REstrictive versus LIberal rate of Extracorporeal Volume removal Evaluation in Acute Kidney Injury

Statistical Analysis Plan

RELIEVE-AKI

ACRONYM:	***RELIEVE-AKI***
VERSION:	***1.0***
PROTOCOL CO-CHAIRS:	***Raghavan Murugan, MD, MS, FRCP*** *Professor of Critical Care Medicine* *Department of Critical Care Medicine* *University of Pittsburgh School of Medicine* ***Kianoush Kashani, MD, MSc, FASN*** *Professor of Medicine* *Division of Nephrology and Hypertension* *Division of Pulmonary and Critical Care Medicine* *Mayo Clinic College of Medicine* ***Paul M. Palevsky, MD*** *Professor of Medicine* *Renal and Electrolyte Division* *Department of Medicine* *University of Pittsburgh School of Medicine* ***Chung-Chou H. Chang, PhD*** *Professor of Medicine, Biostatistics, and Clinical and Translational Science* *Division of General Internal Medicine* *University of Pittsburgh School of Medicine*
SPONSOR:	***NIDDK R01 DK 128100***
DATE:	***9/20/2022***
NCT NO.	***NCT05306964***

1 TABLE OF CONTENTS

2 STUDY OVERVIEW

This document is the Statistical Analysis Plan for the RELIEVE-AKI study. The document describes the statistical methods used to analyze the primary, secondary and safety outcomes in the study. Appendix A is a list of all variables that will be analyzed in the study along with their classification and analysis method. Appendix B is the definition of all derived and composite variables and the data imputation rules for all variables where imputation is used. Appendix C shows the shell tables.

3 TRIAL SUMMARY

The overall objective of RELIEVE-AKI randomized trial is to examine the feasibility of restrictive rate of net fluid removal (*i.e.,* UF_{NET}) during treatment with continuous kidney replacement therapy (CKRT) among critically ill patients with acute kidney injury. Our central hypothesis is that a restrictive UF_{NET} rate strategy embracing a "slow and steady" approach to fluid removal is associated with fewer complications, including cardiac arrhythmias, hypotension, and death, compared with a more liberal "sprint and pause" strategy among critically ill patients.

The RELIEVE-AKI study is a prospective, two-center, unblinded, parallel-group, 2-arm, comparative effectiveness, stepped-wedge cluster-randomized trial (SW-CRT) among 144 critically ill patients with AKI treated with CKRT in 6 ICUs across two hospital systems. The trial will be conducted at 3 ICUs at University of Pittsburgh Medical Center in Pittsburgh, PA, as well as 3 ICUs at Mayo Clinic, Rochester, MN. ICUs will be randomized 1:1 to either a restrictive or a liberal UF_{NET} rate strategy. During the first five months, all ICUs will continue with a liberal UF_{NET} rate strategy. Every three months thereafter, one ICU will be randomized to deploy the restrictive UF_{NET} rate strategy. In the liberal group, the UF_{NET} rate will be titrated between 2.0-5.0 mL/kg/h and maintained throughout fluid removal. In the restrictive group, the UF_{NET} rate will be titrated between 0.5-1.5 mL/kg/h and maintained throughout fluid removal. The UF_{NET} rates used in both strategies are used in current clinical practice.

The primary feasibility outcomes are a.) between-group separation in mean delivered UF_{NET} rates of a minimum of 0.52 mL/kg/h; b.) protocol deviation defined as UF_{NET} rate out of range of >0.5 mL/kg/h lower or higher than the assigned UF_{NET} rate range for six consecutive hours; and c.) patient recruitment of two patients per month per each center. We will explore the effects of restrictive and liberal UF_{NET} rate groups on secondary outcomes such as daily and cumulative fluid balance, duration of kidney replacement therapy and mechanical ventilation, organ-failure free days, ICU and hospital length of stay, hospital mortality, and kidney replacement therapy dependence by hospital discharge.

We will also assess safety outcomes such as intradialytic hypotensive and hypertensive episodes; cardiac arrhythmias; emergent use of rescue UF_{NET} rates higher than the assigned group for treatment of fluid overload; severe hypophosphatemia, hypokalemia, and hypocalcemia; CKRT circuit downtime due to filter clotting or clogging; discontinuation of fluid removal due to hemodynamic instability; inability to close surgical wounds due to edema; new organ dysfunction; diastolic and systolic dysfunction; pulmonary edema; ileus, bowel ischemia, anastomotic break down; pressure ulceration; wound infections; arterial or venous thrombosis; severe anemia requiring red cell transfusion, severe thrombocytopenia requiring platelet transfusions; and secondary infections.

3.1 INCLUSION CRITERIA

1. Age ≥18 years
2. Stage 3 acute kidney injury according to the KDIGO criteria
3. Started or intending to start CKRT for volume management
4. Attending intensivist or nephrologist intending to remove net fluid using CKRT for at least 48 hours

3.2 EXCLUSION CRITERIA

1. Respiratory distress due to pulmonary edema or fluid overload
2. Massive volume infusion (*i.e.,* >200 mL/h for >6 hours of continuous infusion)
3. No intention to remove net fluid as determined by attending intensivist or nephrologist
4. Attending intensivist or nephrologist believes that the protocol will not be followed
5. Continuous net fluid removal for >24 hours prior to study enrollment
6. Body Mass Index >40
7. Patients on chronic outpatient hemodialysis
8. Patients with history of, or current admission for kidney transplantation
9. Patients with comfort measures only orders (*i.e.,* CMO)
10. Moribund not expected to survive >24 hours
11. Confirmed pregnancy
12. Patients treated with extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or intra-aortic balloon pump (IABP)
13. Organ donors with neurological determination of death (*i.e.,* brain dead donors)
14. Drug overdose requiring CKRT for drug clearance
15. Enrollment in a concurrent interventional clinical trial with direct impact on fluid balance (*e.g.,* >500 mL study drug administration)

3.3 ASSESSING ATTENDING PHYSICIAN EQUIPOISE

After meeting inclusion and none of the exclusion criteria, the attending intensivist or nephrologist will be asked twice daily if she/he strongly believed:

a) emergent and rapid fluid removal should occur

OR

b) fluid removal should be deferred

If the answer is negative to both questions, the patient will be considered fully eligible and efforts to obtain informed consent from patient or LAR will commence. If a patient's eligibility is excluded by an attending physician, the patient will be reconsidered for participation in the trial, and the physician will be re-approached later, provided the patient still meets inclusion criteria and none of exclusion criteria.

3.4 STUDY INITIATION TIME WINDOW

All patients will be consented and enrolled within 48 hours of meeting full eligibility. Time of signing the informed consent will be the study enrollment time. Once enrolled, the assigned intervention must be initiated within 24 hours.

3.5 OUTCOMES

3.5.1 PRIMARY OUTCOMES

1. Mean delivered UF_{NET} rates
2. No. of participants with protocol deviation
3. Patient recruitment rate.

3.5.2 SECONDARY OUTCOMES

1. Daily fluid balance
2. Cumulative fluid balance
3. Duration of kidney replacement therapy
4. Duration of mechanical ventilation
5. Organ failure free days
6. ICU length of stay
7. Hospital length of stay
8. Hospital mortality
9. Dialysis dependence at hospital discharge

3.5.3 SAFETY OUTCOMES

1. No. of intradialytic hypotensive episodes
2. No. of intradialytic hypertensive episodes
3. No. of intradialytic new onset cardiac arrhythmias including supraventricular tachycardia, bradycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and cardiac arrest
4. No. of participants with emergent use of rescue UF_{NET} with rates higher than the assigned treatment arm
5. No. of participants with severe hypophosphatemia (<0.5 mg/dL)
6. No. of participants with severe hypokalemia (<3.0 mg/dL)
7. No. of participants with severe hypocalcemia (<1.90 mg/dL or ionized calcium <0.90 mmol/L)
8. No. of episodes of stopping CKRT due to filter clotting or clogging
9. No. of participants with discontinuation of UF_{NET} due to hemodynamic instability
10. No. of participants in whom surgical wounds are left open due to edema
11. No. of participants with new organ dysfunction
12. No. of participants with worsening of systolic or diastolic cardiac function on echocardiogram
13. No. of participants with worsening of pulmonary edema on chest X Ray and/or CT scan
14. No. of participants with worsening of ileus on abdominal X Ray and/or CT scan
15. No. of participants with bowel ischemia or anastomotic breakdown based on intraoperative findings
16. No. of participants with pressure ulcerations
17. No. of participants with new wound infections
18. No. of participants with new arterial or venous thrombosis
19. No. of participants with severe anemia requiring red cell transfusions

20. No. of participants with severe thrombocytopenia requiring platelet transfusions
21. No. of participants with new secondary infections

3.6 SAMPLE SIZE AND MONITORING

1. Using the sample size calculation for stepped wedge cluster randomized trial (SW-CRT) design, 126 patients will have 80% power at a two-sided alpha of 0.05 to reject the null hypothesis that the average UF_{NET} rate was at least 0.52 mL/kg/h different between the two groups, using intra-cluster correlation coefficient of 0.01, at a standard deviation of 0.75, and assuming mean UF_{NET} rate of 1.0 mL/kg/h. After accounting for a potential 10% attrition rate, the sample size was increased to 144 subjects or 72 patients per group.

2. The principal analysis will be intent-to-treat based upon randomization assignment.

3. The trial progress will be evaluated by an independent Data and Safety Monitoring Board (DSMB). Being a feasibility study there will be no interim analyses.

4 DATA ANALYSIS PLAN

4.1 OVERALL ANALYTICAL PLAN

All analyses will be performed on an intention-to-treat basis, which generally biases toward no difference. We will also perform per-protocol analyses where the assigned intervention was followed. We will first examine the data structure, distributions of the outcomes and explanatory variables, and potential missing data elements. Missing data will be imputed after examining the reason for missingness. For data that are missing completely at random or missing related to other collected covariates, we will use the multivariable imputation by chained equation (MICE) to impute data before fitting models.[1]

The individual ICU is the unit of randomization, and the individual patient is the unit of analysis. In SW-CRT, the usual comparisons between two treatments need to be made over a differing time making standard group comparison-based methods biased and potentially ineffective. Therefore, we will use adjusted generalized linear mixed models (GLMM) for all primary and secondary outcomes, as delineated by Hussey and Hughes and others,[2-4] to account for temporal and clustering effects typically encountered in SW-CRT designs. In these models, we will use the ICU as random effects. Time will be treated as random in the main analysis but will also be treated as fixed effects and interact with other covariates.

We will adjust all analyses for prespecified variables such as age, baseline eGFR, severity of illness as measured by the acute physiology and chronic health evaluation (APACHE)-III score, Elixhauser Comorbidity Index score, use or nonuse of mechanical ventilation, admission source, percentage of fluid overload before study enrollment, presence or absence of sepsis, baseline cardiovascular SOFA score and any other variable that are associated with outcome of UF_{NET} and had a between-group difference ($P \leq 0.2$) on univariable analysis. We will assess the stability of final models using routine model diagnostics to identify potential outliers and/or influential observations. We will report both

adjusted and unadjusted analyses stratified by restrictive and liberal UF_{NET} groups.

4.2 ANALYSIS METHODS FOR PRIMARY OUTCOMES

The three primary feasibility outcomes are as follows:

4.2.1 THE BETWEEN-GROUP DIFFERENCE IN MEAN DELIVERED UF_{NET} RATE

The primary objective is to measure a minimum of 0.52 mL/kg/h separation in the delivered patient mean UF_{NET} rates between the restrictive and liberal UF_{NET} rate groups. We chose between-group separation as a feasibility metric because it is a robust measure of adherence to complex protocols and has been used in ICU trials assessing the feasibility of frequently titrated interventions.[5,6] Specifically, we reasoned that a larger study would not be feasible if the separation in the UF_{NET} rates were less than 0.52 mL/kg/h. We chose 0.52 mL/kg/h as a clinically meaningful difference because our preliminary data indicated that a 0.50 mL/kg/h increase in UF_{NET} rate is associated with increased mortality.[7]

For between-group differences in delivered UF_{NET} rates, we will report the patient-averaged UF_{NET} rate with a corresponding 95% confidence interval. The patient averaged UF_{NET} rate was the average of all hours for days where any UF_{NET} was delivered. We will not include hours during which no fluid was removed during CKRT. We will use GLMM with a two-sided alpha of 0.05 to test the null hypothesis that the mean difference in the patient averaged delivered UF_{NET} rate was less than 0.52 mL/kg/h after adjusting for the above prespecified variables.

We will also perform exploratory analysis in which we will examine between-group differences in peak (*i.e.,* maximum) delivered UF_{NET} rates. We will also examine differences in longitudinal trajectories of mean delivered UF_{NET} rate between the restrictive and liberal UF_{NET} groups over time. We will perform subgroup analysis in which we will examine between-group differences in mean delivered UF_{NET} rates among those with and without >10% fluid overload at enrollment; eGFR greater or less than 60mL/min/1.73m^2; duration of UF_{NET} before enrollment (*i.e.,* greater or less than 6 hours); age ≥65 and <65 years; with and without sepsis; and baseline cardiovascular SOFA score ≥3 and <3.

4.2.2 PROTOCOL ADHERENCE

We have defined protocol deviation *a priori* as delivered UF_{NET} rate that lies >0.5 mL/kg/h outside of the target UF_{NET} rate range in the assigned treatment group for greater than six consecutive hours during fluid removal *without* significant changes in MAP (*i.e.,* MAP <65 mmHg or ≥90 mmHg). As such, out of range UF_{NET} rates >0.5 mL/kg/h beyond the target UF_{NET} rate range in the assigned treatment group will not constitute a protocol deviation when the bedside team titrated the UF_{NET} rate as required to manage the patient hemodynamics (*i.e.,* when clinicians appropriately decreased rate or stopped fluid removal for hypotension; increased fluid removal rate for hypertension or for treatment of respiratory distress due to fluid overload and pulmonary edema).

We will report the following stratified by restrictive and liberal UF_{NET} rate groups: i.) no. of occurrences of deviations for six consecutive hours divided by UF_{NET} days (mean events per day); ii.) no. of days with UF_{NET} out of range for at least six consecutive hours; iii.) no. of patients with at least one occurrence of UF_{NET} rate out of range for six consecutive hours. The proportion of patients with protocol deviation will be compared using the Wald test for GLMM and adjusted for prespecified covariates.

As an exploratory analysis, we will also report the proportion of total hours of UF_{NET} rate within, above, or below range for each patient weighted equally and proportionally to total hours of fluid removal.

4.2.3 RECRUITMENT RATE

A successful recruitment rate will be defined as achieving an enrollment rate of 2 patients per month per center during the trial. The recruitment metric will be calculated as the mean number (standard deviation) of recruited patients per active screening month.

4.3 ANALYSIS METHODS FOR SECONDARY AND SAFETY OUTCOMES

We will use GLMM regression after adjusting for various prespecified variables. We will consider observed differences between groups to be statistically significant at a two-sided, nominal alpha of 0.05 for all outcomes.

For binary outcomes, we will use the Wald test for GLMM to compare the proportion of patients in the two UF_{NET} rate groups (Appendix A).

For continuous variables, we will report incident rate ratios calculated with zero-truncated negative binomial regression modeling adjusted for prespecified baseline covariates.

For independence from KRT and hospital mortality, we will fit GLMM regression models and report odds ratios with corresponding 95% confidence intervals from logistic regression after adjusting for prespecified baseline covariates. To safeguard against erroneous type I error inflation in secondary outcomes, we will apply the conservative Hochberg procedure for adjustment on multiplicity to two key secondary outcomes of mortality and KRT dependence.[8,9] Because of the potential for type I error due to multiple comparisons, findings for analyses of the other secondary end points will be interpreted as exploratory.

4.4 HANDLING THREATS TO DATA ANALYSIS

Potential threats include missing data, handling of subject data for individuals who withdraw from the study, and incorrect enrollment. We expect incorrect enrollment to be very rare. Missing data, from either incomplete data entry or subject withdrawal, present a greater challenge. We will minimize missingness by creating a concise web-based data collection form, incorporating extensive logic checks to prevent erroneous data entry, auto-prompts for missingness, and close site coordination. We will apply methods for missingness analyses based on weighted estimating equations,[10] multiple imputations using methods proposed by Rubin and Schenker, and/or pattern mixture models.[11]

5 APPENDICES

5.1 APPENDIX A: OUTCOME VARIABLES AND ANALYSIS METHOD

Variable	Outcome Category	Scale	Analysis Method
Between-group separation in mean delivered UF_{NET} rates	Primary	Continuous	GLMM
Protocol deviation	Primary	Binary	Wald-test for GLMM
Recruitment rate	Primary	Continuous	GLMM
Daily fluid balance	Secondary	Continuous	GLMM
Cumulative fluid balance	Secondary	Continuous	GLMM
Duration of kidney replacement therapy	Secondary	Continuous	GLMM
Duration of mechanical ventilation	Secondary	Continuous	GLMM
Organ failure free days	Secondary	Continuous	GLMM
ICU length of stay	Secondary	Continuous	GLMM
Hospital length of stay	Secondary	Continuous	GLMM
Hospital mortality	Secondary	Binary	Wald-test for GLMM
Dialysis dependence at hospital discharge	Secondary	Binary	Wald-test for GLMM
Hypotensive episodes	Safety	Continuous	GLMM
Hypertensive episodes	Safety	Continuous	GLMM
Cardiac arrhythmias	Safety	Continuous	GLMM
Emergent use of rescue UF_{NET} rates	Safety	Binary	Wald-test for GLMM
Severe hypophosphatemia	Safety	Binary	Wald-test for GLMM
Severe hypokalemia	Safety	Binary	Wald-test for GLMM
Severe hypocalcemia	Safety	Binary	Wald-test for GLMM
CKRT stopping due to hemofilter clotting or clogging	Safety	Continuous	GLMM
Discontinuation of fluid removal due to hemodynamic instability	Safety	Binary	Wald-test for GLMM
Inability to close surgical wounds	Safety	Binary	Wald-test for GLMM
New organ dysfunction	Safety	Binary	Wald-test for GLMM
Worsening systolic/diastolic cardiac function	Safety	Binary	Wald-test for GLMM

Worsening pulmonary edema	Safety	Binary	Wald-test for GLMM
Worsening of ileus	Safety	Binary	Wald-test for GLMM
Bowel ischemia or anastomotic breakdown	Safety	Binary	Wald-test for GLMM
Pressure ulcerations	Safety	Binary	Wald-test for GLMM
New wound infections	Safety	Binary	Wald-test for GLMM
New arterial or venous thrombosis	Safety	Binary	Wald-test for GLMM
Severe anemia	Safety	Binary	Wald-test for GLMM
Severe thrombocytopenia	Safety	Binary	Wald-test for GLMM
New secondary infections	Safety	Binary	Wald-test for GLMM

5.2 APPENDIX B: DERIVED VARIABLES

5.2.1 OUTCOME VARIABLES

5.2.1.1 Delivered UF_{NET} rate

The delivered UF_{NET} rate variable is defined as net intravascular fluid removal rate from the patient after accounting for intravenous fluids infused in the current hour and adjusted for predicted body weight. The overall mean delivered UF_{NET} rate for each hour will be calculated from all patients enrolled in the restrictive and liberal group.

5.2.1.2 Hospital mortality to day 28

Death prior to discharge alive from study hospital will be counted as hospital mortality. Patients whose final status is unknown but who are known to be alive on study day 28 based on known event dates will be counted as alive.

5.2.1.3 Kidney replacement therapy to day 28

Patients receiving any form of kidney replacement therapy 72 hours before discharged alive will be considered dialysis dependent. If a patient dies before day 28, the patient will be considered dialysis dependent. Patients who are not dialysis dependent by day 28 but continue to remain in the hospital or receive dialysis after day 28 will be considered liberated from dialysis.

5.2.1.4 Organ failure free days to day 28

Organ failure is defined as present on any date when the most abnormal vital signs or clinically available lab value meets the definition of clinically significant organ failure according to SOFA scores. Patients will be followed for development of organ failures to death, hospital discharge or study day 28, whichever comes first. Each day a patient is alive and free of a given organ failure will be scored as a failure-free day. Any day that a patient is alive and free of all organ failures will represent days alive and free of all organ failure.

5.2.1.4.1 E. SOFA scoring system

Variables	Sequential Organ Failure Assessment Score				
	0	**1**	**2**	**3**	**4**
Respiratory					
PaO_2/FiO_2 (mmHg)	>400	≤400	≤300	≤200[a]	≤100[a]
Coagulation					
Platelets (x $10^3/\mu L$	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	>12.0

Cardiovascular					
MAP (mmHg)	≥70	<70			
Vasopressor[b] (doses in mcg/kg/min)	None	None	Dopamine ≤5 OR Dobutamine (any dose)	Dopamine >5 OR Epinephrine ≤0.1 OR Norepinephrine ≤0.1	Dopamine >15 OR Epinephrine >0.1 OR Norepinephrine >0.1
Central Nervous System					
Glasgow Coma Scale	15	13 – 14	10 – 12	6 – 9	<6
Kidney					
Creatinine (mg/dL)	<1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 OR	≥5 OR
Urine output (mL/day)				<500	<200

[a] Values are with ventilatory support; the maximum score in patients not receiving ventilatory support is 2

[b] Pressor agents administered for at least 1 hour

We define a clinically significant organ failure as a new SOFA score of ≥2

We treat post-ICU SOFA as normal; post-ICU means getting out and staying out of ICU

5.2.2 OTHER VARIABLES

We will use following criteria to adjudicate safety outcomes from intervention initiation to 12 hours following discontinuation of CRKT.

5.2.2.1 Intradialytic hypotension

Intradialytic hypotension will be defined as a *new* MAP <65 mmHg, SBP<90mmHg or a decline in SBP >40 mmHg, and/or a >30% increase in dose of existing vasopressors, initiating a new vasopressor, administration of fluid bolus, or discontinuation of fluid removal with a goal to maintain (MAP) ≥65 mmHg, systolic blood pressure (SBP) ≥90mmHg.

5.2.2.2 Intradialytic hypertension

Intradialytic hypertension will be defined as *new* onset SBP ≥160 mmHg or MAP ≥80 mmHg for more than 1 hour in the absence of any vasopressor or inotrope use.

5.2.2.3 Intradialytic cardiac arrhythmias

Intradialytic *new* onset cardiac arrhythmias including supraventricular tachycardia, bradycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, asystole/pulseless electrical activity will be diagnosed as per American Heart Association.

5.2.2.4 Rescue net ultrafiltration

Emergent use of rescue UF_{NET} with rates higher than the assigned treatment arm for more than 3 consecutive hours.

5.2.2.5 Severe hypokalemia, hypophosphatemia and hypocalcemia

Severe hypophosphatemia will be defined as intradialytic phosphate level <0.5 mg/dL. Severe hypokalemia is defined as a intradialytic potassium level <3.0 mg/dL. Severe hypocalcemia will be defined as intradialytic serum calcium level <1.90 mg/dL or ionized calcium <0.90 mmol/L.

5.2.2.6 Inability to close post-operative surgical wound due to edema

This will be determined as per the primary surgical service. Abdominal wounds left open for a second look or for abdominal re-exploration should not be counted unless there is concurrent tissue edema precluding abdominal closure.

5.2.2.7 New organ dysfunction due to fluid overload

New and worsening organ dysfunction will be assessed based on SOFA scoring. For instance, a patient with CV SOFA score of 3 at study initiation and now has score of 4 will be counted as worsening CV dysfunction. We will also capture new diastolic/systolic dysfunction on echocardiogram, pulmonary edema on chest X ray/CT scan, ileus on abdominal X ray/CT scan, bowel ischemia and anastomotic breakdown on CT scan/OR, transaminitis or hyperbilirubinemia; delirium using delirium scores on medical records, poor wound healing, wound infection, and pressure ulceration per nursing records, new onset arterial and venous thrombosis as documented by imaging and clinical examination, and anemia, hemolysis and thrombocytopenia as documented in the laboratory studies.

5.2.2.8 Secondary infections

New onset secondary infections occurring after initiation of study intervention will be collected based on culture data, antibiotic use and suspected sepsis as per clinician judgment.

5.3 APPENDIX C: SHELL TABLES

5.3.1 TABLE 1: CHARACTERISTICS OF PATIENTS AT BASELINE

	Characteristics	No. (%)		Unadjusted P value
		Restrictive (N= XX)	Liberal (N=XX)	
Age, years, median (IQR)				
Female sex				
Ethnicity				
	White			
	Black			
	Hispanic			
	Asian			
	Native Hawaiian			
	American Indian			
	Other			
	Prefer not to answer			
Actual body weight at hospital admission, Kilograms, median (IQR)				
Baseline serum creatinine, mg/dL, median (IQR)				
Estimated glomerular filtration rate, mL/min/1.73m^2 median (IQR)				
Elixhauser Comorbidity Index score				
Pre-existing conditions				
	Hypertension			
	Diabetes mellitus			
	Chronic kidney disease			
	Coronary artery disease			
	Heart failure			
	Liver disease			
	Metastatic cancer			
	Chronic pulmonary disease			
Primary diagnosis				
	Cardiovascular			
	Pulmonary			
	Gastrointestinal			
	Toxicology			
	Infection or sepsis			
	Neurologic			
	Oncologic			
	Other			
Etiology of acute kidney injury				
	Sepsis			

	Characteristics	No. (%)		Unadjusted P value
		Restrictive (N= XX)	Liberal (N=XX)	
	Ischemic			
	Nephrotoxic			
	Multifactorial			
Risk factors for fluid overload in the past week				
	Sepsis			
	Hemorrhage			
	Acute pancreatitis			
	Other			
Source of admission				
	Home			
	Skilled Nursing Facility			
	Assisted Living Facility			
	Other			
Admission category				
	Medical			
	Scheduled surgery			
	Emergency surgery			
Clinical condition at study enrollment				
	Sepsis			
	APACHE-III score, median (IQR)			
	Cardiovascular SOFA score, median (IQR)			
	Vasopressor support			
	Mechanical ventilation			
	Fluid overload percentage			
	Median cumulative fluid balance at study enrollment, median (IQR) mL			
	Median UF rate at study enrollment, (IQR), mL			
	Oliguria/anuria			
	Urinary output, mL/24 hours, median (IQR)			
	Corticosteroid use			

5.3.2 TABLE 2: PRIMARY AND SECONDARY OUTCOMES

		Unadjusted Analysis			Adjusted Analysis			
	Outcomes	**Restrictive (N= XX)**	**Liberal (N=XX)**	**P value**	**Restrictive (N= XX)**	**Liberal (N=XX)**	**Estimated Effect of Intervention (95% CI)**	**P value**
Primary								
	Delivered UF_{NET} rate, mean (SD)							
	Delivered UF_{NET} rate, median (IQR)							
	No. of participants with protocol deviation							
	Recruitment rate per month per site							
Secondary								
	Daily fluid balance excluding UF, mL, median (IQR)							
	Cumulative fluid balance excluding UF, mL, median (IQR)							
	Daily fluid balance including UF volume, mL, median (IQR)							
	Cumulative fluid balance including UF volume, mL, median (IQR)							
	Duration of kidney replacement therapy, days, median (IQR)							
	Duration of mechanical ventilation, days, median (IQR)							
	Organ failure free days, days, median (IQR)							
	ICU length of stay, days, median (IQR)							
	Hospital length of stay, days, median (IQR)							

		Unadjusted Analysis			Adjusted Analysis			
	Outcomes	**Restrictive (N= XX)**	**Liberal (N=XX)**	**P value**	**Restrictive (N= XX)**	**Liberal (N=XX)**	**Estimated Effect of Intervention (95% CI)**	**P value**
	Kidney replacement therapy dependence at discharge among survivors							
	Hospital mortality							

[$] Adjusted for differences in age, baseline eGFR, APACHE-III score, Elixhauser Comorbidity Index score, mechanical ventilation, admission source, percentage of fluid overload, sepsis, and baseline cardiovascular SOFA score.

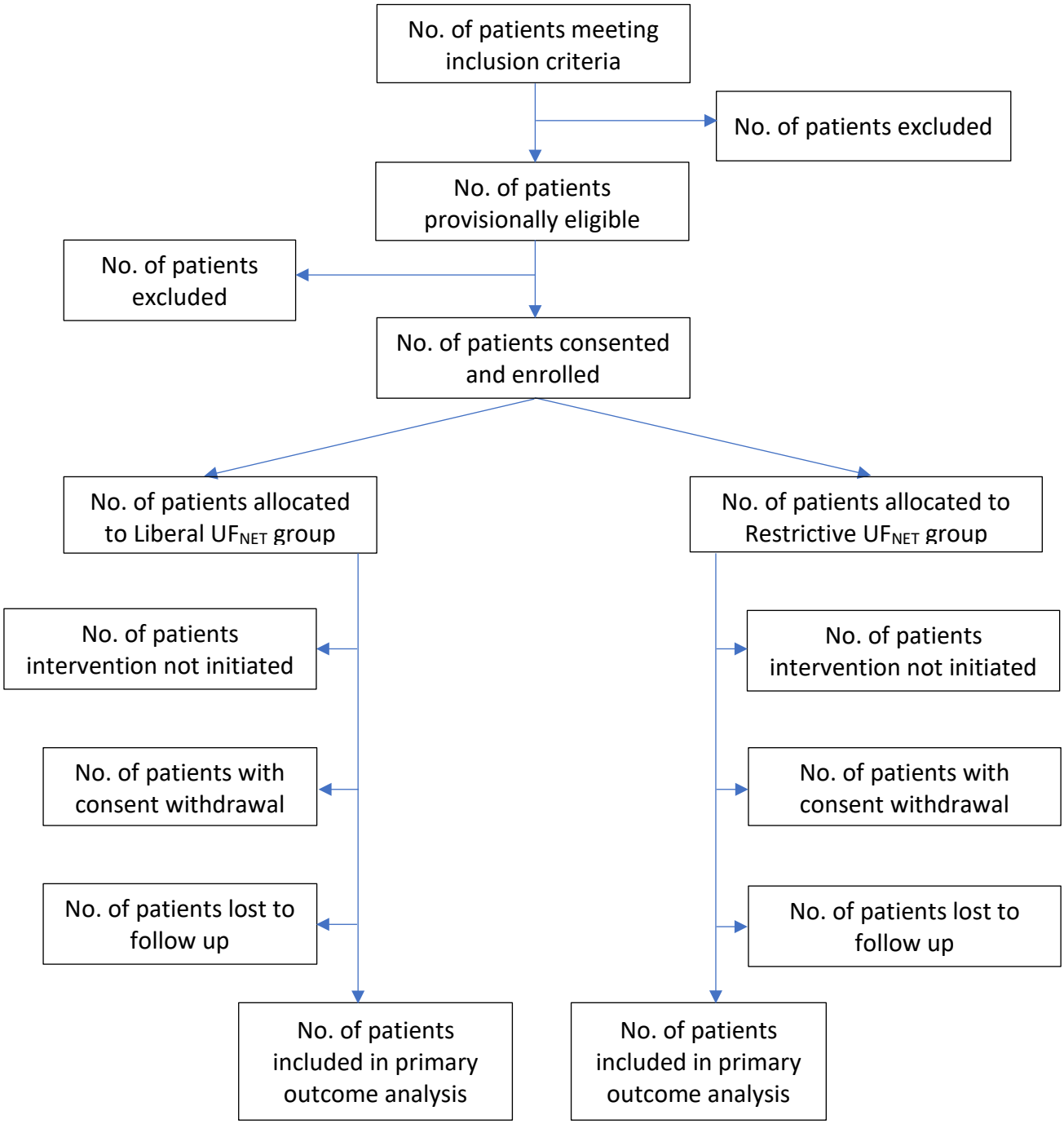
5.3.3 TABLE 3: SAFETY OUTCOMES

Safety Outcomes	Restrictive		Liberal		Unadjusted P value	Adjusted P value[$]
	No. of Patients (%)	No. of episodes	No. of Patients (%)	No. of episodes		
Intradialytic hypotension						
Intradialytic hypertension						
Cardiac arrhythmias						
Use of rescue net ultrafiltration						
Hypophosphatemia (<0.5 mg/dL)						
Hypokalemia (<3.0 mg/dL)						
Hypocalcemia (<1.90 mg/dL)						
Hemofilter clotting or clogging						
UF_{NET} discontinuation due to instability						
Surgical wounds edema						
New organ dysfunction						
Worsening cardiac function						
Worsening of pulmonary edema						
Worsening of ileus						
Bowel ischemia or anastomotic breakdown						
New pressure ulcerations						
New wound infections						
New arterial or venous thrombosis						
Severe anemia						
Severe thrombocytopenia						
New secondary infections						

[$] Adjusted for differences in age, baseline eGFR, APACHE-III score, Elixhauser Comorbidity Index score, mechanical ventilation, admission source, percentage of fluid overload, sepsis, and baseline cardiovascular SOFA score. P values are for the between-group differences in the percentage of patients with a specific event and have not been adjusted for multiple comparisons.

5.4 APPENDIX D

5.4.1 FIGURE 1: PATIENT FLOW THROUGH THE TRIAL

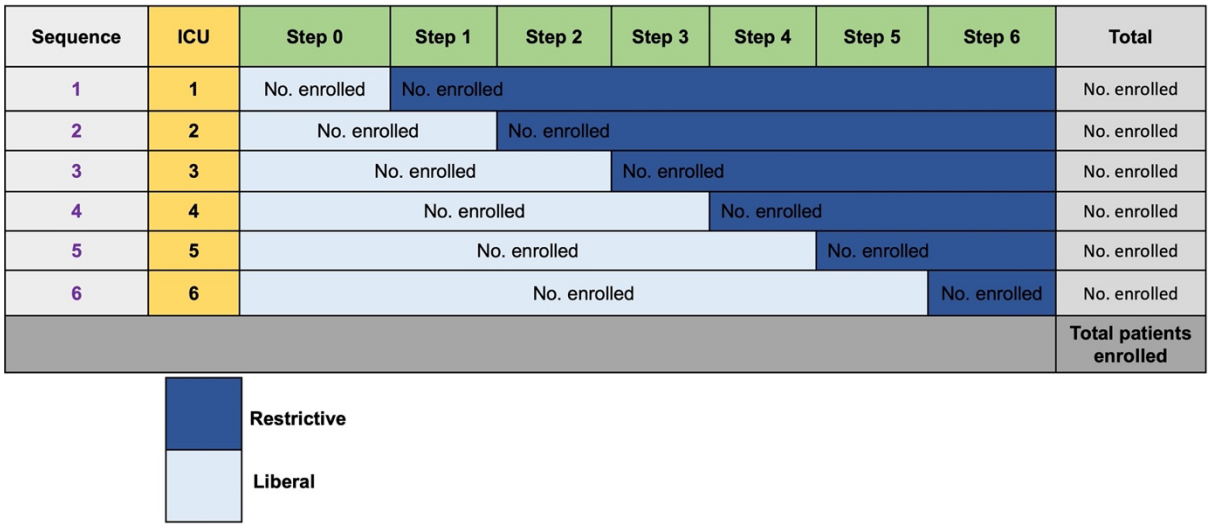


5.4.2 FIGURE 2

Figure showing the distribution of delivered UF_{NET} over time by restrictive and liberal UF_{NET} rate groups.

5.4.3 FIGURE 3

Stepped Wedge Allocation of Trial Participants



6 REFERENCES

1. Buuren SV, Groothuis-Oudshoorn K. MICE: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*. 2011;45(3):1-67.

2. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. Feb 2007;28(2):182-91. doi:10.1016/j.cct.2006.05.007

3. Thompson JA, Fielding KL, Davey C, Aiken AM, Hargreaves JR, Hayes RJ. Bias and inference from misspecified mixed-effect models in stepped wedge trial analysis. *Stat Med*. Oct 15 2017;36(23):3670-3682. doi:10.1002/sim.7348

4. Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: An overview. *Stat Methods Med Res*. Jul 6 2020:962280220932962. doi:10.1177/0962280220932962

5. Lamontagne F, Meade MO, Hebert PC, et al. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med*. Apr 2016;42(4):542-550. doi:10.1007/s00134-016-4237-3

6. Lauzier F, Adhikari NK, Seely A, et al. Protocol adherence for continuously titrated interventions in randomized trials: an overview of the current methodology and case study. *BMC Med Res Methodol*. Jul 17 2017;17(1):106. doi:10.1186/s12874-017-0388-3

7. Murugan R, Kerti SJ, Chang CH, et al. Association of Net Ultrafiltration Rate With Mortality Among Critically Ill Adults With Acute Kidney Injury Receiving Continuous Venovenous Hemodiafiltration: A Secondary Analysis of the Randomized Evaluation of Normal vs Augmented Level (RENAL) of Renal Replacement Therapy Trial. *JAMA Netw Open*. Jun 5 2019;2(6):e195418. doi:10.1001/jamanetworkopen.2019.5418

8. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75(4):800-802. doi:10.1093/biomet/75.4.800

9. Vickerstaff V, Omar RZ, Ambler G. Methods to adjust for multiple comparisons in the analysis and sample size calculation of randomised controlled trials with multiple primary outcomes. *BMC Medical Research Methodology*. 2019/06/21 2019;19(1):129. doi:10.1186/s12874-019-0754-4

10. Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable non-response. *Stat Med*. Jan 15-Feb 15 1997;16(1-3):81-102. doi:10.1002/(sici)1097-0258(19970115)16:1<81::aid-sim473>3.0.co;2-0

11. Little RJ, Wang Y. Pattern-mixture models for multivariate incomplete data with covariates. *Biometrics*. Mar 1996;52(1):98-111.