Data Creation Plan for Secondary Analyses

Name and Number of Study	RRT for Metabolic Acidosis in Severe AKI: A Post-Hoc Analysis of the STARRT-AKI trial.
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DCP Update History	Version 2 – December 22, 2025
Short Description of Research Question	In the standard (delayed) arm of STARRT-AKI, RRT was discouraged unless conventional indications developed, including metabolic acidosis, hyperkalaemia, fluid overload with respiratory compromise, or persistent severe renal dysfunction. The clinical significance of metabolic acidosis as a trigger for RRT in this setting is unclear. Specifically, it is unknown whether patients initiated on RRT for protocol-defined metabolic acidosis represent a distinct high-risk subgroup, how they compare with acidotic patients managed without RRT, and whether they differ from patients receiving RRT for non-acidosis indications. Characterising the incidence, severity and management of metabolic acidosis within the standard strategy, and the associated risk-adjusted outcomes, may help inform clinical thresholds for initiating RRT specifically for acidosis and help identify patient subgroups suitable for future studies. Therefore, we ask two questions: a) In critically ill patients with severe AKI managed with a standard RRT strategy, how does metabolic acidosis influence RRT initiation, illness severity, and clinical outcomes? b) Do patients started on RRT for acidosis differ in characteristics and prognosis from those managed conservatively or started on RRT for other indications?
List of Datasets Used	Data obtained during the STARRT-AKI trial

Time of Data Extraction	Estimate February 1 2026

Defining the Cohort	
Cohort	We will define two subcohorts within the standard (delayed) arm for analysis: Analysis 1: A “metabolic acidosis cohort” consisting of standard-arm patients who develop protocol-defined metabolic acidosis after randomisation Analysis 2: An “RRT cohort” consisting of standard-arm patients who receive RRT for any reason after randomisation.
Exclusion Criteria	Patients with missing data on metabolic acidosis / acid-base status.
Size of Cohort	Analysis 1: All patients randomised to the standard strategy; N = 1462. Analysis 2: All patients receiving RRT in the standard strategy.

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

Variable Definitions	
Main Exposure or Risk Factor	Protocol defined clinically important metabolic acidosis (serum bicarbonate ≤ 12 mmol/L) at RRT initiation.
Baseline Characteristics (Table 1 data)	Same as in STARRT-AKI trial analysis (see below)

Covariates **(To Inform Model Development)**	Same as in STARRT-AKI main analysis but specifically including metabolic acidosis, sepsis/septic shock.
Outcome(s) Definitions	Same as in STARRT-AKI main analysis, with a focus on 90-day all-cause mortality, RRT dependence at 90-day, a composite of 90-day all-cause mortality and RRT dependence; RRT-free days at 90-days; vasoactive and mechanical ventilation-free days at day 28; ICU-free days at day 28; and hospital-free days at day 90.

Outline of Analysis Plan	
Primary Outcome Variables	90-day all-cause mortality
Secondary Outcome Variables	MAKE-90 (death, RRT dependence, sustained reduction in kidney function; at 90 days), estimated GFR at 90 days, ICU and hospital length of stay and RRT-related adverse events.
Detailed Analysis Plan	Within the standard arm of STARRT-AKI we will perform two complementary analyses addressing (1) the occurrence and management of metabolic acidosis and (2) clinical phenotypes among patients who initiated RRT. Analysis 1 (Acidosis occurrence and management) - *Analysis 1A:* incidence of moderate-severe significant metabolic acidosis (pH ≤ 7.20 OR HCO_3^- ≤ 15) by day 7 As death may preclude observation of acidosis, mortality before acidosis incidence will be treated as a competing event, and cumulative incidence functions will be reported. - *Analysis 1B:* Among standard-arm participants who develop incident first metabolic acidosis after randomisation, we will evaluate whether initiating RRT soon after acidosis is associated with differences in clinical outcomes. The exposure of interest here is RRT within 1 day of acidosis development, versus no RRT within 1 day of acidosis development ('early RRT' versus 'no early RRT', still within the standard arm). Because early RRT is not randomly assigned and is likely influenced by illness severity and evolving

	physiology, we will estimate risk-adjusted associations using propensity scores to account for confounding by indication. Analysis 2 (RRT recipient phenotypes) - Among standard-arm participants who initiate RRT after randomisation, we will characterise whether patients initiated on RRT in the presence of protocol-threshold metabolic acidosis represent a distinct clinical phenotype and whether they exhibit different outcomes compared with those initiated for non-acidosis indications. Follow up analysis will begin at time of RRT commencement. We will also compare clinical characteristics of patients measured at or immediately prior to RRT commencement, such as markers of organ dysfunction (SOFA, vasopressor use, mechanical ventilation), acid-base parameters, and renal function. We will then determine associations between acidosis status at RRT initiation and outcomes (90-day mortality and MAKE-90) using multivariable regression clustered by site. These analyses will be interpreted as risk-adjusted associations among patients selected to receive RRT.
Proposed Tables and Figures	Table 1: baseline characteristics of standard-arm patients at randomisation, stratified by acidosis status by day 7 Table 2: comparison of clinical status at time of acidosis incidence and subsequent outcomes Table 3: Among participants who started RRT, comparison of characteristics at RRT initiation and outcomes between acidosis and non-acidosis indications (e.g., hyperkalaemia, fluid overload, or persistent AKI). Figure 1: flow chart and schematic of secondary analysis design Figure 2: Cumulative incidence plot of first acidosis by day 7, adjusting for the competing risk of death

Mock table 1

Characteristic	Acidosis by day 7 (n =)	No acidosis (n =)
Demographic		
Age		
Female sex		
Weight		
Serum creatinine		
Estimated glomerular filtration rate		
Acid base status		
Lactate		
Arterial pH		
$PaCO_2$		
Base excess		
Chloride / anion gap		
Serum bicarbonate		
Serum potassium		
Pre-existing conditions		
Chronic kidney disease		
Diabetes mellitus		
Hypertension		
Heart failure		
Coronary artery disease		
Liver disease		
Metastatic cancer		
Hematologic cancer		
Illness severity		
SOFA		
SAPS II		
Mechanical ventilation		
Vasopressor		