Data Creation Plan for Secondary Analyses

Name and Number of Study	Bayesian Re-analysis of the STARRT-AKI Trial
Principal Investigator(s)	ZAMPIERI, Fernando and BAGSHAW, Sean
DCP Update History	Version 3 (Oct 20, 2021) Version 2 (Oct 1, 2021). Version 1 (Sept 27, 2021).
Short Description of Research Question	The STARRT-AKI trial found no difference in 90-day mortality with an accelerated strategy to commencing RRT in critically ill patients with severe AKI compared with a more conservative standard strategy. The trial also found the accelerated strategy increased the risk for dialysis dependence at 90-days among survivors compared with the standard strategy.[1] The aim of this secondary post-hoc analysis is to perform a reanalysis of the STARRT-AKI trial, focused on the primary (90-day all-cause mortality) and key secondary endpoints (RRT dependence at 90-day; composite for death/RRT at 90-days; ICU and hospital lengths of stay), employing a Bayesian approach and using conservative estimates of prior beliefs combined with the observed trial data to derive posterior probability distributions of benefit/harm for the trial intervention. The intent is to enhance the intuitive interpretability of the main trial findings for clinicians, aligning with common reasoning and the decision-making approach undertaken at the bedside.[2,3] This has recently been performed for the multi-centre ANDROMEDA-SHOCK and EOLIA trials, respectively, where both studies were primarily designed and analyzed using a frequentist approach and showed clinically important but non-statistically significant effects.[4,5]
List of Datasets Used	Modified ITT dataset (analytic cohort)
Time of Data Extraction	TBD

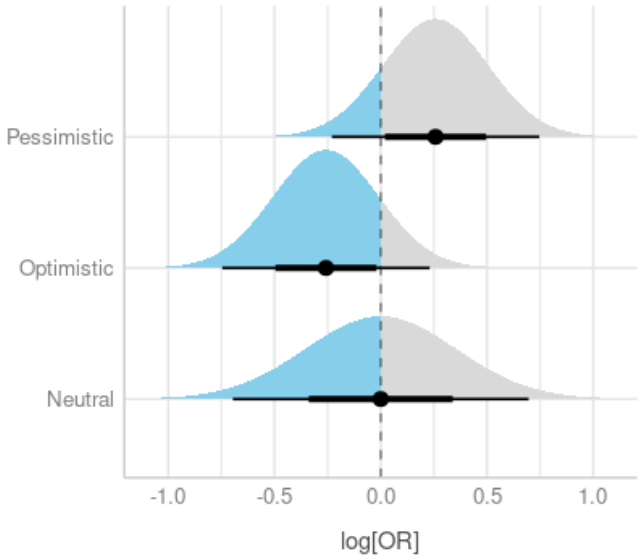
Defining the Cohort	
Cohort	Modified ITT dataset (analytic cohort)

Exclusion Criteria	No exclusion
Size of Cohort	2927

Time Frame Definitions	
Accrual Start/End Dates	Randomization through 90-days.
Max Follow-up Date	90-days, aligned with the primary endpoint (90-day mortality).[6]

Variable Definitions	
Main Exposure or Risk Factor	Allocated intervention (randomization to accelerated vs. standard strategies for RRT initiation).
Baseline Characteristics (Table 1 data)	This will include core cohort data, including a priori subgroups (age, sex, pre-existing conditions, admission category [medical, scheduled surgery, unscheduled surgery]), clinical conditions (sepsis, septic shock), acuity (SAPS II and SOFA scores), organ support (mechanical ventilation, vasoactive support) and laboratory values (serum creatinine; urine output; oliguria; fluid balance). Table 1 will show aggregate and stratification by allocated intervention. We propose to examine specific subgroups of patients: i) sepsis/septic shock (ordinal) (given IDEAL-ICU trial focused specifically on this subject[7]); ii) surgical status (ordinal) (given the ELAIN trial predominantly included surgical patients[8]); and baseline CKD status (continuous).
Covariates **(To Inform Model Development)**	The primary model will be adjusted by presence/absence of sepsis, surgical status and baseline CKD status.
Outcome(s) Definitions	Same as main trial primary and key secondary endpoints.[1,6,9]

Outline of Analysis Plan	
Primary Outcome Variables	Same as main trial primary endpoint.[1,6,9]
Secondary Outcome	We will examine key selected trial secondary endpoints, including RRT dependence at 90-days, a composite of death and/or RRT dependent at

Variables	90-days, lengths of stay (ICU, hospital) and rehospitalization.[1,6,9]
Detailed Analysis Plan	Step 1: Create STARRT-AKI specific priors for treatment arms for the primary endpoint. A *prior* is defined as the prior belief or summary existing evidence regarding the possible effects of variable strategies (i.e., accelerated vs. standard) of RRT initiation in critically ill patients with AKI on outcomes (see Appendix Table 1). The spectrum of methods for estimating priors for this reanalysis may include several methods. The analysis will be based on two sets of priors: (1) Theoretical set of clinically relevant priors. For the primary endpoint, we will consider three priors (neutral, optimistic and pessimistic). The priors will be defined on a log scale for the odds ratio (OR) and assume a normal distribution. The neutral prior will follow N(0,0.355). The optimistic and pessimistic priors will be mirrored around the effect size that the STARRT-AKI trial was designed to detect (a 6% absolute risk reduction in 90-day mortality from 40 to 34%, representing OR 0.77 [log[OR]=-0.257]). Standard deviation will be set to consider a 0.15 probability of harm for the optimistic prior and 0.15 probability of benefit for the pessimistic trial. Therefore, optimistic prior will be N(-0.257,0.249) and pessimistic prior will be N(0.257,0.249). These priors reflect the variable existing evidence base and expert opinion and will be labeled: neutral/skeptical prior with moderate strength[7,8,10-12]; optimistic prior with moderate strength[7,8,10-12]; pessimistic prior with moderate strength. These priors can be visualized on Figure 1, below:  Figure 1 – Priors for effect size of the intervention on log[OR] scale. Blue-shaded areas mark the probability of benefit considered on each prior. (2) We will also evaluate a secondary set of priors based on previous studies, including: i) the STARRT-AKI pilot trial observations[10]; ii) the AKIKI/ELAIN trial observations[8,11] (given divergent results); iii) the IPDMA

	observations (that included all trials prior to publication of the main STARRT-AKI trial)[12]. Finally, the members of the STARRT-AKI steering committee will evaluate the priors and may suggest different values not represented by the previous attempts. These analyses will be considered alternative to the primary analysis based on theoretical priors. Establishing specific priors for secondary endpoints can be cumbersome. Due to their exploratory nature, we will mostly use regularizing priors that may be only weekly informative. This approach will be applied for the following secondary endpoints: 1) secondary endpoint (90-day RRT dependence and "days alive and free of RRT"); 2) secondary endpoint (90-day composite death/RRT); 3) secondary endpoint (length of ICU stay); 4) secondary endpoint (length of hospital stay); 5) secondary endpoint (re-hospitalization and "days alive and free of hospital"). These endpoints were selected because these were the most relevant to the interpretation of the trial findings. Step 2: Bayesian regression models will be used to calculate posterior distribution of the odds ratios (OR), given data and priors, with 95% credible intervals obtained by high density posterior intervals. We will explore days alive and free of RRT and free of hospital using Bayesian beta-binomial regression. All models will be adjusted by presence of sepsis, surgical status and baseline CKD status. Priors for covariates will be neutral and weakly informative, defined as N(0,1). Step 3: We will also calculate posterior probabilities that the accelerated strategy to RRT initiation was associated with benefit (OR <1.0; OR <0.9; OR < 0.8) and harm (OR >1.0; OR >1.2; OR >1.4) for primary and secondary endpoints. We will survey the STARRT-AKI steering committee members for opinion on what would constitute a clinically minimum important difference (MID) in selected outcomes (e.g., mortality and RRT dependence at 90-days). We will also display a region of practical equivalence, defined as an odds ratio between 1/1.1 and 1.1. Data sensitivities to different priors will be assessed through a meta-analysis of effect sizes given different priors. Analysis will be performed using R package (version 4.1.1) (https://www.r-project.org/) with commands: brms; rstanarm; lme4; dplyr; and ggplot2.
Proposed Tables and Figures	Table 1. Summary characteristics stratified by allocated treatment arm. Figure 1. Summary of data-derived and expert opinion priors. Figure 2. Plot of posterior probability distribution (See mock Table) Table 2. Summary of results of Bayesian reanalysis of STARRT-AKI primary and key secondary endpoints.

Mock Table 2. Summary of OR, 95% credible interval and probability that ORs are below given thresholds for mortality at 90-days and RRT dependence at 90-days.

a) mITT analytic cohort overall.

Prior	90-day Mortality			90-day RRT			Rational for prior use
	OR (95% CI)	Prob OR <1 (Prob OR <0.80)	Absolute Difference (95% CI)	OR (95% CI)	Prob OR >1 (Prob OR >1.2)	Absolute Difference (95% CI)	
Optimistic							Assumes the intervention is beneficial with a median estimate similar to the effect size STARRT-AKI was designed to detect, but still acknowledges a 0.15 probability of harm
Neutral							Assumes harm and benefit are equally probable, makes the model skeptic to effect sizes larger than 0.5 or 2.0
Pessimistic							Mirror of the optimistic prior. Assumes a 0.15 probability of benefit
Abbreviations: CI = credible interval							

b) Subgroup according to eGFR (CKD status).

Prior	90-day Mortality			90-day RRT			Rational for prior use
	OR (95% CI)	Prob OR <1 (Prob OR <0.80)	Absolute Difference (95% CI)	OR (95% CI)	Prob OR >1 (Prob OR >1.2)	Absolute Difference (95% CI)	
Optimistic							
Neutral							
Pessimistic							
Abbreviations: CI = credible interval							

c) Subgroup stratified by sepsis.

Prior	90-day Mortality			90-day RRT			Rational for prior use
	OR (95% CI)	Prob OR <1 (Prob OR <0.80)	Absolute Difference (95% CI)	OR (95% CI)	Prob OR >1 (Prob OR >1.2)	Absolute Difference (95% CI)	

Optimistic							
Neutral							
Pessimistic							
Abbreviations: CI = credible interval							

d) Subgroup stratified by surgical status.

Prior	**90-day Mortality**			**90-day RRT**			**Rational for prior use**
	OR (95% CI)	**Prob OR <1 (Prob OR <0.80)**	**Absolute Difference (95% CI)**	**OR (95% CI)**	**Prob OR >1 (Prob OR >1.2)**	**Absolute Difference (95% CI)**	
Optimistic							
Neutral							
Pessimistic							
Abbreviations: CI = credible interval							

Appendix 1: Existing data sources to inform priors.

Endpoint (Effect Estimates)	STARRT-AKI[1]	STARRT-AKI[10] (pilot)	AKIKI[11] (main)	ELAIN[8] (main)	IDEAL-ICU[7] (main)	IPDMA[12] (excluding STARRT-AKI)
Mortality 90-days	1.00 (0.93-1.09) (unadjusted)	1.03 (0.62-1.71) (unadjusted)	0.97 (0.83-1.14)[a]	0.66 (0.45-0.97)[b]	1.07 (0.91-1.26)	0.98 (0.83-1.16)
Mortality 28-days	1.03 (0.93-1.13)	-	0.95 (0.79-1.15)	0.64 (0.37-1.11)	1.07 (0.87-1.31)	1.01 (0.91-1.13)
RRT (90-days)	1.74 (1.24-2.43)	-	1.35 (1.08-1.68)[a]	0.87 (0.31-2.44)	1.04 (0.56-1.96)	1.31 (0.84-2.04)[c]
Death or RRT (90-days	1.06 (0.98-1.14)	-	-	-	1.04 (0.56-1.96)	-
ICU stay (d)	9 vs 10[d]	11 vs 13.5[d]	13 vs 13[d]	19 vs 22[d]	12 vs 12 [d]	
Hospital stay (d)	28 vs 29[d]	29 vs 31[d]	29 vs 32[d]	51 vs 82[d]	22 vs 21 [d]	29.6 vs 32.7
Rehospitalization (90-days)	1.23 (1.02-1.49)	-	-	-	-	-

a – 60-days – calculated odds ratio (not provided in manuscript)
b – hazard ratio
c – hospital discharge
d – among survivors

References:

1. Investigators S-A, Canadian Critical Care Trials Group, Australian and New Zealand Intensive Care Society Clinical Trials Group, et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med 2020;383:240-51.
2. Zampieri FG, Casey JD, Shankar-Hari M, Harrell FE, Jr., Harhay MO. Using Bayesian Methods to Augment the Interpretation of Critical Care Trials. An Overview of Theory and Example Reanalysis of the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial. Am J Respir Crit Care Med 2021;203:543-52.
3. Wijeysundera DN, Austin PC, Hux JE, Beattie WS, Laupacis A. Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. J Clin Epidemiol 2009;62:13-21 e5.
4. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial. JAMA 2018;320:2251-9.
5. Zampieri FG, Damiani LP, Bakker J, et al. Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status versus Serum Lactate Levels among Patients with Septic Shock. A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. Am J Respir Crit Care Med 2020;201:423-9.
6. Investigators S-A. STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury: Study Protocol for a Multi-National, Multi-Center, Randomized Controlled Trial. Can J Kidney Health Dis 2019;6:2054358119852937.
7. Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med 2018;379:1431-42.
8. Zarbock A, Kellum JA, Schmidt C, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 2016;315:2190-9.
9. Investigators S-A. Statistical analysis plan for the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial. Crit Care Resusc 2019;21:162-70.
10. Wald R, Adhikari NK, Smith OM, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int 2015;88:897-904.
11. Gaudry S, Hajage D, Schortgen F, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016;375:122-33.
12. Gaudry S, Hajage D, Benichou N, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet 2020;395:1506-15.