Data Creation Plan for Secondary Analyses

Name and Number of Study	Secondary analysis of the association between initial RRT modality and outcomes in the STARRT-AKI trial.
Principal Investigator(s)	Sean M Bagshaw; Ron Wald; Neill K.J. Adhikari; Rinaldo Bellomo; Bin Du; Martin P. Gallagher; Eric A. Hoste; François Lamontagne; Michael Joannidis; Kathleen D. Liu; Daniel F. McAuley; Shay P. McGuinness; Alistair D. Nichol; Marlies Ostermann; Paul M. Palevsky; Haibo Qiu; Ville Pettilä; Antoine G. Schneider; Orla M. Smith; Suvi T. Vaara; Matthew Weir
DCP Update History	January 13, 2021 (Version 1) December 19, 2021 (Version 2) June 22, 2022 (Version 3) August 8, 2022 (Version 4 – revision to Investigator(s) only)
Short Description of Research Question	If this secondary analysis shows no evidence that continuous renal replacement therapy (CRRT) is superior to intermittent hemodialysis (IHD) in critically ill patients with acute kidney injury (AKI), this may have major consequences for daily clinical practice in intensive care unit. The use of IHD provides several advantages for ICU patients. First, CRRT initiation implies that the patient will receive an extra-corporal therapy 24 hours a day for several days which may be less convenient for mobilization, rehabilitation and physiotherapy. This might be deleterious since growing evidence suggests that early rehabilitation interventions may influence and even prevent physical impairment of ICU patients. Second, the use of CRRT results in more frequent blood sampling since the monitoring of CRRT usually necessitate blood sampling every 4-6 hours. Third, moving the patient for diagnostic (CT-scan examination for example) or therapeutic (operating room) procedures is easier with IHD as the session is of short duration. Fourth, kidney function recovery may be easily assessed in the context of IHD since the upcoming IHD session may be postponed if diuresis resumes. Fifth, in the context of persistent kidney dysfunction with RRT dependency, the use of IHD may facilitate ICU discharge to another department (nephrology ward for instance). The use of IHD also provides several public health benefits. First, acute and proximate costs with CRRT are greater compared to IHD in ICU settings (see post-hoc secondary analysis BEST Kidney study [Srisawat N et al Crit Care 2010;14(2):R46 - https://pubmed.ncbi.nlm.nih.gov/20346163/). Second, the bedside workload may be higher with CRRT. Third, IHD allows to care 3 to 4 patients each day with a single machine which may be crucial in the context of COVID-19 crisis and ICU overwhelmed.
List of Datasets Used	Patients randomized in the STARRT-AKI trial who were initiated on RRT.

Time of Data Extraction	TBD

Defining the Cohort	
Cohort	Assemble a cohort of all patients who initiated RRT in the STARRT-AKI trial (n = 2321).
Exclusion Criteria	Exclude individuals missing initial RRT modality information (n = 24, 1 in accelerated arm and 23 in standard arm). Exclude patients who commenced SLED as their initial modality (n = 101; 65 in accelerated arm and 36 in standard arm).
Size of Cohort	Final sample size for this analysis is 2196.

Time Frame Definitions	
Accrual Start/End Dates	Date of RRT initiation
Max Follow-up Date	90 days from randomization

Variable Definitions	
Main Exposure or Risk Factor	Initial RRT modality – CRRT or IHD.
Baseline Characteristics (Table 1 data)	Same as in STARRT-AKI main analysis.
Covariates **(To Inform Model Development)**	Age (Years), body weight (kg), female sex (%), baseline serum creatinine (sCr), baseline eGFR (ml/min/1.73 m2), known chronic kidney disease, hypertension, diabetes mellitus, heart failure, liver disease, SOFA score at randomization, SAPS II score at randomization, sCr at randomization, mg/dl, hemoglobin at randomization, serum urea at randomization, cardiopulmonary bypass, aortic aneurysm repair, other vascular surgery, trauma, sepsis, receipt of mechanical ventilation, receipt of vasoactive medication, cumulative fluid balance at randomization. At RRT initiation: time from ICU admission, days from hospital admission, SOFA score components, TOTAL SOFA score, urine output in preceding 24 hours, cumulative fluid balance at RRT initiation, sCr, serum urea, serum potassium, bicarbonate, pH, hemoglobin. STARRT-AKI allocated intervention: accelerated vs. standard.
Outcome(s) Definitions	Primary: Composite of death or RRT dependence at 90-days. Secondary: death through day 90, RRT dependence at 90-days, ICU length of stay, hospital length of stay, ICU-free days at 28-days, hospital-free days at 90-days, ventilator-free days at 28-days, vasoactive-free days

	at day-28

Outline of Analysis Plan	
Primary Outcome Variables	Composite of death or RRT dependence at 90-days
Secondary Outcome Variables	Death through day 90, RRT dependence at 90 days, ICU length of stay, hospital length of stay, ICU-free days at 28-days, hospital-free days at 90-days, ventilator-free days at 28-days, vasoactive-free days at 28-days.
Detailed Analysis Plan	Evaluate the association between initial RRT modality (primary exposure CRRT vs IHD [referent]) and composite outcome of death or RRT dependence at 90-days (primary outcome). 1. Use multiple imputation to account for missing pre-treatment and outcome data with all pre-treatment and outcome variables as explanatory variables (Supplementary Table 1) in the imputation model, to create 20 imputed datasets. 2. Create a propensity score (PS) for the receipt of CRRT as the initial modality using all available baseline and RRT initiation variables (Supplementary Table 1). 3. Using overlap weighting derived from the PS that was developed in Step 1, evaluate the relationship between the primary exposure (initial RRT modality) and primary outcome (death or RRT dependence at 90 days) using logistic regression. 4. Evaluate the following secondary outcomes using the same methodology as in Step 2: Death through 90-days, RRT dependence at 90-days. 5. Evaluate the following secondary outcomes using linear regression accounting for the PS developed in Step 6: ICU length of stay, hospital length of stay, ICU free days at 28-days, hospital free days at 90-days, ventilator free days at 28-days, vasoactive-free days at 28-days 6. Subgroup analyses - we will only assess primary outcome association between the primary exposure (initial RRT modality) and the primary outcome (death or RRT dependence at 90-days) in the following baseline subgroups: • Allocated RRT strategy: accelerated vs standard arm • Age ≥ 65 vs < 65 • Women vs men • CKD vs no CKD • Sepsis vs no sepsis • Mechanical ventilation vs no mechanical ventilation • Vasoactive support vs no vasoactive support • Baseline SOFA score (quartiles) • SOFA score at RRT initiation (quartiles)

	• Cumulative Fluid balance at RRT initiation (quartiles) 7. Sensitivity analyses – a) Using the original cohort, determine the association between initial RRT modality and the primary outcome (death or RRT requirement at 90 days) using conventional IPTW, IPTW with truncation and IPTW with trimming. b) restrict the cohort size in 3 ways and determine the relationship be-tween initial RRT modality and the primary outcome: i) restrict to patients who received only CRRT or IHD for all RRT sessions (i.e., exclusive modality); ii) restrict to patients who received RRT for 3 days or more; and iii) restrict to patients who had SOFA CV Score of ≥2 on the day of RRT initiation.
Proposed Tables and Figures	Detailed below.

Proposed Tables and Figures (legends):

Tables:

Table 1: Baseline characteristics according to initial RRT modality.

Table 2: Clinical outcomes according to initial RRT modality.

Figures:

Figure 1. Flow diagram.

Figure 2. Subgroup analyses.

Supplementary Tables:

Supplementary Table 1. Summary of pre-treatment and outcome variables used as explanatory variables in the imputation model.

Supplementary Table 2. Summary of pre-treatment variables considered to be associated with outcomes as explanatory variables.

Supplementary Table 3. Sensitivity analyses.