Data Creation Plan for Secondary Analyses

Name and Number of Study	Hierarchical endpoint analysis through win ratio in critical care: An exploration using the Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) Trial
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DCP Update History	Version 1 – September 26, 2023
Short Description of Research Question	Critical care trials are frequently designed considering a single endpoint, with mortality being one of the most used [1]. While mortality is undoubtedly important and perceived as patient-centered, the lack of granularity results in the need for very large sample sizes to obtain reasonable effect sizes that can be translated as clinically meaningful. Alternatives include composite endpoints [2], hierarchical endpoints [3], and "free days" (where mortality can be accounted by penalizing the analysis by attributing zero or -1 to patients that died) [4]. More recently, Pocock described the concept of a sequential, hierarchical, endpoint analysis based on a win ratio [5,6]. In brief, the win ratio (WR) is a ratio of wins and losses obtained by comparing all possible combinations between patients in the control group and the intervention group. Each possible pair is compared for a series of endpoints which are compared sequentially, resulting in "wins", "losses" and "ties" between the treatment and control group. These results can then be summarized as the WR, net benefit (NB), and win odds (WO) [5-7]. The WR has been mostly used in cardiology trials [8-9] and has seldom been applied to trials in acutely ill patients [10]. However, it does have interesting properties that may be useful for critical care community, including higher power, ability to consider endpoints in a hierarchical fashion (which accommodates competing risks and prioritization from stakeholders [e.g., patients]) and customizability [5,6]. The STARRT-AKI trial [11], for example, had mortality at 90-days as the primary endpoint but also included important, clinically relevant, and patient-centered endpoints as secondary or tertiary outcomes. The trial's key secondary outcome was renal replacement therapy (RRT) dependency at 90-days, an endpoint that is only relevant (and conditional to) those surviving to this timepoint. Additional endpoints included, for example, hospital length of stay (LOS), and days of hospitalization, which are also conditional to survival. STARRT-AKI reported neutral results for mortality. Therefore, reappraising

	STARRT-AKI under the WR framework may provide new insights on the data and serve as a demonstration for how this hierarchal approach to endpoints can be utilized in future critical care clinical trials.
List of Datasets Used	Data obtained during the STARRT-AKI trial
Time of Data Extraction	September 26, 2023

Defining the Cohort	
Cohort	Modified intention to treat (mITT) cohort of STARRT-AKI.
Exclusion Criteria	Patients with missing data on hospital or ICU LOS or KRT dependency at 90 days.
Size of Cohort	Full mITT cohort (n = 2,927).

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	Same as the original trial.
Baseline Characteristics (Table 1 data)	Same as in STARRT-AKI main analysis.
Covariates **(To Inform Model Development)**	None for the primary analysis. For the stratified WR analysis, patients will be stratified according to illness severity quartiles, baseline CKD status (eGFR <60 vs. eGFR ≥ 60), admission type (medical vs. surgical), and presence of sepsis (yes/no), resulting in five subgroups. See below.
Outcome(s) Definitions	The primary endpoint will be a hierarchical endpoint considering: (1) Mortality at 90 days; (2) Kidney replacement therapy dependence up to 90 days (binary); (3) ICU LOS; (4) Hospital LOS. This sequence follows a pattern from the most important endpoint (survival) to hospital LOS, passing through KRT-dependency. A margin of equivalence of 1 day will be considered for ICU LOS and a margin of 3 days will be considered for

	ICU LOS.

Outline of Analysis Plan	
Primary Outcome Variables	Hierarchical endpoint
Secondary Outcome Variables	None; all incorporated in the hierarchical endpoint
Detailed Analysis Plan	The WR will be estimated using the {BuyseR} package in R. For the primary analysis, there will be no stopping for early ties in the hierarchical endpoint. A sensitivity analysis will be performed by allowing early ties for mortality (i.e., if mortality occurs, no comparison beyond that point will take place); this analysis will use a dedicated script and will provide estimates of WR using bootstrap, without p-values. Alternatively, a stratified WR approach will be applied by stratifying patients according to quartiles of illness severity (using SAPS II score), and according to CKD status (yes/no), reason for admission (surgical, medical) and sepsis (yes/no). Finally, different thresholds of equivalence will be explored for ICU and hospital LOS. Win Odds (WO) and Net Benefit will also be calculated and reported.
Proposed Tables and Figures	See below.

Mock Tables and Figures (legends):

Table 1: Baseline Characteristics

Table 2: Numerical results of WR, WO, and NB.

Figure Legend:

Figure 1. The hierarchical endpoint decision rule

Figure 2. Number of wins, losses, and ties for the WR.

Figure 3. Forest plot for stratified WR.

Figure 4. Sensitivity analysis for different thresholds for hospital and ICU LOS.

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