Data Creation Plan for Secondary Analyses

Name and Number of Study	Long-term dialysis dependence among dialyzed participants in STARRT-AKI
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DCP Update History	Version 1 (April 13, 2023)
Short Description of Research Question	A subgroup analysis to answer this question: "if a patient is ultimately going to require RRT for AKI-D, does delaying/accelerating RRT initiation affect long-term dialysis dependence?" • Approach: Subgroup analysis of STARRT-AKI participants who received more than the median number of days of RRT (6 days). The aim of this subgroup is to remove participants who may not have needed RRT (e.g., those who never received RRT in the standard arm and those who only received RRT for a short time in accelerated arm). In this subgroup, did dialysis dependence differ at 90 days between the accelerated and standard arms? • Hypothesis: Among participants who required more than the median number of days of RRT, dialysis dependence at 90 days will be no different between the accelerated and standard arm participants. Background/Rationale: The main STARRT-AKI trial showed that, in comparison with a standard strategy of RRT initiation, an accelerated strategy resulted in more RRT dependence at 90 days (10.4% versus 6.0%; relative risk 1.74; 95% CI, 1.24 to 2.43). However, it is unclear whether this difference exists among the participants ultimately treated with RRT (only 62% of those assigned to the standard strategy) or if it only exists because so many patients in the standard strategy never needed RRT. The potential harm of the accelerated strategy to long-term RRT dependence may solely be due to treatment inertia to continue RRT after starting, rather than biologic factors such as kidney damage from RRT due

	to intradialytic hypotension. This proposed secondary analysis of STARRT-AKI data seeks to distinguish the effects of initiating RRT (since RRT was never initiated in 3% of accelerated and 38% of standard arm participants) from the effects of additional/earlier RRT (likely 1-2 additional treatments in the accelerated arm) on long-term dialysis dependence. The results may help clarify whether the timing of RRT initiation affects long-term dialysis dependence among patients in whom RRT is ultimately needed.
List of Datasets Used	
Time of Data Extraction	Ideally these analyses could be completed at the Applied Health Research Centre since most of the analyses proposed are essentially repeating the analyses from the original manuscript in subgroups, and thus time required for data extraction should be relatively short. Alternatively, the proposed analyses could be completed at UCSF by Dr. McCoy and colleagues.

Defining the Cohort	
Cohort	Our main analysis proposes to analyze the subgroup of STARRT-AKI participants who were treated with RRT for more than the median number of days (as a proxy for truly requiring RRT under usual care, independent of treatment arm criteria). If we find that long-term dialysis dependence does not differ in this subgroup that excludes those who never or only transiently received RRT, then that would suggest that the harm of the accelerated arm to long-term dialysis dependence is largely due to treatment inertia. On the other hand, if we unexpectedly find that there is still a difference in long-term dialysis dependence, then that would suggest a mechanism other than treatment inertia, such as kidney damage from the additional, 1-day earlier RRT session. Additional sensitivity analysis using slightly different subgroup criteria to define the subgroup who ultimately needed RRT (e.g., instead of receiving more than the median number of days of RRT, could instead select the subgroup who had more than 72 hours of oligoanuria and received RRT) can be considered.
Inclusion/Exclusion Criteria	1. Main analysis: Include only those who received ≥ the median number of days of RRT (6 days). 2. Sensitivity analysis #1: Include only those who had > 72 hours of oligoanuria (< 400 mL/24 hrs as defined in Table 1 of the original STARRT-AKI manuscript) and received RRT.

	3. Sensitivity analysis #2: Include only those who received any RRT.
Size of Cohort	Main analysis: Will include half of those who received RRT in each arm: 50% of the ~97% of 1465 accelerated arm participants who received RRT and 50% of the ~62% of 1462 standard arm participants who received RRT = 711 + 453 = ~1164 participants

Time Frame Definitions	
Accrual Start/End Dates	No date restrictions for STARRT-AKI participants (start with all enrolled participants, trial enrolled from 2015-2019)
Max Follow-up Date	90 days of follow-up

Variable Definitions	
Main Exposure or Risk Factor	The exposure will be the randomized treatment arm (accelerated vs standard) to see if the difference in RRT dependence among survivors at 90 days persists in the subgroup who received more than the median number of days of RRT. Although randomization is lost in this subgroup analysis, that is a caveat common to many useful secondary analyses of randomized trials (1,2). The resultant creation of any imbalance in baseline characteristics will be assessed in the new Table 1. We initially considered defining our cohort as all patients who received any RRT, but we felt that the potential for imbalance in baseline characteristics might be too great in that subgroup (i.e., the accelerated group patients might be less sick since many patients who received RRT may not have needed it and thus may have been stopped after only 1 or 2 RRT treatments), so we now assess that subgroup in sensitivity analysis #2. We think that our primary subgroup definition requiring several days of RRT will minimize the potential for baseline imbalances and best answer our question of whether an accelerated RRT initiation strategy affects long-term dialysis dependence among patients who receive RRT. If a difference in long-term dialysis dependence is unexpectedly found, then that may prompt exploration of other exposures (e.g., the number of RRT sessions delivered) as part of a search for the reason why a difference was found (e.g., was it due to a greater number of days on RRT?). 1. Vijayan A, Delos Santos RB, Li T, Goss CW, Palevsky PM. Effect of Frequent Dialysis on Renal Recovery: Results From the Acute Renal Failure Trial Network Study. Kidney Int Reports. 2018;3(2):456–63.

	2. Jongs N, Chertow GM, Greene T, McMurray JJV, Langkilde AM, Correa-Rotter R, et al. Correlates and Consequences of an Acute Change in eGFR in Response to the SGLT2 Inhibitor Dapagliflozin in Patients with CKD. J Am Soc Nephrol. 2022;33(11):2094–107.
Baseline Characteristics (Table 1 data)	Report the same baseline characteristics included in Table 1 in the main STARRT-AKI manuscript.
Covariates **(To Inform Model Development)**	Use the same approach as used in the original manuscript (logistic regression with inverse probability treatment weighting and multinomial logistic regression to account for the probability of not surviving to 90 days) to report unadjusted relative risks with 95% confidence intervals for the primary outcome of RRT dependence among survivors at 90 days
Outcome(s) Definitions	RRT dependence among survivors at 90 days

Outline of Analysis Plan	
Primary Outcome Variables	RRT dependence among survivors at 90 days
Secondary Outcome Variables	Selected secondary outcomes, presented as they were in Tables 2 and S7 in the original manuscript: 1. Days of RRT 2. Days of CRRT 3. Days of SLED 4. Days of iHD 5. Initial RRT modality (CRRT, SLED, iHD) 6. Ultrafiltration achieved during first RRT session, mL 7. Death during hospitalization and at 90 days
Detailed Analysis Plan	1. Remove participants who received less than the median number of days of RRT (among all participants in both arms who ever received RRT). 2. Recreate Table 1 with this subset, add number of hours from randomization to RRT initiation. Report standardized differences to assess imbalance. 3. Repeat steps 1 and 2 for the other two subsets: those who had more than 72 hours of oligoanuria and received RRT and those who received any RRT.

	Pause and share Table 1's with co-authors to decide if approach needs to be modified before looking at outcomes **4.** Report the number of participants in each arm still alive at 90 days and the number still dialysis dependent at 90 days, along with the other secondary outcomes listed above, as was done in Table 2 of the original manuscript. **5.** Use the same approach as used in Table S8 of the original manuscript (logistic regression with inverse probability treatment weighting or multinomial logistic regression to account for the probability of not surviving to 90 days) to report unadjusted relative risks with 95% confidence intervals for the primary outcome of RRT dependence among survivors at 90 days. **6.** Sensitivity analyses: Repeat steps 4-5 on the subgroup who had more than 72 hours of oligoanuria and received RRT and on the subgroup who received any RRT.
Proposed Tables and Figures	Anticipated conclusion: Among patients who received RRT, there was no difference between those randomized to the accelerated and standard RRT initiation arms in 90-day RRT dependence among survivors. This result suggests that the harm of the accelerated strategy to long-term RRT dependence may be largely due to the treatment inertia of starting RRT. This result may be reassuring to providers and their patients that the odds of long-term dialysis dependence do not seem to be worsened if dialysis is initiated a day early. Table 1. Recreate the same Table 1 from the original manuscript in this subgroup. Table 2. Outcomes.