Data Creation Plan for Secondary Analyses

Name and Number of Study	A study of the impact of sex on RRT strategy and outcome in the STARRT-AKI trial.
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DCP Update History	Version 1 – December 4, 2023 Version 2 – December 10, 2023
Short Description of Research Question	Sex differences in acute kidney injury (AKI) risk, initiation of renal replacement therapy (RRT), and outcome are well described. It is hypothesized that biological differences driven by testosterone and estrogen may contribute to this variation. Sex differences may also apply to the way RRT is delivered, mediated by a combination of biological, social, and cultural influences that impact delivery and acceptability of RRT in the setting of critical illness and AKI. It is therefore plausible that criteria for RRT initiation, choice of RRT modality (IHD versus CRRT), treatment time, RRT dose, anticoagulation, and ultrafiltration may differ between males and females. Many such elements of RRT delivery were collected in the daily form from randomization to day 14, together with biochemical, physiological, and organ dysfunction data. We therefore aim to ask these questions. In the STARRT-AKI trial: 1. When used, did the delivery of RRT in the standard and accelerated arms differ between males and females in terms of physiological parameters, biochemical variables, and SOFA score at enrollment and at RRT initiation? Was there an interaction of sex with age and/or frailty? 2. When used, did the delivery of RRT in the standard and accelerated arms differ between males and females in terms of treatment time, RRT dose, anticoagulation, ultrafiltration, and indications for RRT? 3. Did variation between sexes show a significant association with exclusions for enrolling eligible patients and patient outcomes (i.e., mortality, kidney recovery)? The necessary information to answer all the above questions is contained in the STARRT-AKI CRF.

	We will test the primary hypothesis that there are significant differences in how RRT is delivered between males and females and that such differences are associated with differential physiological, biochemical, SOFA-related, adverse event-related and outcome-related findings (primary, secondary and health services outcomes).
List of Datasets Used	Data obtained during the STARRT-AKI trial
Time of Data Extraction	January to March 2024

Defining the Cohort	
Cohort	All males and females included in STARRT AKI
Exclusion Criteria	No exclusion
Size of Cohort	Full cohort

Time Frame Definitions	
Accrual Start/End Dates	From randomization to trial treatment and vital and clinical status at 90-days.
Max Follow-up Date	To 90-day follow up after randomization

Variable Definitions	
Main Exposure or Risk Factor	Sex
Baseline Characteristics (Table 1 data)	Same as in STARRT-AKI main analysis; however, stratified by sex
Covariates (To Inform Model Development)	Same as in STARRT-AKI main analysis but with RRT delivery (indications, reason for starting, timing, dose, duration, anticoagulation, ultrafiltration, fluid balance) as key co-variates
Outcome(s) Definitions	Same as in STARRT-AKI main analysis, with focus on physiological, biochemical, and SOFA-related daily changes, adverse events, and a

	focus on 90-day all-cause mortality, RRT dependence at 90-day, and RRT-free days at 90-days.

Outline of Analysis Plan	
Primary Outcome Variables	Mortality at 90 days
Secondary Outcome Variables	Physiological, biochemical, and SOFA-related daily changes, adverse events, and additional secondary and health services outcomes, as in the main trial.
Detailed Analysis Plan	Comparative analysis of process of care, outcome, and adverse events as in the primary STARRT-AKI study but stratified by sex. Unadjusted and adjusted comparison for process of care features and patient outcomes. Interaction tests for effect of sex on process of care variables and outcome but split by modality so that all patients treated with IHD are analyzed separately in relation to the approach (the way IHD was applied) and CRRT patients are analyzed separately in relation to the approach (the way that CRRT was applied). The way each initial modality was applied will be compared between sexes within each modality (i.e., comparison of CRRT with CRRT; and IHD with IHD in relation to patient physiology and biochemistry at the start, timing, frequency, duration, dose and subsequent physiological, biochemical SOFA-related, adverse events and outcomes).
Proposed Tables and Figures	Same as in STARRT-AKI main analysis; however, stratified by sex and adjusted for baseline differences in patient characteristics and confined to each modality and its management.

Mock Tables and Figures (legends) (manuscript No 1):

Table 1: Baseline characteristics according to sex.

Table 2: Comparison of RRT process of care variables as described above according to sex.

Table 3: Clinical Outcomes According to sex for patients treated with RRT.

Table 4: Adjusted Clinical Outcomes According to sex for patients with RRT.

Figure Legend:

Figure 1. Flow diagram.

Figure 2. Box plot graph of mean creatinine/urea levels stratified by sex over time in RRT treated patients.

Figure 3. Box plot graph of mean urinary output/fluid balance stratified by sex over time in RRT treated patients.

Preliminary Analysis (Abstract for AKI & CRRT):

Table 1.

Variable	Total	Female (n, %)	Male (n,%)	p
Age, yr (mean [SD])				
Weight, kg (mean [SD])				
Admission category, (n,%)				
Medical				
Scheduled surgery				
Unscheduled surgery				
Diagnostic category, (n,%)				
Cardiovascular				
Gastrointestinal/hepatic				
Hematologic				
Metabolic				
Neurologic				
Respiratory				
Septic				
Trauma				
Other				
Pre-existing conditions, (n,%)				
Hypertension				
Diabetes mellitus				
Heart failure				
Coronary artery disease				
Liver disease				
CKD (eGFR < 60)				
SAPS II score (mean [SD])				
SOFA score (mean [SD])				
Mechanical ventilation, (n,%)				
Vasopressors, (n,%)				
Initiated RRT, (n,%)				
Initial RRT modality, (n,%)				
CRRT				
IHD				
SLED				
Mortality 90-day, (n,%)				
RRT dependence 90-day, (n,%)				
Death or RRT 90-day, (n,%)				

Table 2.

Variable	Female	Male	Effect Estimate (95% CI)	P for interaction
Mortality 90-day, (n,%)				
RRT 90-day, (n,%)				
Death/RRT 90-day, (n,%)				
Stratified by Allocation	**Accelerated**	**Standard**		
Mortality 90-day, (n,%) Female Male				
RRT 90-day, (n,%) Female Male				
Death/RRT 90-day, (n,%) Female Male				