Data Creation Plan for Secondary Analyses

Name and Number of Study	**Delayed RRT in the Standard RRT Initiation Strategy.**
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DCP Update History	December 10, 2023 (Version 3) February 19, 2023 (Version 2) June 1, 2021 (Version 1)
Short Description of Research Question	How late is too late to start RRT in the ICU? What are the predictors of timing of RRT in ICU in the standard-strategy group in STARRT-AKI, and predictors of poor outcomes?
List of Datasets Used	Data obtained during the STARRT-AKI trial
Time of Data Extraction	Dec 7, 2020

Defining the Cohort	
Cohort	Standard-strategy RRT initiation group in the STARRT AKI trial - only those who started RRT.
Exclusion Criteria	Patients who did not receive RRT.
Size of Cohort	N=903

Time Frame Definitions	
Accrual Start/End Dates	From randomization.
Max Follow-up Date	90-day follow-up after randomization.

Variable Definitions	
Main Exposure or Risk Factor	Time from randomization to RRT initiation (stratified by time [hours] in quartiles)
Baseline Characteristics (Table 1 data)	Same as Table 1 from main STARRT-AKI analysis (see Table 2 below).
Covariates **(To Inform Model Development)**	Same as main STARRT-AKI analysis (see Table 2 below).
Outcome(s) Definitions	Same as main STARRT-AKI analysis.

Outline of Analysis Plan	
Primary Outcome Variables	Primary outcome: all-cause mortality at 90 days post randomization.
Secondary Outcome Variables	Secondary outcomes: RRT dependence at 90 days post randomization; ICU length of stay, hospital length of stay, RRT-free days at 90 days; hospitalization-free days through 90 days.
Detailed Analysis Plan	1. Categorize patients in the standard-strategy group based on whether they received RRT (n=903) vs no RRT (n=559); compare baseline characteristics of groups. 2. Evaluate the time from randomization to the time of RRT initiation in the 903 patients in the standard-strategy group who started RRT; stratify by quartiles and characterize baseline characteristics. 3. Evaluate the time from randomization to the time of RRT initiation in the 903 patients in the standard-strategy group who started RRT; stratify by quartiles and characterize as per clinical condition at time of RRT initiation. 4. Evaluate the time from randomization to the time of RRT initiation in the 107 patients in the standard-strategy group who received RRT **less than 12 hours from randomization;** stratify by quartiles and characterize as per clinical condition at the time of RRT initiation. 5.Evaluate the time from randomization to the time of RRT initiation in the 903 patients in the standard-strategy group who started RRT based on **protocol-specified indications only;** stratify by quartiles and characterize as per clinical condition at time of RRT initiation. 6. Evaluate the time from randomization to the time of RRT initiation in the

	903 patients in the standard-strategy group who started RRT based on **clinician-driven indications only;** stratify by quartiles and characterize as per clinical condition at time of RRT initiation. 7. Describe primary and secondary outcomes, unadjusted, by time of RRT initiation quartile. Perform adjusted analysis on outcomes, adjusted for age, sex, baseline estimated glomerular filtration rate, Simplified Acute Physiology Score (SAPS) II, sepsis, and admission type at the time of randomization. 8. Perform sensitivity analyses for primary and secondary outcomes stratified by quartile **excluding patients who started RRT <12 hours** from randomization. 9. Perform sensitivity analyses for primary and secondary outcomes stratified by quartiles **excluding those who died before the median of the fourth quartile (96 hours)**. 10. Perform sensitivity analyses using multivariable logistic regression with restricted cubic spline and inverse probability weighted analysis using time as a continuous variable. 11. Perform sub-group analyses for the primary outcome based on the following **at the time of RRT initiation** (i.e., age, sex, CKD, SAPS II score, surgical status, sepsis).
Proposed Tables and Figures	Table 1: Summary of quartiles of time from randomization to RRT initiation among patients allocated to standard-strategy who started RRT. Table 2. Baseline characteristics of patients in the standard-strategy group, stratified by quartiles of timing of RRT initiation. Table 3. Clinical characteristics, physiologic and organ support at initiation of RRT in the standard-strategy group, stratified by quartiles of timing of RRT initiation. Table 4 and Figure 1. Summary of outcomes, stratified by quartiles of timing of RRT initiation. Figures 2-4. Sensitivity analysis of outcomes, using time as a continuous variable and restricted cubic spline and inverse probability weighted analysis. Table S1. Baseline characteristics of patients in the standard-strategy group who did and did not receive RRT. Table S2. Clinical characteristics, physiologic and organ support at initiation of RRT in the standard-strategy group who received RRT less than 12 hours from randomization, stratified by quartiles of timing of RRT initiation. Table S3. Clinical characteristics, physiologic and organ support at

	initiation of RRT in the standard-strategy group, based on protocol-specified criteria indications, stratified by quartiles of timing of RRT initiation. Table S4. Clinical characteristics, physiologic and organ support at initiation of RRT in the standard-strategy group, based on clinician-driven criteria indications, stratified by quartiles of timing of RRT initiation. Table S5. Sensitivity analysis of outcomes, stratified by quartiles of timing of RRT initiation among those initiated RRT >12 hours from randomization. Table S6. Sensitivity analysis of outcomes, stratified by quartiles of timing of RRT initiation among those initiated RRT >96 hours from randomization.

Table 1. Summary of quartiles of time from randomization to RRT initiation among patients allocated to Standard-strategy who started RRT.

Time from randomization to RRT initiation in the standard-strategy group, by quartiles.				
	Q1	**Q2**	**Q3**	**Q4**
Time to RRT initiation	12.1 (8.3-13.8)	24.5 (21.8-26.5)	46.8 (35.2-52.1)	96.1 (76.7-139.2)
Time to RRT <12hr n(%)	107/226 (47.3)	0 (0.0)	0 (0.0)	0 (0.0)
Time to RRT >72hr n(%)	0 (0.0)	0 (0.0)	0 (0.0)	214/225 (95.1)

Data are presented as median (interquartile range) or n (%).

Time to RRT initiation by quartile: Q1: 0 to 17.3 hours; Q2: 17.3 to 29.1 hours; Q3: 29.1 to 68.4 hours; Q4: 68.4 to 1466.7 hours.

Table 2. Baseline characteristics of patients in the standard-strategy group who received RRT, across quartiles of time from randomization to RRT initiation.

Table 1. Baseline characteristics of patients in the standard-strategy group who received RRT, across quartiles of time from randomization to RRT initiation.					
Time from Randomization to RRT initiation in hours	**Q1**	**Q2**	**Q3**	**Q4**	**p-value**
n	226	226	226	225	
Age – yr	66 (55, 73)	66 (57, 73)	65 (57, 73)	65 (55, 74)	0.89
Female sex – no. (%)	83 (36.7)	77 (34.1)	62 (27.4)	63 (28.0)	0.09
Weight – kg	80 (67, 99)	86 (73, 105)	85 (73, 98)	82 (70, 96)	0.43
Baseline SCr[a] – mg/dl	1.07 (0.79, 1.50)	1.10 (0.85, 1.40)	1.04 (0.80, 1.41)	1.11 (0.85, 1.58)	0.29
Baseline eGFR[b] (med [IQR])	67 (46, 92)	623 (44, 89)	70 (46, 92)	63 (43, 91)	0.61
CFS score (med [IQR])	3 (1, 4)	2 (1, 4)	3 (1, 4)	3 (1, 4)	0.23
CFS score > 4 – no. (%)	53 (23.6)	46 (20.4)	39 (17.3)	47 (21.1)	0.44
EQ-VAS[c]	60 (40, 80)	65 (50, 80)	70 (50, 80)	65 (50, 80)	0.09
Pre-existing conditions – no. (%)					
CKD – no. (%)	93 (41.2)	106 (46.9)	84 (37.2)	102 (45.3)	0.15
eGFR – mL/min/1.73m^2					
≥60 – no. (%)	133 (58.8)	120 (53.1)	142 (62.8)	123 (54.7)	0.20
45-59 – no. (%)	38 (16.8)	49 (21.7)	35 (15.5)	40 (17.8)	
30-44 – no. (%)	22 (9.7)	30 (13.3)	29 (12.8)	25 (11.1)	
<30 – no. (%)	33 (14.6)	27 (11.9)	20 (8.8)	37 (16.4)	
Hypertension	128 (56.6)	125 (55.3)	116 (51.3)	127 (56.4)	0.64
Diabetes mellitus	83 (36.7)	77 (34.1)	67 (29.6)	62 (27.6)	0.15
Heart failure	36 (15.9)	30 (13.3)	22 (9.7)	30 (13.3)	0.28
Coronary artery disease	51 (22.6)	54 (23.9)	57 (25.2)	40 (17.8)	0.25
Liver disease	23 (10.2)	26 (11.5)	29 (12.8)	31 (13.8)	0.67
Metastatic cancer	15 (6.6)	13 (5.8)	16 (7.1)	10 (4.4)	0.65
Hematologic malignancy	17 (7.5)	10 (4.4)	10 (4.4)	16 (7.1)	0.33
HIV/AIDS	1 (0.4)	0 (0)	2 (0.9)	4 (1.8)	0.17
Admission category – no. (%)					
Scheduled surgery	31 (13.7)	35 (15.5)	25 (11.1)	17 (7.6)	0.11

Unscheduled surgery	36 (15.9)	41 (18.1)	47 (20.8)	37 (16.4)	
Medical	159 (70.4)	150 (66.4)	154 (68.1)	171 (76)	
Hospital-acquired risk factors for AKI in the 7 days – no. (%)					
Cardiopulmonary bypass	18 (8)	21 (9.3)	20 (8.8)	8 (3.6)	0.08
Aortic aneurysm repair	7 (3.1)	14 (6.2)	17 (7.5)	9 (4)	0.13
Other vascular surgery	14 (6.2)	14 (6.2)	7 (3.1)	10 (4.4)	0.36
Major trauma	6 (2.7)	6 (2.7)	10 (4.4)	6 (2.7)	0.62
Obstetric complications	2 (0.9)	1 (0.4)	0 (0)	2 (0.9)	0.53
Radiocontrast exposure	47 (20.8)	61 (27)	65 (28.8)	60 (26.8)	0.23
Receipt of aminoglycoside	20 (8.8)	16 (7.1)	26 (11.5)	24 (10.7)	0.39
Receipt of amphotericin B	2 (0.9)	3 (1.3)	3 (1.3)	1 (0.4)	0.75
Clinical condition at randomization					
Sepsis – no. (%)	138 (61.1)	123 (54.4)	141 (62.4)	140 (62.2)	0.26
Septic Shock – no. (%)	119 (52.7)	93 (41.2)	104 (46.0)	113 (50.2)	0.07
SAPS II score[d]	62 (50, 76)	61 (51, 74)	64 (50, 77)	61 (50, 72)	0.34
SOFA score[e]	13 (10, 15)	13 (10, 15)	13 (10, 15)	12 (10, 15)	0.44
Mechanical ventilation	176 (77.9)	186 (82.3)	187 (82.7)	192 (85.3)	0.22
Vasoactive support	177 (78.3)	163 (72.1)	164 (72.6)	170 (75.6)	0.39
Diuretic therapy	100 (44.2)	85 (37.6)	78 (34.7)	86 (38.2)	0.2
Enteral nutrition	80 (35.4)	99 (43.8)	93 (41.2)	88 (39.1)	0.31
Total parenteral nutrition	26 (11.5)	23 (10.2)	18 (8)	39 (17.3)	0.02
Physiological parameters					
Heart rate – beats/min	115 (93,130)	103 (90, 116)	106 (91, 125)	105 (90, 122)	0.02
SBP – mmHg	92 (80, 110)	94 (85, 116)	95 (82, 112)	97 (84, 116)	0.09
Temp – C	38 (37, 39)	38 (37, 38)	38 (37, 39)	38 (37, 38)	0.04
Glasgow coma scale	9 (3, 15)	6 (3, 14)	7 (3, 13)	8 (3, 14)	0.98
Urine output – mL/24hr	295 (103, 712)	355 (100, 647)	400 (159, 836)	500 (200, 1090)	<0.01
Oliguria or anuria[f]– no. (%)	130 (57.5)	121 (53.5)	108 (47.8)	92 (40.9)	<0.01
Cumulative FB[g] – mL	2120 (500, 4453)	3626 (1364, 6371)	3066 (1184, 7026)	3141 (1346, 5627)	0.04
% cumulative FB[h] (%)	2 (1, 6)	4 (2, 8)	4 (1, 8)	3 (2, 7)	0.08
Laboratory parameters					

Hemoglobin – g/L	95 (82, 113)	93 (82, 112)	95 (83, 115)	96 (80, 116)	0.47
WBC count – cells x 10^9/L	15 (9, 22)	15 (10, 21)	14 (10, 19)	15 (10, 20)	0.49
Platelets – cells x 10^9/L	118 (71, 205)	148 (80, 217)	132 (75, 209)	143 (84, 221)	0.29
Serum bilirubin – mg/dL	19 (11, 41)	17 (9, 38)	20 (11, 43)	20 (10, 56)	0.08
Arterial pH	7.31 (7.22, 7.38)	7.32 (7.26, 7.37)	7.31 (7.24, 7.38)	7.33 (7.29, 7.39)	<0.01
Serum sodium – mmol/L	137 (133, 142)	138 (134, 141)	137 (133, 141)	138 (133, 143)	0.31
SCr – mg/dL	3.12 (2.41, 4.20)	3.47 (2.58, 4.62)	3.22 (2.53, 4.41)	3.17 (2.42, 4.26)	0.54
Serum potassium – mmol/L	4.6 (4.0, 5.1)	4.7 (4.2, 5.1)	4.6 (4.0, 5.1)	4.3 (3.7, 4.9)	0.01
Serum HCO3 – mmol/L	18 (16, 21)	18 (16, 21)	19 (16, 22)	19 (17, 23)	<0.01
Serum urea – mmol/L	22 (13, 33)	22 (14, 32)	21 (13, 28)	22 (15, 31)	0.99

Data are presented as no. (%) or median [IQR]. Quartiles represent time from randomization to RRT initiation: Q1: 0 to 17.3 hours; Q2: 17.3 to 29.1 hours; Q3: 29.1 to 68.4 hours; Q4: 68.4 to 1466.7 hours.

[a]At baseline, the serum creatinine level was defined as the most recent outpatient level obtained during the year preceding the current hospitalization. If this value was not available, the lowest serum creatinine level obtained during the current hospitalization was used to establish the baseline. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

[b]The estimated glomerular filtration rate was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation, which incorporates the baseline serum creatinine level, age, sex, and Black race.

[c]Scores on the Visual Analogue Scale of the EQ-5D-5L questionnaire range from 0 to 100, with higher scores indicating better health.

[d]Results range from 0 to 163, with higher scores indicating more severe disease and a higher risk of death.

[e]Scores range from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.

[f]Oliguria was defined as a urinary output of less than 400 mL per 24-hour period.

[g]Data regarding cumulative fluid balance after admission to an intensive care unit were available for 852 in the standard-strategy group who received RRT.

[h]Percent cumulative fluid balance was defined as the sum of [total fluid in – total fluid out]/weight x 100.

Abbreviations: AIDS, acquired immunodeficiency syndrome; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; EQ-5D-5L, European Quality of Life-5-Dimensions 5-Level questionnaire, EQ-VAS, Visual Analogue Scale of the EQ-5D-5L questionnaire; HIV, human immunodeficiency virus; IQR, interquartile range; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; RRT, renal-replacement therapy; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment