



Data Creation Plan for Secondary Analyses

Name and Number of Study	Renal rEplacement theRapy in the older populatioN with Acute Kidney Injury (LEARN-AKI): a secondary analysis of STARrrT-AKI trial
Principal Investigator(s)	Amanda Y Wang, Martin Gallagher, Rinaldo Bellomo, Sean Bagshaw, Ron Wald, Ary Serpa Neto
DCP Update History	Version 1 - 29 November 22 Version 2 - 12 July 2023 Version 3 - 18 July 2023
Short Description of Research Question	The objectives of this study are: <ol style="list-style-type: none"> 1. To assess differences in mortality and kidney recovery (RRT defined as independence from RRT at 90 days) between younger and older groups among critically ill patients with severe AKI who were allocated to the accelerated versus standard arm in the STARrrT-AKI study. 2. To determine whether in older critically ill patients (age\geq65) with severe AKI who do NOT have urgent clinical indicators, supportive care approach versus commencement of RRT (in the standard strategy arm) leads to i) Differences in survival (primary outcome) at 90 days; ii) Differences in kidney recovery (principal secondary outcome), defined as independence from RRT at 90 days. 3. To assess for interaction between patients age and baseline frailty status, as measured by the Clinical Frailty Scale (CFS) score, allocated RRT strategy and outcomes.
List of Datasets Used	Data obtained during the STARrrT-AKI trial
Time of Data Extraction	August 2023

Defining the Cohort	
Cohort	A whole STARrrT-AKI cohort
Exclusion Criteria	NA
Size of Cohort	2927 participants

Time Frame Definitions

Accrual Start/End Dates	From randomization to trial treatment.
Max Follow-up Date	To 90-day follow up after randomization.

Variable Definitions	
Main Exposure or Risk Factor	Patient age and baseline CFS score.
Baseline Characteristics (Table 1 data)	Same as in STARRT-AKI main analysis; however, stratified by the patient age (using 65 as a cut off according to World Health Organization conventional definitions of older age, younger versus older group).
Covariates (To Inform Model Development)	Same as in STARRT-AKI main analysis, with a focus on patient age and baseline CFS score.
Outcome(s) Definitions	Same as in STARRT-AKI main analysis, with a focus on 90-day all-cause mortality and RRT dependence at 90-days.

Outline of Analysis Plan	
Primary Outcome Variables	The primary outcome is: 90-day all-cause mortality.
Secondary Outcome Variables	<p>The following secondary outcomes will be considered:</p> <ul style="list-style-type: none"> • RRT dependence at 90 days among surviving patients. • Composite of death or RRT dependence at 90 days; • Major adverse kidney events (MAKE), defined as death, dependence on renal-replacement therapy, or a sustained reduction in kidney function (i.e., an estimated glomerular filtration rate [eGFR] of <75% of the baseline value) at 90-days; • Mechanical ventilation-free days through day 28. • Vasoactive therapy-free days through day 28. • Death in the ICU, at 28 days or during hospitalization; • ICU-free days through day 28. • Hospitalization-free days through at 90-days. • RRT free days at 90-days; • Health-related quality-of-life, assessed by means of the European Quality of Life–5-Dimensions 5-Level questionnaire (EQ-5D-5L) at 90-days at 1 year among survivors; • CFS score at 90-days and changes in CFS score (frailty status) from day 0 to day 90, by allocated treatment strategy. <p>The LEARN-AKI study will also assess for interaction between age and CFS score and the RRT strategy and outcomes.</p>
Detailed	The statistical analysis will be performed using the intention-to treat principle.

Analysis Plan	<ul style="list-style-type: none"> • The primary outcome of 90-day mortality will be evaluated using a chi-square test (RR and 95% CI). • To assess the differences in the primary and secondary outcomes between the younger and older groups. • To assess the primary and secondary outcomes in the older group with age ≥ 65. • To add CFS scores for interaction and effect modification in the primary and key secondary (RRT dependence and HRQoL). • Sensitivity analysis using age strata, age as a continuous variable, competing risk analysis and the heterogeneity of treatment effect. • The primary outcome will be analysed using conditional survival (KM) curves +/- Cox PH analysis (adjusting for CKD, CFS etc.). • A chi-square test will be performed to assess the secondary outcomes (reported as dichotomous variables (e.g., death in ICU at 28 days, RRT dependence at 90 days)) in patients receiving RRT versus supportive care therapy. T-test will be used to evaluate secondary outcomes that are reported as continuous variables (e.g., RRT free days, ICU free days, etc). • $P < 0.05$ will be considered statistically significant. SAS 9.3 will be used for all statistical analysis.
Proposed Tables and Figures	<p>Table 1: Baseline characteristics of the patients stratified by age.</p> <p>Table 2: Primary and secondary outcomes in the patients stratified by age and allocated RRT strategy: accelerated or standard RRT initiation.</p> <p>Table 3: Primary and secondary outcomes in patients stratified by age and allocated to the standard RRT strategy stratified by whether RRT was received.</p> <p>Figure 1: Flow diagram of cohort assembly.</p> <p>Figure 2: Kaplan–Meier Estimates of Survival at 90 Days.</p> <p>Supplementary Table 1: Baseline characteristics of older patients in the standard strategy group (supportive care approach vs RRT)</p> <p>Supplementary Table 2: Characteristics of the patients stratified by age and frailty status (CFS score ≥ 5).</p> <p>Supplementary Table 3: Characteristics of the older patients stratified by frailty status (CFS score ≥ 5) and allocated RRT strategy: accelerated or standard RRT initiation.</p>