# Data Creation Plan for Secondary Analyses

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| **Name and Number of Study** | The association between sepsis/septic shock and outcomes according to accelerated or standard timing of renal replacement therapy initiation in the STARRT-AKI trial. |
| **Principal Investigator(s)** | Sean Bagshaw, Ron Wald, Fernando Zampieri, Javier Neyra et al. |
| **DCP Update History** | Version 1 – September 20, 2023 |
| **Short Description of Research Question** | It is possible that the presence of sepsis or septic shock might have influenced the impact of RRT initiation strategies on key outcomes of the STARRT-AKI trial. This was not shown in a secondary analysis of the AKIKI trial (https://pubmed.ncbi.nlm.nih.gov/29351007/) or in the IDEAL-ICU trial (https://pubmed.ncbi.nlm.nih.gov/30673539/). However, the total numbers of patients evaluated in these two RRT timing trials with sepsis was only 825 patients (56% [348/621] with septic shock in AKIKI; 100% [477/477] with sepsis in IDEAL-ICU. Whereas the proportion of patients with sepsis and septic shock in the STARRT-AKI trial was 57.7% (n=1689/2927) and 43.8% (n=1283/2927), respectively.<br><br>We therefore asked the question: Did sepsis (or septic shock) modify key outcomes according to accelerated or standard timing of RRT initiation in the STARRT-AKI trial? |
| **List of Datasets Used** | Data obtained during the STARRT-AKI trial |
| **Time of Data Extraction** | September 2023 |

| **Defining the Cohort** | |
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| **Cohort** | Patients with evidence of sepsis, defined as per SEPSIS-3, or septic shock, defined as SEPSIS-3 plus vasoactive support. |
| **Exclusion Criteria** | Patients with missing data on sepsis status (Yes/No). |
| **Size of Cohort** | Full mITT cohort (n=2927). Sepsis and septic shock subgroups were 57.7% (n=1689/2927) and 43.8% (n=1283/2927) of the full mITT cohort. |

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

| Variable Definitions | |
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| **Main Exposure or Risk Factor** | Sepsis (defined as per SEPSIS-3) and septic shock (defined as per SEPSIS-3 plus vasoactive support) (see Form 6; page 41) (https://www.ualberta.ca/critical-care/media-library/documents/research-documents/starrtaki-manual-of-operations-v-40--02apr2018--clean.pdf). |
| **Baseline Characteristics (Table 1 data)** | Same as in STARRT-AKI main analysis; however, stratified by the presence or absence of sepsis (and septic shock). |
| **Covariates**<br><br>**(To Inform Model Development)** | Same as in STARRT-AKI main analysis, except sepsis and septic shock will be specifically included. |
| **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 | |
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| **Primary Outcome Variables** | Mortality at 90 days. |
| **Secondary Outcome Variables** | Subgroup analysis will further explore the interaction of sepsis/septic shock with the following outcomes: bleeding (adverse event); hypotension (RRT associated; adverse event); arrhythmia (RRT associated; adverse event). |
| **Detailed Analysis Plan** | Comparative analysis of process of care, outcomes, and adverse events as in the primary STARRT-AKI study but stratified by i) sepsis (Yes/No) and ii) septic shock (Yes/No) adjusting for other factors related to sepsis.<br><br>Further sensitivity analysis will explore: i) septic shock vs. non-septic shock; ii) categorical variables created by sepsis x shock (sepsis – no |

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| | shock; septic shock; no sepsis – no shock; no sepsis – shock). |
| **Proposed Tables and Figures** | Same as in STARRT-AKI main analysis; however, stratified by sepsis and by septic shock. |

**Mock Tables and Figures (legends):**

**Table 1:** Baseline Characteristics According to the Presence of Sepsis and Presence of Septic Shock.

**Table 2:** Clinical Outcomes According to Sepsis and Septic Shock.

**Table 3:** Clinical Outcomes According to Allocation Group, Stratified by Sepsis and Septic Shock.

**Figure Legend:**

**Figure 1.** Flow diagram.

**Figure 2.** Survival stratified by sepsis and by septic shock and allocated RRT initiation strategy.

**Figure 3.** Forest plot of outcomes by sepsis status and allocated RRT initiation strategy.

**Figure 4.** Summary of RRT-free, vasoactive-free, ventilator-free and ICU-free days by sepsis and septic shock status.