aminoglycoside use				
Amphotericin use				
Clinical condition at baseline				
SOFA score				
SAPS II value				
Mechanical ventilation				
Vasoactive support				
Serum creatinine – mg/dl				
Oliguria or anuria – no. (%)				

Plus–minus values are means ±SD. AIDS denotes acquired immunodeficiency syndrome, AKI acute kidney injury, HIV human immunodeficiency virus.

1. Means are compared with Student's T test; medians with Wilcoxon; proportions with Fisher's exact test.

Table 2. Factors associated with initiation of renal replacement therapy among critically ill adult patients with acute kidney injury

Characteristic	**Hazard ratio (95% confidence interval)**	**p value[1]**
Age - years		
Male sex		
Weight - Kg		
Sepsis diagnosis (yes vs. no)		
Cardiovascular diagnosis (yes vs. no)		
Trauma diagnosis (yes vs. no)		
Vascular surgery (yes vs. no)		
Baseline serum creatinine – mg / dl		
Proteinuria[1] (yes vs. no)		
Hypertension (yes vs. no)		
Diabetes mellitus (yes vs. no)		
Liver disease (yes vs. no)		
Cardiovascular comorbidity[2] (yes vs. no)		
IV contrast exposure (yes vs. no)		
Nephrotoxic medications[3] (yes vs. no)		
SOFA score pre randomization – point score		
Cumulative fluid balance – in ml		
Previous diuretic treatment (yes vs. no)		
Oliguria or anuria (yes vs. no)		
PF ratio – for every 10 point increase		
Serum potassium – meq / l		
Serum bicarbonate – meq / l		

1. Either based on urine albumin or protein concentration thresholds
2. Either heart failure or coronary heart disease
3. Either aminoglycosides or amphotericin.

Figure 2. Forest plot of associated factors with renal replacement therapy initiation among critically ill adult patients with acute kidney injury.