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

ACRONYM:	***RELIEVE-AKI***
VERSION:	***1.8***
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2 ABBREVIATIONS AND DEFINITIONS

2.1 ABBREVIATIONS

AKI = Acute Kidney Injury
COVID = Coronavirus Disease
CKRT = Continuous Kidney Replacement Therapy
CMO = Comfort Measures Only
CVVHDF = Continuous Venovenous Hemodiafiltration
CVVHD = Continuous Venovenous Hemodialysis
CVVH = Continuous Venovenous Hemofiltration
CVP = Central Venous Pressure
CPR = Cardiopulmonary Resuscitation
DSMB = Data and Safety Monitoring Board
DNR = Do Not Resuscitate
DNI = Do Not Intubate
ECMO = Extracorporeal Membrane Oxygenation
EMR = Electronic Medical Records
ESKD = End Stage Kidney Disease
FiO_2 = Fraction of Inspired Oxygen
FO = Fluid Overload
GCS = Glasgow Coma Scale
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HR = Heart Rate
HRPO = Human Research Protection Office
ICU = Intensive Care Unit
IDH = Intradialytic Hypotension
IHD = Intermittent Hemodialysis
IBW = Ideal Body Weight
IRB = Institutional Review Board
ITT = Intent to Treat
KDIGO = Kidney Disease Improving Global Outcomes
LAR = Legally Authorized Representative
MAP = Mean Arterial Pressure
MBW = Measured Body Weight
NBAC = National Bioethics Advisory Commission
NIH = National Institute of Health
OHRP = Office of Human Research Protection
PaO_2 = Partial pressure of arterial oxygen
PBW = Predicted Body Weight
RENAL = Randomized Evaluation of Normal versus Augmented Level of Kidney Replacement Therapy
KRT = Kidney Replacement Therapy
SAEs = Adverse events that are serious and unexpected and have a reasonable possibility that the event was due to a study procedure
SBP = Systolic Blood Pressure
SCUF = Slow Continuous Ultrafiltration
SpO_2 = Oxygen Saturation via pulse oximetry
S/F = SpO_2/FiO_2 ratio
SUSAR = Serious and Unanticipated Suspected Adverse Reactions
SOFA = Sequential Organ Failure Assessment
SW-CRT = Stepped-wedge Cluster Randomized Trial
TPN = Total Parenteral Nutrition
UPMC = University of Pittsburgh Medical Center
UF_{NET} = Net Ultrafiltration

2.2 DEFINITIONS

Adverse Event: Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered related to the drug or study procedure.

Adverse Reaction: Any adverse event caused by a drug or a study procedure. An adverse reaction is a subset of all suspected adverse reactions where there is a reason to conclude that the drug or the study procedure caused the event.

Continuous Kidney Replacement Therapy (CKRT): A form of continuous dialysis frequently used to remove solutes and fluid in critically ill patients with acute kidney injury.

Continuous Venovenous Hemodiafiltration (CVVHDF): A modality of continuous dialysis in which solute clearance occurs by diffusion and convection.

Continuous Venovenous Hemodialysis (CVVHD): A modality of continuous dialysis in which solute clearance occurs only by diffusion.

Continuous Venovenous Hemofiltration (CVVH): A modality of continuous dialysis in which solute clearance occurs only by convection.

Slow Continuous Ultrafiltration (SCUF): A modality of continuous dialysis in which only fluid is removed without any solute clearance.

Funding: National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases).

Intention to Treat (ITT): All eligible and consented patients who undergo randomization will be included in the ITT cohort for the purposes of analyzing the primary and secondary study outcomes.

Intravascular Volume: The circulating volume of red cells and plasma within arteries and veins.

Intermittent Hemodialysis: A modality of dialysis done intermittently in which the solute clearance occurs by diffusion.

Legal Representative: An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

Net Ultrafiltration: The net volume of fluid removed from the patient by the dialysis machine after discounting fluids administered (*e.g.,* replacement fluids and dialysate given during CVVHDF) via the dialysis machine for the purpose of conducting the dialysis as well as fluids given to the patient (*e.g.,* IV fluids, medications).

Net Ultrafiltration Rate: The rate at which the net ultrafiltration volume is removed from the patient adjusted for patient body weight and unit time (*i.e.,* milliliters/kilogram/hour). This is the rate of depletion of circulating intravascular volume in the patient by fluid removal.

Stepped-Wedge Cluster Randomized Trial: A clinical trial in which randomization occurs at the group level (*e.g.,* ICU) rather than the individual patient level. Each group then "crosses over" from control to intervention at a randomized time point and multiple "time steps" of data collection occur.

Study Day: The day of study enrollment is study day zero. The next day is study day one etc.

Study Hospital: Defined as the hospital where the patient was enrolled.

Study ICU: Defined as the study ICU in which patient was enrolled.

Study Withdrawal: Defined as permanent withdrawal from study before completion of study activities. This does not include those subjects who have completed the protocol procedures or stopped procedures because they have reached independence from CKRT. If a patient or surrogate requests withdrawal from the study the clinician will seek explicit permission to continue data collection.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies less certainty about causality than an adverse reaction (21 CFR 312.32(a)).

Ultrafiltration: Ultrafiltration is the process by which plasma water devoid of cells and colloids is forced by hydrostatic pressure across an extracorporeal, biosynthetic, semipermeable, hemofiltration membrane, resulting in removal of patient intravascular volume.

3 EXECUTIVE SUMMARY

"Net ultrafiltration (UF_{NET})," also known as net fluid removal during kidney replacement therapy, has been used in the treatment of fluid overload among critically ill patients with acute kidney injury (AKI) for more than seven decades. However, the optimal rate of fluid removal (*i.e.,* UF_{NET} rate) remains uncertain, complications such as hypotension and cardiac arrhythmias occur frequently, and more than 40% of patients die. Observational studies in critically ill patients receiving continuous kidney replacement therapy (CKRT) show that UF_{NET} rate has a "J" shaped association with mortality with both slower and faster UF_{NET} rates associated with increased risk of death compared with moderate UF_{NET} rates.

Our long-term goal is to determine whether a restrictive UF_{NET} rate strategy is associated with lower 90-day mortality compared with a liberal UF_{NET} rate strategy in a multicenter, randomized, clinical trial in critically ill patients with AKI. The overall objective of this randomized trial is to establish the feasibility of maintaining patients in the restrictive UF_{NET} rate strategy during treatment with CKRT. 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.

We propose a prospective, two-center, unblinded, parallel-group, 2-arm, comparative effectiveness, stepped-wedge cluster-randomized trial among 112 critically ill patients with AKI treated with CKRT in 10 ICUs across two hospital systems. The trial will be conducted at 5 ICUs at University of Pittsburgh Medical Center in Pittsburgh, PA, as well as 5 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 six months, all ICUs will continue with a liberal UF_{NET} rate strategy. Thereafter, one ICU will be randomized to deploy the restrictive UF_{NET} rate strategy using a rolling randomization 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 0.53 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 one patient per time window per ICU. 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; intradialytic 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.

This feasibility trial will be used to support the rationale and design of a future multicenter phase III randomized trial to examine the effects of alternative UF_{NET} rate strategies on patient-centered clinical outcomes.

4 TRIAL SUMMARY

Title: REstrictive versus LIberal rate of Extracorporeal Volume removal Evaluation in Acute Kidney Injury (RELIEVE-AKI) – a comparative-effectiveness, stepped-wedge cluster-randomized feasibility trial.

Objective: To evaluate the feasibility of alternative UF_{NET} rate strategies among critically ill adults with AKI and treated with CKRT.

Study Design: Two-center, prospective, unblinded, parallel-group, 2-arm, comparative effectiveness, stepped-wedge cluster-randomized trial (SW-CRT) of two UF_{NET} rate strategies conducted across 10 ICUs.

1. We will emphasize early screening and protocol initiation and enroll a maximum of 112 patients with AKI (KDIGO stage 3) who are treated with CKRT.
2. We will assess attending physician's equipoise twice daily as to whether fluid should be removed emergently or deferred.
3. We will emphasize safety by initiating UF_{NET} only when fluid removal is indicated as determined by the attending physician.
4. UF_{NET} rate will be calculated based on predicted body weight (PBW) to avoid confounding of actual weight by fluid overload.
5. Study protocol will be continued until the end of UF_{NET} while on CKRT.
6. We will allow enrollment of patients initiated on net fluid removal for less than 48 hours.
7. We will emphasize that the final decision to set and titrate UF_{NET} rate is at the discretion of the treating clinician.
8. We will allow not removing fluid per study protocol when the goal is to maintain patient in euvolemia.

9. Restrictive UF_{NET} rate strategy
    a. UF_{NET} rate will be initiated at 0.5 mL/kg/h of patient PBW.
    b. UF_{NET} rate will be gradually increased 0.5 mL/kg/h as tolerated to maintain between 0.5-1.5 mL/kg/h throughout the study period.
    c. We will recommend rescue intervention with faster UF_{NET} rates beyond 1.5 mL/kg/h only for emergent treatment of respiratory distress or severe hypoxia due to fluid overload.

10. Liberal UF_{NET} rate strategy
    a. UF_{NET} rate will be initiated at 0.5 mL/kg/h of patient PBW.
    b. UF_{NET} rate will be gradually increased 0.5 mL/kg/h as tolerated to maintain between 2.0-5.0 mL/kg/h throughout the study period.
    c. We will emphasize safety by stipulating a maximum UF_{NET} rate of 5.0 mL/kg/h.
    d. We will recommend rescue intervention with faster UF_{NET} rates beyond 5.0 mL/kg/h only for emergent treatment of respiratory distress or severe hypoxia due to fluid overload.

11. Hemodynamic management
    a. We will recommend continuous monitoring of MAP in both the study arms.
    b. We will recommend withholding of UF_{NET} in both arms for hypotensive episodes as determined by bedside clinicians.
    c. We will recommend titration of vasopressors by bedside clinicians, as needed, during fluid removal for hemodynamic management.

12. CKRT management
    a. We will protocolize solute clearance with an effluent flow rate of 20-30 mL/kg/h.
    b. We will recommend CKRT modality, hemofilter, blood flow rate, dialysate use, dialysate flow rate, buffers, pre- and post-filter substitution fluids, and anticoagulation as determined by attending nephrologist.
    c. We will recommend that CKRT machine is functioning at least 20 hours a day.
    d. We will recommend CKRT circuit change every 48-72 hours.

13. Other care
    a. We will provide recommendations for conservative fluid management in both study arms.
    b. We will provide criteria for initiation of rapid rescue net ultrafiltration.

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

Exclusion Criteria

1. Respiratory distress due to pulmonary edema or fluid overload in un-intubated patients
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 >48 hours prior to study enrollment
6. Patients on chronic outpatient hemodialysis
7. Patients with history of, or current admission for kidney transplantation
8. Patients on comfort measures only orders (*i.e.,* CMO)
9. Moribund not expected to survive >24 hours
10. Confirmed pregnancy
11. Patients treated with extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or intra-aortic balloon pump (IABP)
12. Organ donors with neurological determination of death (*i.e.,* brain dead donors)
13. Drug overdose requiring CKRT for drug clearance

14. Enrollment in a concurrent interventional clinical trial with direct impact on fluid balance (*e.g.,* >500 mL study drug administration)

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 defered

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.

Study Initiation Time Window: All patients must 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.

Discontinuation of Study Protocol: The study protocol will be continued until one of the following occurs:

1. Attending intensivist or nephrologist determines that fluid removal is no longer necessary using CKRT.
2. Attending intensivist or nephrologist decides to stop CKRT and transition the patient to IHD.
3. The patient or surrogate decision-makers decide to withdraw life-sustaining treatment.
4. The patient dies.
5. Day 28 after study enrollment, whichever occurs first.

Primary Outcomes: The primary feasibility outcomes are as follows:

1. Between-group separation in mean delivered UF_{NET} rates of a minimum of 0.53 mL/kg/h.
2. 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.
3. Patient recruitment of one patient per time window per ICU.

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

Safety Outcomes

1. Intradialytic hypotensive episodes
2. Intradialytic hypertensive episodes
3. Intradialytic new onset cardiac arrhythmias including supraventricular tachycardia, bradycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and cardiac arrest
4. Emergent use of rescue UF_{NET} with rates higher than the assigned treatment arm
5. Severe hypophosphatemia (<0.5 mg/dL)
6. Severe hypokalemia (<3.0 mg/dL)
7. Severe hypocalcemia (<1.90 mg/dL or ionized calcium <0.90 mmol/L)
8. CKRT system downtime due to filter clotting or clogging
9. Discontinuation of UF_{NET} due to hemodynamic instability
10. Inability to close surgical wounds due to edema
11. New organ dysfunction
12. Worsening of systolic or diastolic cardiac function on echocardiogram
13. Worsening of pulmonary edema on chest X Ray and/or CT scan
14. Worsening of ileus on abdominal X Ray and/or CT scan
15. Bowel ischemia or anastomotic breakdown based on intraoperative findings
16. Pressure ulcerations
17. New wound infections
18. New arterial or venous thrombosis
19. Severe anemia requiring red cell transfusions
20. Severe thrombocytopenia requiring platelet transfusions
21. New secondary infections

Sample Size/Interim Monitoring

1. Using the sample size calculation for SW-CRT design, 111 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 0.53 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. We will enroll 112 subjects or 56 patients per group.

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

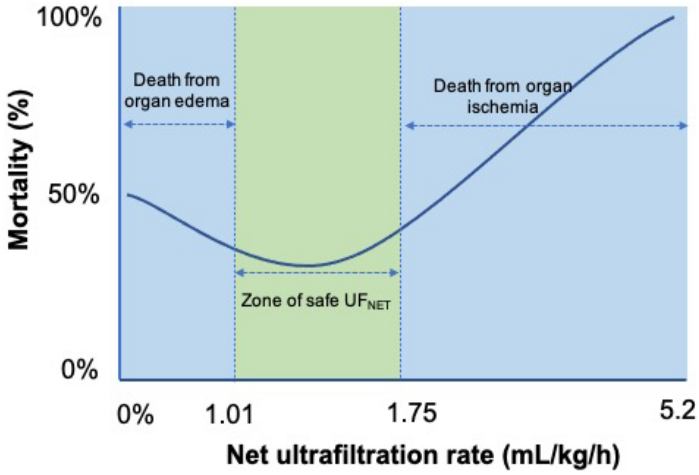
3. The trial progress will be evaluated by an independent Data and Safety Monitoring Board (DSMB). Being a feasibility study there will be no interim analyses.

5 TRIAL DESCRIPTION

5.1.1 BACKGROUND

Fluid overload is present in two-thirds of critically ill patients with AKI before initiation of KRT,[1] and despite fluid removal, mortality ranges between 40% to 60%.[1-3] Emerging evidence suggests that the UF_{NET} rate, a process of care variable, has a "J" shaped association with mortality (Figure 1). Slower UF_{NET} rates, compared with faster rates, increase exposure to fluid overload and organ edema.[2,4,5] In contrast, faster rates compared with slower rates are associated with hemodynamic instability, hypotension and ischemic organ injury.[6] Thus, both slower and faster rates are associated with mortality compared with moderate UF_{NET} rates in observational studies (Section 5.2).[2,6-8] Thus, it is imperative to determine whether the UF_{NET} rate-mortality relationship is causal. By establishing the feasibility of the restrictive UF_{NET} rate group, this proposal will be the harbinger of a phase III trial to examine causal effects of UF_{NET} rate on patient-centered clinical outcomes.

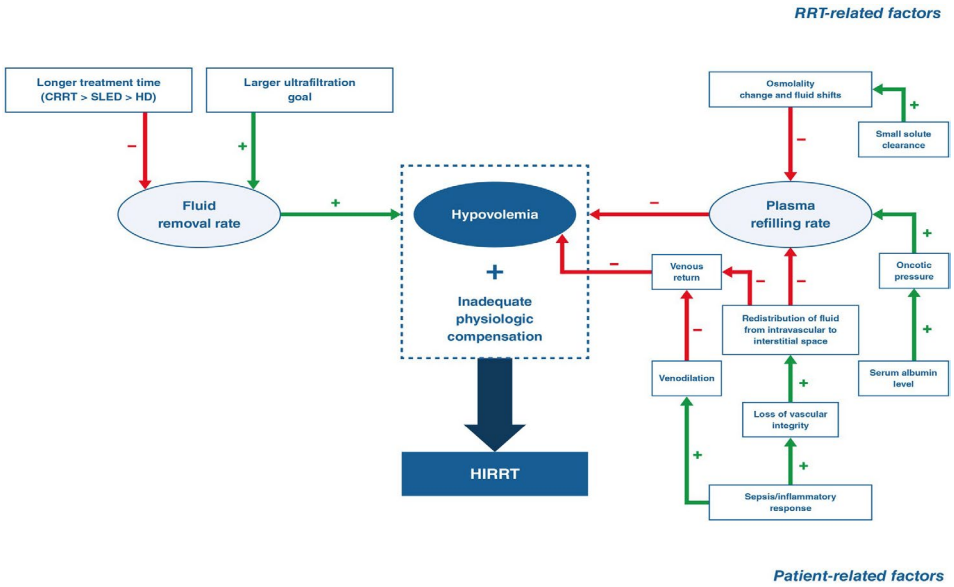
Figure 1: An emerging conceptual model of the association between UF_{NET} rate and mortality in critically ill patients.



5.1.2 PATHOPHYSIOLOGIC CHANGES DURING UF_{NET}

As fluid is removed from the intravascular space during extracorporeal ultrafiltration, vascular refill occurs due to fluid shifting from the extravascular and interstitial spaces into the intravascular space. When the rate of fluid removal is higher than the rate of vascular refill, intravascular hypovolemia results in hypotension, decreased organ perfusion and ischemic injury.[9,10] Although there are patient-related (*e.g.,* comorbid conditions, reduced vasomotor tone) and other dialysis-related factors (*e.g.,* reduced plasma osmolality due to solute clearance) that contribute to hemodynamic instability (Figure 2), several studies indicate that there is a direct relationship between higher UF_{NET} rate, a process of care variable, and subsequent risk of hypotension and mortality.[11-15]

Figure 2: **Pathophysiology of hemodynamic instability during UF_{NET}.**



HIRRT, Hemodynamic instability related to kidney replacement therapy; CKRT, Continuous kidney replacement therapy; SLED, Slow extended daily dialysis; HD, hemodialysis; KRT, Kidney replacement therapy

5.1.3 ASSESSMENT OF INTRAVASCULAR VOLUME

Clinical assessment of intravascular volume is the holy grail of hemodynamic management in critically ill patients during ultrafiltration. Conventionally used hemodynamic parameters such as blood pressure, central venous pressure, pulmonary artery occlusion pressures are insensitive to early changes in intravascular volume. Although dynamic parameters such as pulse pressure variation, stroke volume variation, IVC collapsibility, passive leg raising are used to predict fluid responsiveness in critically ill patients, these technologies have several pitfalls.

First, assessing pulse pressure variation and stroke volume variation to predict fluid responsiveness require that the patient is mechanically ventilated, not on low tidal volume ventilation, sedated and not spontaneously breathing. Second, IVC collapsibility and passive leg raising tests are not feasible as they cannot be done continuously. Third, while these technologies have been validated for predicting fluid responsiveness in critically ill patients, its validity for predicting intradialytic hypotension during fluid removal in critically ill patients is unknown. Other technologies such as hematocrit monitoring and bioimpedance analysis used in outpatients undergoing hemodialysis have not been validated in critically ill patients for fluid removal. Thus, current assessment of intravascular volume during ultrafiltration is mostly clinical based on surrogate measures such as blood pressure, fluid balance, and physical examination of the patient (*e.g.,* capillary refill).

5.1.4 CURRENT CLINICAL PRACTICE

Currently there is a wide variation in the clinical practice of UF_{NET}.[16,17] Clinicians arbitrarily set UF_{NET} rates based on blood pressure and severity of FO and titrate UF_{NET} rate as tolerated by patient hemodynamics. However, blood pressure is insensitive to early changes in intravascular volume. Thus, hypotension can occur abruptly during fluid removal when intravascular hypovolemia occurs and is difficult to predict. Despite careful titration of UF_{NET}

rate, hypotensive episodes complicate 19% to 97% of patients during CKRT,[18-20] and intradialytic hypotension has been independently associated with three-fold increase in odds of death in critically ill patients.[21]

5.2 PRELIMINARY WORK

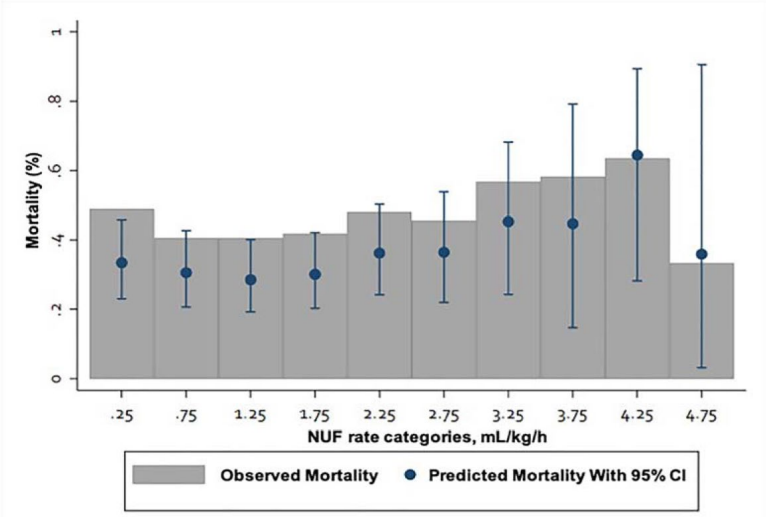
5.2.1 HIGH UF_{NET} RATES DURING CKRT ARE ASSOCIATED WITH MORTALITY AND KRT DEPENDENCE

Using the Randomized Evaluation of Normal versus Augmented Level (RENAL) of the Renal Replacement Therapy trial cohort,[3] we examined the association of the UF_{NET} rate with outcomes. Of 1,434 patients, the 90-day mortality among patients who received UF_{NET} rate >1.75 vs. 1.01-1.75 vs. <1.01 mL/kg/h was: 48.6% vs. 39.2% vs. 44.9%; P=0.01, respectively. Using Gray model, UF_{NET} rates >1.75 mL/kg/h compared with rates 1.01-1.75 mL/kg/h (adjusted HR range, 1.44-1.77, P=0.004) and rates <1.01 mL/kg/h (aHR range, 1.51-1.66; P=0.01) was associated with lower survival. Every 0.5 mL/kg/h increase in UF_{NET} rate was associated with 7% increased odds of death (aOR, 1.07; 95%CI, 1.00-1.15; Figure 3).[6] Using a joint model, longitudinal increase and variation in UF_{NET} rates over time was also associated with risk of death (β=0.056; P<0.001). UF_{NET} rates of >1.75 mL/kg/h, were also associated with an increased risk of cardiac arrhythmias requiring treatment (36.8% vs. 30.8%; P=0.08).

After accounting for competing risk of death, UF_{NET} rates >1.75 mL/kg/h compared with UF_{NET} rates, 1.01-1.75 mL/kg/h (cause-specific aHR, 0.79, 95%CI, 0.66 – 0.95) and UF_{NET} rates <1.01 mL/kg/h (aHR, 0.69, 95%CI, 0.56-0.85) was associated with lower renal recovery and longer dependence on KRT.[22]

We also investigated whether the daily fluid balance was a mediator of the relationship between UF_{NET} rate and mortality, with baseline day one fluid balance as moderator.[23] We found that a more negative daily fluid balance attenuated the harmful mortality effect of high UF_{NET} (>1.75 mL/kg/h) rate group compared with moderate (1.01-1.75 mL/kg/h) and low (<1.01 mL/kg/h) UF_{NET} rate groups. However, despite this attenuation, the high UF_{NET} rate (>1.75 mL/kg/h) group remained significantly and directly associated with higher mortality compared with the moderate UF_{NET} rate group (average direct effect, 1.10, 95%CI, 1.04-1.16). These data add to the scientific premise and support the further need to conduct a randomized trial.[23]

Figure 3: In the RENAL cohort, a patient receiving a UF_{NET} rate of 1 mL/kg/h had a 30.6% predicted risk of death and a patient receiving UF_{NET} rate of 4.5 mL/kg/h had a 64.5% predicted risk of death.



5.2.2 HIGHER UF_{NET} RATES IN THE FIRST 48 HOURS OF CKRT ARE ASSOCIATED WITH MORTALITY

We also examined the association between the UF_{NET} rate within the first 48-hours of use of CKRT and hospital mortality in an independent cohort of 347 critically ill patients.[7] UF_{NET} rates >1.75 mL/kg/h compared with rates <1.01 mL/kg/h (aHR range, 1.27-4.18, P=0.03) was associated with 28-day mortality. In a subsequent mediation analysis, we found that this higher risk of death was not mediated by fluid balance, blood pressure, vasopressors, or electrolytes, implying that higher UF_{NET} rates may have a direct causal effect on the risk of death.[24]

5.2.3 LOWER UF_{NET} RATES ARE ALSO ASSOCIATED WITH MORTALITY IN PATIENTS WITH FLUID OVERLOAD

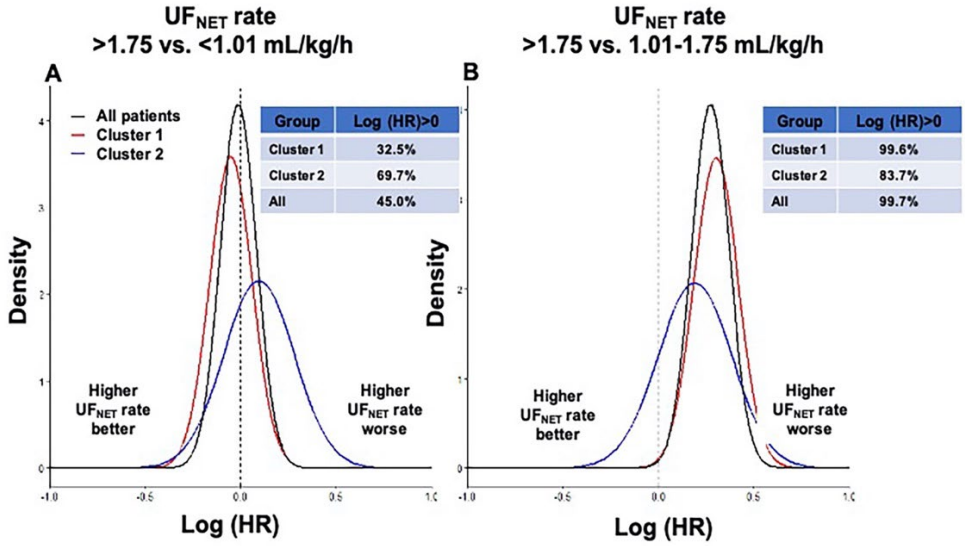
Using the UPMC ICU database of patients with >5% fluid overload and treated with CKRT and IHD (n=1,075), we evaluated the association of UF_{NET} rate over 24-hour period and 1-year mortality.[2] We found that the UF_{NET} rates <20 mL/kg/day, compared with rates >25 mL/kg/day, were associated with increased risk-adjusted mortality. Of the CKRT subgroup, hourly UF_{NET} rates <0.5 mL/kg/h compared with rates >1.0 mL/kg/h was also associated with death. These findings suggest that minimum UF_{NET} rates of >20 mL/kg/day or >1.0 mL/kg/h using CKRT is associated with a lower risk of death among patients with fluid overload. Using Mayo Clinic data, UF_{NET} rates <35 mL/kg/day compared with ≥35 mL/kg/day were also associated with the risk of major adverse kidney events.[8] These studies suggest that a minimum rate of at least 1.0 mL/kg/h is associated with reduced mortality compared with slower rates.

5.2.4 BAYESIAN HETEROGENEITY IN TREATMENT EFFECT ASSOCIATED WITH THE UF_{NET} RATE

Using cluster analysis in RENAL, the probability of harm associated with UF_{NET} rates >1.75 mL/kg/h was 99.6% compared with UF_{NET} rates of 1.01-1.75 mL/kg/h, and 32.5% compared with UF_{NET} rates <1.01 mL/kg/h among the subgroup of severely ill patients who had sepsis,

metabolic acidosis, organ edema, those treated with mechanical ventilation and vasopressors (Figure 4).[25] The probability of harm associated with UF_{NET} rates between 1.01-1.75 mL/kg/h compared with the rates <1.01 mL/kg/h was only 0.2%. Of patients who are hemodynamically unstable with cardiovascular sequential organ failure assessment (SOFA) score of 3 or more, both UF_{NET} rates >1.75 mL/kg/h and rates <1.01 mL/kg/h were associated with increased mortality compared with rates 1.01-1.75 mL/kg/h.[25]

Figure 4: Posterior probability of the UF_{NET} rate group treatment effect (log [HR]) in each cluster. The tables contain the probability that the hazard ratio for 90–day mortality in the high UF_{NET} group (plots A and B) is above 0 (*i.e.,* a hazard ratio above 1, suggestive of harm).



5.2.5 ADVERSE EVENTS FREQUENTLY OCCUR DURING CONTINUOUS DIALYSIS

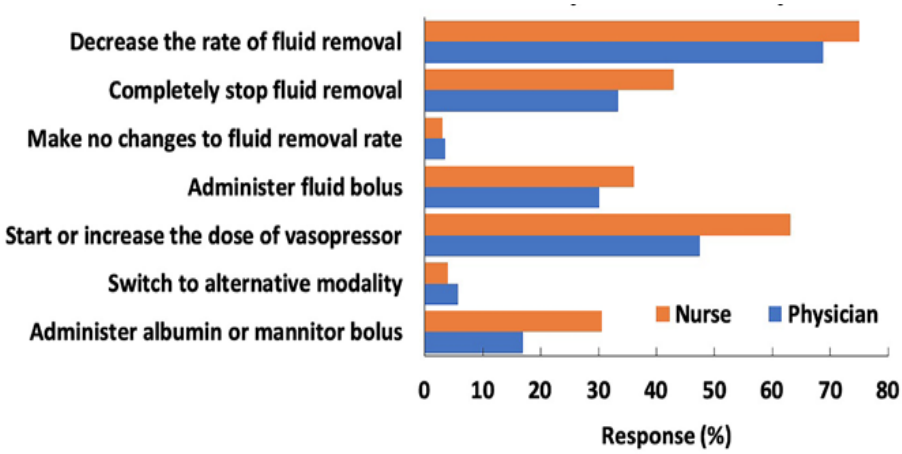
In a cohort of 1,743 patients receiving continuous KRT at Mayo Clinic ICUs, intradialytic hypotension (IDH) occurred frequently.[18] IDH was defined as MAP ≤60 mmHg, SBP <90mmHg or a decline in SBP >40mmHg from baseline, a positive fluid balance >500mL or increased vasopressor requirement. Early IDH occurred in 1,124 patients (64.6%) and was independently associated with mortality (Odds Ratio, 1.56, 95% CI: 1.25–1.9). IDH within the first hour occurred in 43% of patients, and 81% of patients had new onset of cardiac arrhythmias.[19] Sinus tachycardia was present in 51% and atrial fibrillation in 11% (Table 1).

In a multinational survey of ICU practitioners in 80 countries[17] IDH was reported by 20% (range, 20%–38%) of practitioners. When IDH occurred, practitioners decreased the rate of fluid removal (70.3%; Figure 5); started or increased vasopressor dose (51.5%); completely stopped fluid removal (35.8%); and/or administered a fluid bolus (31.6%) for treatment.[17] Thus, IDH and interventions for IDH are common during KRT. Using the Acute Renal Failure Trial Network cohort,[26] we found that IDH events occurred in 43.2% of patients. Of all hypotensive complications, hypotension requiring vasopressor use, discontinuation of KRT, and other interventions occurred in 13.2%, 8.4%, and 78.4%, respectively.

Table 1: Incidence of adverse events during continuous KRT

Parameter	No. (%)
Hypotension	258 (43)
Sinus tachycardia	306 (51)
Atrial fibrillation	64 (11)
Atrial flutter	6 (1)
Ventricular tachycardia	14 (2)
Sinus bradycardia	43 (7)
Ventricular fibrillation	19 (3)
Asystole	20 (3)
Others	12 (2)
Cardiac arrest	28 (5)

Figure 5: Reported interventions performed for intra-dialytic hypotension by critical care practitioners



5.2.6 MULTINATIONAL SURVEY OF ATTITUDES TOWARDS UF_{NET} PRACTICES

In a survey of 80 countries, two-thirds of practitioners (71%, regional range, 55%-95.5%) reported using CKRT for volume management.[16,17] In the U.S., the reported initial median UF_{NET} rate prescription was 100 (IQR, 78-200) mL/h and the maximum rate was 285 (IQR, 200-341) mL/h for hemodynamically stable patients and 51 (IQR, 25-100) mL/h for hemodynamically unstable patients. For an average 80-kg patient, a UF_{NET} volume of 285 mL/h would be equivalent to a rate of 3.56 mL/kg/h, and 341 mL/h would be equal to a rate of 4.26 mL/kg/h in hemodynamically stable patients. These data suggest that the UF_{NET} rates used in the liberal group is within the range of clinical practice. More than 80% of critical care practitioners believed a protocol-based fluid removal would be useful.

5.2.7 CLINICIAN EQUIPOISE TO ENROLL IN CLINICAL TRIAL

In our survey, we asked critical care practitioners about attitudes towards UF_{NET} practice and equipoise to enroll patients in a clinical trial of protocol based UF_{NET}.[27] Across regions, most practitioners (90.0%, range, 84.5% – 91.7%) agreed that early UF_{NET} would be beneficial and protocol (81.4%, range, 62.3% – 88.3%) outlining the rate, volume and duration of UF_{NET} would be useful. Two-thirds of clinicians (78.3%, range, 72.7% – 83.7%) indicated that they would be agreeable to enroll patients in a clinical trial of protocol based UF_{NET}.

5.2.8 FEASIBILITY OF ENROLLMENT

In 2019, 412 unique patients were admitted to UPMC Presbyterian hospital ICUs and received treatment with CKRT. This averages 34 patients per month, and thus, an average of 2 patients per month enrollment would be feasible. The average duration of treatment with CKRT was four days. At Mayo Clinic, approximately 15 patients per month were treated with CKRT across the 3 ICUs in 2020. Thus, enrolling 144 patients across six ICUs over 30 months is feasible.

5.2.9 PHYSICIAN EQUIPOISE TO ENROLL AT UPMC AND MAYO CLINIC

Both at the UPMC and the Mayo Clinic, fluid removal is co-managed by intensivists and nephrologists. Thus, we conducted an email survey of intensivists and nephrologists (n=43) at both clinical sites. An overwhelming number of physicians (n=41; 95%) were willing to enroll in this trial. Reasons for unwillingness included massive fluid overload with ongoing large infusions, refractory hypoxemia, inability to close the abdominal surgical wound due to edema, and the decision already made to remove fluid rapidly. Our study design already excludes such patients. We have also discussed the protocol with ICU directors, chiefs of nephrology, intensivists, and nephrologists, at the Mayo Clinic and at the UPMC, and they are willing to aid with screening and enrollment.

5.3 RESTRICTIVE UF_{NET} RATE STRATEGY

5.3.1 POTENTIAL ADVANTAGES

There are several potential benefits to restrictive UF_{NET} rate strategy. First, it will allow more time for vascular refill and will reduce blood pressure variability and hypotensive episodes as both intradialytic blood pressure variability and hypotensive episodes have been associated with ischemic organ injury and increased mortality.[11,21] Second, by preventing hypotensive episodes, restrictive UF_{NET} rate is likely to reduce the need for subsequent interventions such as completely stopping UF_{NET}, fluid administration, starting or increasing the dose of new vasopressor. Both discontinuing UF_{NET} and administering fluids will offset any potential benefit of UF_{NET} and increase risk of fluid overload. Third, restrictive UF_{NET} rates may preserve myocardial blood flow and prevent episodes of cardiac arrhythmias. Fourth, restrictive UF_{NET} rate may reduce the workload and burden on nursing staff due to decreased number of interventions required to treat intradialytic hypotension.

5.3.2 POTENTIAL DISADVANTAGES

Restrictive UF_{NET} rate strategy may theoretically be associated with longer tissue exposure to fluid overload and may increase time to achieving euvolemia. Prolonged exposure to fluid overload may impair kidney recovery, prolong the duration of kidney replacement therapy, or increase ventilator dependence. However, the risks of prolonged exposure to FO associated with restrictive UF_{NET} rate strategy must be balanced against the risk of ischemic organ injury due to hypotensive episodes and blood pressure variability associated with faster and more liberal UF_{NET} rates used in clinical practice.

5.4 LIBERAL UF_{NET} RATE STRATEGY

5.4.1 POTENTIAL ADVANTAGES

Liberal UF_{NET} rate based on hemodynamics may result in better and earlier volume control including achieving daily negative fluid balance and overall, less positive cumulative fluid balance as documented in observational studies.[2,6] By varying UF_{NET} across a range of UF_{NET} rates, the liberal U_{FNET} group affords more flexibility to clinicians for rapid fluid removal for treatment of fluid overload.

5.4.2 POTENTIAL DISADVANTAGES

Liberal UF_{NET} rate strategy might be associated with rapid and unpredictable decline in intravascular volume. Intravascular hypovolemia in turn reduces cardiac preload.[9] Decreases in preload is associated with lower cardiac output and hypotension. Moreover, faster and frequent titration of UF_{NET} will increase the workload for the clinicians, poor compliance with closer monitoring of hemodynamics, and increase subsequent interventions for treatment of hypotensive episodes including bolus fluid administration thereby offsetting potential benefits of rapid fluid removal.

5.5 A TRIAL OF UF_{NET} STRATEGY IS WARRANTED IN CRITICALLY ILL PATIENTS

There are several compelling reasons why trial of UF_{NET} rate strategy should be conducted. First, the net risk-benefits of treatment of fluid overload and UF_{NET} rate on clinical outcomes remains unclear as current observational studies have significant limitations. Thus, there is a critical need to determine the optimal process of care for patients undergoing UF_{NET}. In the absence of such a knowledge, effective treatment of fluid overload and safe provision of UF_{NET} among critically ill patients will be problematic.

Second, the current clinical practice of UF_{NET} is highly variable in ICUs and is not evidenced-based. Generation of robust evidence will result in development and adoption of clinical practice guidelines and is likely to reduce variability in clinical practice.

Third, critically ill patients are a more vulnerable population sensitive to hemodynamic perturbations. For instance, studies show that more than 19% to 97% of patients on CKRT have episodes of sudden hypotension,[18-20] and IDH is associated with mortality in critically ill patients.[21] Thus, generation of robust evidence base is needed to ensure there is no harm associated with current clinical practice as the existing practice is to use liberal UF_{NET} rates in patients with stable hemodynamics until hypotension occurs.

Fourth, more than two-thirds of critical care practitioners surveyed indicated that they have equipoise to enroll patients in a clinical trial of protocol-based UF_{NET} strategy suggesting uncertainty as to the optimal approach to fluid removal in critically ill patients. Finally, several aggressive interventions in critically ill patients have not found to be associated with improved outcomes, and perhaps harmful, underpinning the principle of “less is more”. For instance, among patients with acute respiratory distress syndrome (ARDS) higher tidal

volume strategy was associated with increased risk of ventilator-induced lung injury and mortality than lower tidal volume ventilation.[28] Thus, dialysis-associated organ injury due to faster rate of fluid removal needs further evaluation.

5.6 POTENTIAL PITFALLS OF THE PROPOSED STUDY DESIGN AND ALTERNATIVE TRIAL DESIGNS

5.6.1 POTENTIAL PITFALLS OF THE PROPOSED STUDY DESIGN

5.6.1.1 Why use Predicted Body Weight for Dosing UF_{NET}?

In this protocol, we propose to use predicted body weight (PBW) for setting UF_{NET} rate in both treatment groups. PBW will be estimated using a gender-specific calculator (Appendix A) based on measurement of patient's height by research staff at the time of study enrollment. We chose PBW for the following reasons: (i.) PBW has been used in several NIH sponsored ICU trials,[28,29] (ii.) shown closely to approximate with IBW in males and females,[30] (iii.) free of confounding by FO and catabolism due to critical illness, and other measurement errors by nursing staff, (iv.) could be precisely determined at study enrollment from patient height accurately measured by trained research staff.

We chose not to use measured body weight (MBW) and actual body weight for the following reasons. First, precise premorbid MBW is unknown in most critically ill patients. Weight documented in EMR during prior hospitalization cannot be used as a surrogate for premorbid weight because of confounding by underlying illness. Second, index hospital admission weight is likely to be confounded by the underlying condition that led to hospitalization (*e.g.,* dehydration from sepsis may result in underestimation, and fluid overload from underlying worsening congestive heart may result in overestimation of MBW). Third, retrospective collection of hospital and ICU admission weights are prone to measurement errors[31] and also confounded by daily fluid intake and output which are inaccurately documented on hospital wards.[32] Fourth, following initiation UF_{NET}, the patient MBW is likely to fluctuate widely with decreasing weight overtime due to UF_{NET} and due to catabolic nature of many ICU illness.

5.6.1.2 Why not use both IHD and CKRT for UF_{NET} instead of only CKRT?

We chose CKRT for this feasibility trial instead of IHD for the following reasons: (i.) our survey revealed that more than 70% of respondents indicated using CKRT for volume management in the ICU,[27] (ii.) evidence suggests that CKRT is superior to IHD for volume control in critically ill patients due to continuous nature of ultrafiltration over a 24-hour period in patients with severe fluid overload,[33] (iii.) the UF_{NET} rates used during IHD would be very different to that of UF_{NET} rates used during CKRT thus confounding the effect of UF_{NET} rates while on CKRT, on clinical outcomes, iv.) the optimal ultrafiltration rates in critically ill patients with AKI treated with CKRT is uncertain; and v.) CKRT is the predominant modality used for volume management at the UPMC and the Mayo Clinic ICUs.

5.6.2 ALTERNATIVE STUDY DESIGNS

We considered several alternative study designs in addition to the proposed study design (Table 2).

Table 2: Strengths and Weaknesses of Alternative Study Designs

Intervention	Control	Strengths	Weakness
<0.5 mL/kg/h	>1.75 mL/kg/h	• Less episodes of hemodynamic instability in the intervention arm • More flexibility in dosing in the control arm	• May not be feasible to randomize to a rate <0.5 mL/kg/h as most clinicians would consider UF_{NET} rate <0.5 mL/kg/h is clinically insignificant volume removal. • Exposure to wide UF_{NET} rate ranges in the control arm. • May increase risk of hemodynamic instability in the control arm
0.5 – 1.0 mL/kg/h	1.7 – 2.2 mL/kg/h	• More flexibility in the slower arm • Less episodes of hemodynamic instability in the intervention arm	• Too narrow range in the control arm and does not represent current clinical care. • Most clinicians would consider UF_{NET} rate <1.0 mL/kg/h is clinically insignificant volume removal.
1.0 mL/kg/h	Clinicians determine the UF_{NET} rate	• Mirrors clinical practice in the control arm	• Variability among clinicians in titrating UF_{NET} • May not have adequate separation between the two treatment arms to detect meaningful difference.
1.0 – 1.7 mL/kg/h	>2.0 mL/kg/h	• Observational studies suggest lower mortality in the intervention arm	• Exposure to wide UF_{NET} rate ranges in the control arm
UF_{NET} rate guided by continuous monitoring of intravascular volume status (*e.g.,* pulse pressure variation, stroke volume variation)	UF_{NET} rate guided by traditional hemodynamic monitoring (*i.e.,* heart rate, MAP)	• Precision UF_{NET} rate guided by intravascular volume assessment • May reduce episodes of hemodynamic instability	• Functional hemodynamic monitoring has only been validated for fluid administration but not fluid removal • Most clinicians do not use functional hemodynamic monitoring for fluid removal • Requires patient to be on a controlled mode of ventilation with no spontaneous respiratory effort to accurately assess pulse pressure and stroke volume variation.

5.7 OBJECTIVES

Primary Objective

The primary objective of this randomized trial is to assess the feasibility of maintaining patients in restrictive and liberal UF_{NET} rates, adherence to the protocol, and assess recruitment rate in preparation for a large multicenter randomized clinical trial.

5.8 END POINTS

5.8.1 PRIMARY OUTCOME

The three primary feasibility outcomes are as follows:

1. *The between-group difference in mean delivered UF_{NET} rate*: The primary objective is to measure a minimum of 0.53 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.[34,35] Specifically, we reasoned that a larger study would not be feasible if the separation in the UF_{NET} rates were less than 0.5 mL/kg/h. We chose 0.5 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.[6]

2. *Protocol adherence*: Adherence assessed by protocol deviation varies as the function of the definition of deviation and the frequency of measurements. Thus, in this trial, we will define 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 rate for hypertension or for treatment of respiratory distress due to fluid overload and pulmonary edema).

   We chose the above metric for protocol deviation because with complex interventions, as the frequency of monitoring increases, so does the resources required to track protocol adherence. Close monitoring of protocol deviations is unlikely in trials that lack resources, introducing a risk of ascertainment bias. In contrast, with very frequent monitoring of continuous interventions, the likelihood of recording protocol deviations increases but the clinical impact of each deviation diminishes proportionately. Similarly, criteria for protocol deviations that are too sensitive would exaggerate the impact of protocol deviations beyond what is clinically important and unduly undermine the apparent feasibility and internal validity of the trial.[35]

   All reasons for non-adherence will be recorded for both groups using pretested taxonomy distinguishing clinical reasons (*e.g.,* hypotension, hypertension, difficulty in oxygenation, respiratory distress, hemodynamic instability, attending override of protocol) and research-related reasons (*e.g.,* consent withdrawal).

3. *Recruitment rate*: A successful recruitment rate will be defined as achieving an enrollment rate of 1 patient per ICU per time window during the trial. While this feasibility trial is ongoing, recruitment will be reviewed weekly; the screening records

will be reviewed monthly, and the numbers of missed eligible patients will be investigated. If applicable, we will discuss barriers to enrollment and use well-developed strategies to improve recruitment. Therefore, recruitment will be maximized as necessary over the course of the trial. The recruitment metric will be measured and interpreted at the end of the trial by calculating the mean number (standard deviation) of recruited patients per active screening month.

5.8.2 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. Dependence on kidney replacement at hospital discharge

5.8.3 SAFETY OUTCOMES

1. Intradialytic hypotensive episodes
2. Intradialytic hypertensive episodes
3. Intradialytic new onset cardiac arrhythmias including supraventricular tachycardia, bradycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and cardiac arrest
4. Emergent use of rescue UF_{NET} with rates higher than the assigned treatment arm
5. Severe hypophosphatemia (<0.5 mg/dL)
6. Severe hypokalemia (<3.0 mg/dL)
7. Severe hypocalcemia (<1.90 mg/dL or ionized calcium <0.90 mmol/L)
8. CKRT system downtime due to hemofilter clotting or clogging
9. Discontinuation of UF_{NET} due to hemodynamic instability
10. Inability to close surgical wounds due to edema
11. New organ dysfunction
12. Worsening of systolic or diastolic cardiac function on echocardiogram
13. Worsening of pulmonary edema on chest X Ray and or/or CT scan
14. Worsening of ileus on abdominal X Ray and/or CT scan
15. Bowel ischemia or anastomotic breakdown based on intraoperative findings
16. Pressure ulcerations
17. New wound infections
18. New arterial or venous thrombosis
19. Severe anemia requiring red cell transfusions
20. Severe thrombocytopenia requiring platelet transfusions
21. New secondary infections

6 STUDY POPULATION AND ENROLLMENT

6.1 SETTING

The trial will accrue a maximum of 112 patients. Participants will be enrolled from 5 ICUs at the UPMC, Pittsburgh, PA, and 5 ICUs at the Mayo Clinic, Rochester, MN. At the UPMC, we will include the Transplant ICU, Medical ICU, and the Surgical Trauma ICU at the Presbyterian hospital, and the Medical-surgical ICU and Neuro-ICU (ICU8) at the Mercy hospital. At Mayo Clinic, we will enroll at the Medical-surgical ICU from the Methodist campus, and the Cardiac, Medical, Surgical, and CV Surgery ICUs at St. Mary's campus. No study ICU has a protocolized approach to fluid removal, and instead, clinicians determine the timing and rate of UF_{NET}. All ICUs use specialized ICU nurses trained and certified in delivering CKRT. We expect each ICU to recruit one or more subjects per time window based on annual volume and past enrollment, allowing complete enrollment in 2.0 years.

6.2 EDUCATION AND TRAINING

One month before patient recruitment begins at each site, we will prepare standardized educational materials for academic detailing, including slide presentations, videos, and "virtual" sessions, prominently placed posters, and pocket cards. We will provide study orientation to clinicians at the study ICUs using the following methods: i.) we will create education materials including frequently asked questions (FAQs) and power point presentation that will be circulated via newsletters and emails; ii.) we will present the study at clinician meetings and answer questions; iii.) we will schedule webinars for the clinicians before study initiation and at periodic intervals; iv) we will provide just-in-time training for the ICU nurse before starting the study intervention; v.) we will create a short video regarding the study protocol that will be embedded in the web application and mounted on the tablet computer that the clinicians can watch at any time; and vi.) we will also provide impromptu training sessions, as needed.

6.3 RANDOMIZATION

6.3.1 RATIONALE

In a Stepped-Wedge Cluster Randomized Trial (SW-CRT)[36-38] a) randomization occurs at the group level (*e.g.,* ICU) rather than the individual level (*e.g.,* patient); b) each group "crosses over" from the control to intervention at a randomized time point; and c) multiple "time steps" of data collection occur.

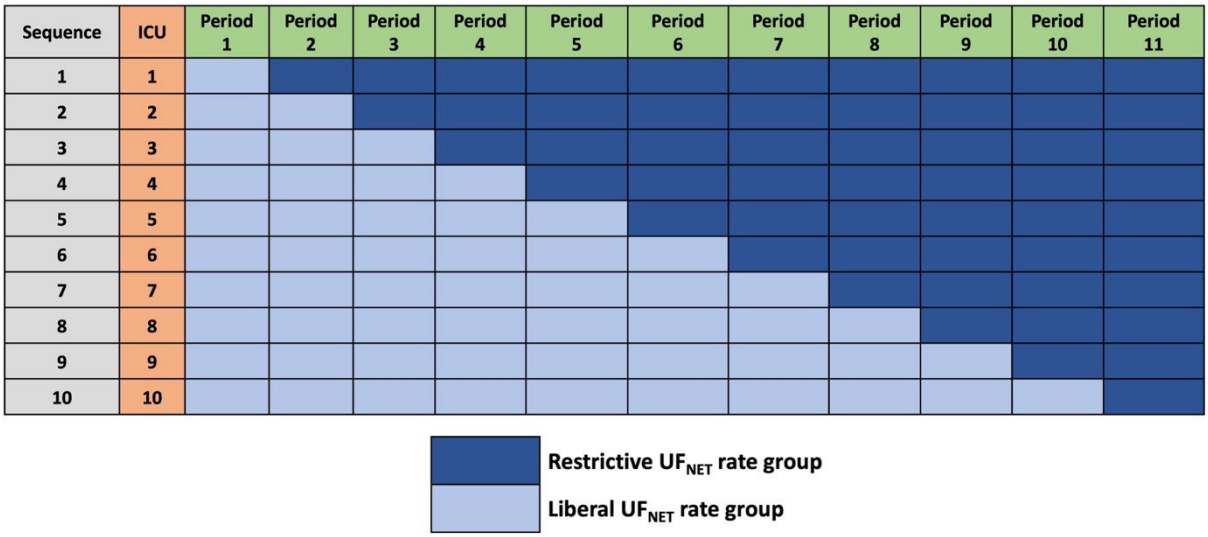
We chose SW-CRT because i.) individual patient-level randomization is scientifically problematic due to a high risk of contamination between the two UF_{NET} rate groups (*i.e.,* Hawthorne effect), ii.) a cluster RCT is infeasible because ICUs are unwilling to continue with a single intervention (*i.e.,* only restrictive or liberal UF_{NET} rate group) during the entire study period, iii.) each ICU act as their control and thus fewer units or clusters are required than a traditional cluster-randomized trial,[39] iv.) to alleviate logistical challenges associated with introducing the intervention (*i.e.,* the restrictive group) in all ICUs at once – an SW-CRT will

provide adequate time for training all staff on liberal UF_{NET} rate group before transitioning to the restrictive group, v.) offers the opportunity to evaluate ICU-level effectiveness of a new intervention, and vi.) to study the effect of time on intervention effectiveness (*i.e.,* time since the introduction and delayed treatment effects).

6.3.2 RANDOMIZATION UNIT

Following best practice recommendations for evaluation of system-level interventions, the unit of randomization is the cluster (*e.g.,* ICU) rather than the individual patient.[40] During the first six months of data collection, all sites will continue with a liberal UF_{NET} rate strategy. Thereafter, one ICU will be randomized to deploy the restrictive UF_{NET} rate strategy every two months or when a maximum of 10 patients have been enrolled, whichever occurs first, and stay in this strategy until the end of the study (Figure 6).

Figure 6: **Stepped-wedge cluster-randomized trial design**



We will use a computer-generated randomization scheme to determine the order in which each ICU would cross over from the liberal group to the restrictive group, with new crossover occurring every two months or whenever 10 patients have been enrolled, whichever occurs first. This trial design will allow us to stagger the implementation of the restrictive UF_{NET} strategy while maintaining concurrent control over data collection in the ICUs that were not yet using the restrictive UF_{NET} strategy.

6.4 SCREENING

The overall strategy is to screen and enroll early. Research coordinators will screen the ICU population at each participating site using electronic medical records with screening sweeps occurring in the morning and afternoon. We will screen every new ICU patient with severe AKI (KDIGO stage 3) and follow up with each screened patient with AKI daily for the need for CKRT. The coordinator will confirm the inclusion and exclusion criteria as listed in Section 6.5.

6.5 INCLUSION CRITERIA

1. Age ≥18 years
2. Stage 3 acute kidney injury according to KDIGO criteria (Appendix B)
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

6.6 EXCLUSION CRITERIA

1. Respiratory distress due to pulmonary edema or fluid overload in un-intubated patients
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 the attending intensivist or nephrologist
4. Attending intensivist or nephrologist believes that the protocol will not be followed
5. Continuous net fluid removal for >48 hours before study enrollment
6. Patients on chronic outpatient hemodialysis
7. Patients with history of, or current admission for kidney transplantation
8. Patients on comfort measures only orders (*i.e.*, CMO)
9. Moribund not expected to survive >24 hours
10. Confirmed pregnancy
11. Patients treated with extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or intra-aortic balloon pump (IABP).
12. Organ donors with neurological determination of death (*i.e.,* brain dead organ donors)
13. Drug overdose requiring CKRT for drug clearance
14. Enrollment in a concurrent interventional clinical trial with direct impact on fluid removal (*e.g.,* >500 mL study drug administration)

6.6.1 REASONS FOR EXCLUSIONS

Patients <18 years old are excluded because of limited data on UF_{NET} rate on these individuals. In addition, we will only be enrolling patients from adult ICUs, and the staff may be less well-trained in CKRT and UF_{NET} practices in children. Patients with severe pulmonary edema, respiratory distress who are not on mechanical ventilator, and massive volume infusion are excluded because they may have emergency indication for rapid fluid removal, and it would be considered unethical to randomize patients to a restrictive UF_{NET} rate. Patients with anticipated net fluid removal <48 hours are excluded because KRT might be terminated early, or patients might be transitioned to IHD and thus the exposure to UF_{NET} rate during CKRT would be minimal. Patients with UF_{NET} for more than 48 hours are excluded because UF_{NET} rates used prior to study enrollment may confound assessment of outcomes.

Patients on chronic outpatient dialysis are excluded because the UF_{NET} rates used in IHD are different than UF_{NET} rates used in CKRT and thus would confound outcome assessment.

Patients with kidney transplantation are excluded because their prognoses are different from those of AKI or complicates the assessment of secondary outcomes (*e.g.,* kidney function recovery). Criteria 9 and 10 exclude patients who may not survive to important study endpoints or whose underlying condition complicates assessment of at least one of the outcomes. Criteria 11 is excluded as there is not sufficient data on UF_{NET} rates in pregnant women. Criteria 12 is excluded as ECMO, VAD, and IABP precludes UF_{NET} rate titration based on hemodynamics as well as confounds the assessment of influence of UF_{NET} rates on patient hemodynamics. Brain-dead organ donors are excluded as one or more of the outcomes cannot be assessed; and drug overdose requiring KRT is excluded because there is not sufficient data on UF_{NET} rates in such patients.

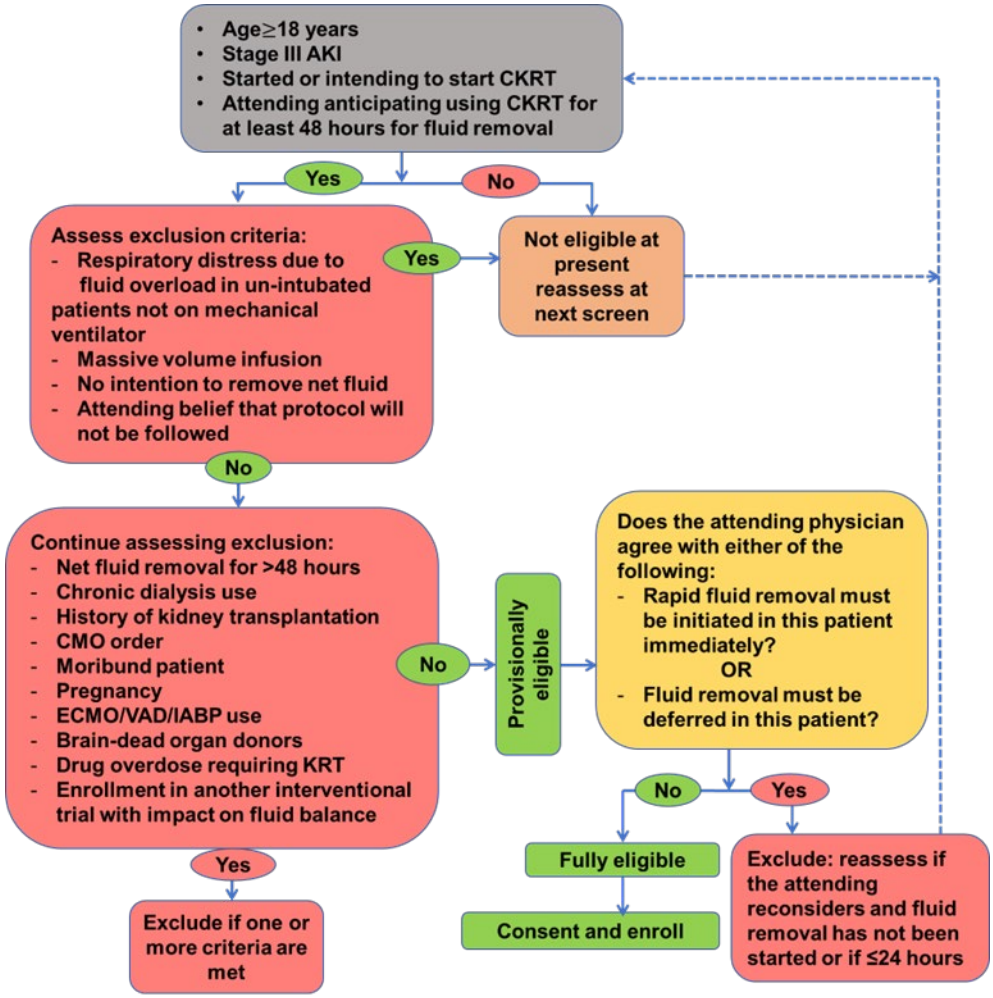
6.6.2 ASSESSING PHYSICIAN EQUIPOISE

If all inclusion and none of the exclusion criteria are met, the patient will be considered provisionally eligible (Figure 7). Once provisionally eligible, the attending intensivist or nephrologist will be asked twice daily: a) if he/she strongly believed that emergent and rapid fluid removal should occur, or b) if he/she strongly believed deferral of fluid removal. If the answer is negative to both questions, the patient will be considered fully eligible and efforts to obtain informed consent will commence.

If a patient's eligibility is excluded by a 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. This approach integrates the principle of clinical equipoise in the trial protocol and has been successfully used in clinical trials of AKI.[3,41] We will continue to screen patients for 7 days following initiation of CKRT but less than 24 hours of initiation of UF_{NET}.

Once the patient is fully eligible, with permission from the intensivist or nephrologist, a study investigator or study resident/fellow physician will discuss informed consent with the patient or legally authorized representative (LAR). Informed consent will be obtained within 48 hours of meeting full eligibility.

Figure 7: Screening and Recruitment Algorithm



6.7 INFORMED CONSENT

Informed consent will be obtained from each patient or LAR prior to enrollment in the trial. No study procedures will be done prior to obtaining informed consent. All patients meeting inclusion criteria will be entered on a screening log. If the patient is not enrolled, the screening log will include information explaining why enrollment did not occur (e.g., exclusion criteria, attending physician denial, patient refusal) and a minimum dataset to the extent allowed (Appendix C). If consent is obtained by LAR and later, while still in the study, the enrolled patient regains capacity to self-consent, the patient will be reconsented.

6.8 STUDY ENROLLMENT

Time of signing the informed consent will be the study enrollment time. Following study enrollment, the UF_{NET} must be initiated according to study protocol within 24 hours.

6.9 MINORITIES AND WOMEN

No patient will be excluded from the study based on gender, race, ethnicity or sexual preference.

7 STUDY PROCEDURES

Clinical trials should be conducted in a setting reflective of best practice that can be clearly described and reproduced in a clinical non-trial setting. Thus, we will ensure that there are no imminent indications for emergent and rapid UF_{NET} rates after discussing with the attending physician. Blinding is not feasible due to the nature of the intervention. To calculate the UF_{NET} rate, we will use patient predicted body weight (PBW) determined from patient height and has been used in several NIH sponsored ICU trials (Appendix A).[42,43]

Close oversight will be provided by ICU attending and/or designee. Before initiation of UF_{NET}, we will ensure i.) the CKRT is operational; ii.) a study investigator or designee will assess the hemodynamic appropriateness for initiation of UF_{NET} using the following as guidelines: MAP ≥65 mm Hg and no fluid bolus has been administered or new vasopressor started or vasopressor dose increased in the last hour; iii.) study investigator or designee will discuss with the attending physician to ensure there are no emergency indications for fluid removal; and iv.) UF_{NET} according to protocol will be initiated within 24 hours of enrollment in both groups.

To calculate the correct and dynamic UF_{NET} rate for the two intervention groups, we will use a web-based UF_{NET} rate calculator located on a password protected secure database accessed via a tablet computer, desktop computer, or computer on wheels. This UF_{NET} rate calculator will be programmed to automatically calculate the net fluid removal rate based on the allocation to the intervention group, predicted body weight, and rate of fluids infused into the patient. At all times, we will emphasize that the clinicians retain complete decision-making authority with respect to selecting and titrating the UF_{NET} rate, if the protocol cannot be followed for patient related reasons. **Thus, the final decision to set a UF_{NET} rate will be at the discretion of the treating clinician.**

Since the goal of this protocol is to assess feasibility of intravascular volume removal at a given UF_{NET} rate, the protocol will also not be applied when the clinicians do not plan to remove fluid but rather use CKRT to maintain euvolemia (*e.g.,* using CKRT with a goal to remove administered IV fluids and medication volume rather than to achieve net negative fluid balance).

7.1 RESTRICTIVE UF_{NET} GROUP

Fluid removal will not be started until the MAP ≥65 mm Hg with or without the need for vasopressors. The initial UF_{NET} rate will be set at 0.5 mL/kg/h and then increased 0.5 mL/kg/h, up to a maximum of 1.5 mL/kg/h, as tolerated (Figure 8). The UF_{NET} rate can be titrated and maintained between 0.5-1.5 mL/kg/h, throughout the study as per clinician discretion. For instance, in a patient with PBW 70 kilograms, the UF_{NET} rate will be initiated at 35 mL/h (*i.e.,* 70x0.5=35 mL/h) and increased by 35 mL/h to a maximum of 105 mL/h (*i.e.,* 70x1.5= 105 mL/h). The UF_{NET} rate can then be titrated between 35-105 mL/h throughout the study as per clinician discretion.

If fluid removal was started less than 48 hours before enrollment, and if the UF_{NET} rate before study enrollment was <0.5 mL/kg/h, the UF_{NET} rate will be reset at 0.5 mL/kg/h. In contrast, if the UF_{NET} before enrollment was >1.5 mL/kg/h, the rate will be reset at 1.5 mL/kg/h. If the UF_{NET} rate before enrollment is between 0.5-1.5 mL/kg/h, it will be continued at that current rate between 0.5-1.5 mL/kg/h.

We will also ensure that the UF_{NET} rate is adjusted for any ongoing volume infusion in the patient. For instance, in a patient with PBW of 70 kilograms, if the patient is also receiving an infusion of 100 mL/h in fluids (*e.g.,* medications, parenteral nutrition etc.), the initial UF_{NET} rate will be set at 135 mL/h (*i.e.,* [70x0.5]+100= 135 mL/h). The UF_{NET} rate can be increased to a maximum of 205 mL/h (*i.e.,* [70x1.5]+100= 205 mL/h) and maintained between 135 mL/h to 205 mL/h, as tolerated, for the duration the patient is receiving 100 mL/h volume infusion. If the additional 100 mL/h fluid is discontinued in the patient, the UF_{NET} rate will be reset between 35 mL/h and 105 mL/h. This will ensure that the net intravascular volume removal rate is equivalent to the set UF_{NET} rate.

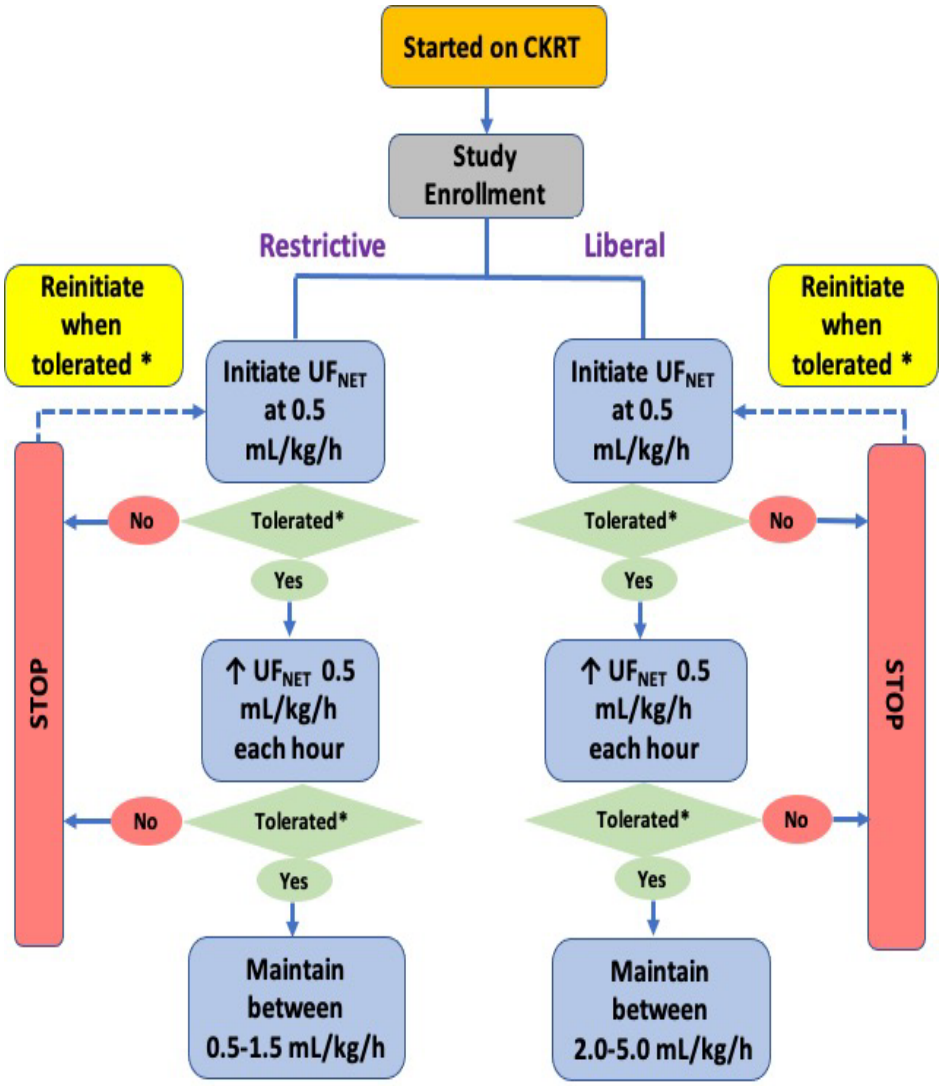
7.2 LIBERAL UF_{NET} GROUP (CONTROL ARM)

Fluid removal will not be started until the MAP ≥65 mm Hg with or without the need for vasopressors. The initial UF_{NET} rate will be set at 0.5 mL/kg/h and then increased 0.5 mL/kg/h, up to a maximum of 5.0 mL/kg/h, as tolerated (Figure 8). The UF_{NET} rate can be titrated and maintained between 2.0-5.0 mL/kg/h, throughout the study as per clinician discretion. For instance, in a patient with PBW 70 kilograms, the UF_{NET} rate will be initiated at 35 mL/h (*i.e.,* 70x0.5=35 mL/h) and increased by 35 mL/h to a maximum of 350 mL/h (*i.e.,* 70x5.0= 350 mL/h) as tolerated. The UF_{NET} rate can then be titrated between 35-350 mL/h throughout the study as per clinician discretion.

If fluid removal was started less than 48 hours before enrollment, and if the UF_{NET} rate before study enrollment was <2.0 mL/kg/h, the UF_{NET} rate will be gradually increased to 2.0 mL/kg/h. In contrast, if the UF_{NET} before enrollment was >5.0 mL/kg/h, the rate will be reset at 5.0 mL/kg/h. If the UF_{NET} rate before enrollment is between 2.0-5.0 mL/kg/h, it will be continued at that current rate between 2.0-5.0 mL/kg/h and titrated per clinician discretion.

We will also ensure that the UF_{NET} rate is adjusted for any ongoing volume infusion in the patient. For instance, in a patient with PBW of 70 kilograms, if the patient is also receiving an infusion of 100 mL/h in fluids (*e.g.,* medications, parenteral nutrition etc.), the initial UF_{NET} rate will be set at 135 mL/h (*i.e.,* [70x0.5]+100= 135 mL/h). The UF_{NET} rate can be increased and maintained between 240 mL/h (*i.e.,* [70x2.0]+100= 240 mL/h) and 450 mL/h (*i.e.,* [70x5.0]+100= 450 mL/h) for the duration the patient is receiving 100 mL/h volume infusion. If the additional 100 mL/h fluid is discontinued in the patient, the UF_{NET} rate will be maintained between 140 mL/h (*i.e.,* 70x2.0=140 mL/h) and 350 mL/h (*i.e.,* 70x5.0=350 mL/h). This will ensure that the net intravascular volume removal rate is equivalent to the set UF_{NET} rate.

Figure 8: Study interventions



* Tolerance assessed by MAP ≥65 mmHg and systolic blood pressure ≥90mmHg

7.3 DISCONTINUATION OF STUDY PROTOCOL

The study protocol will be continued until one of the following occurs: i.) the attending physician determines that fluid removal is no longer needed; ii.) a decision is made to stop CKRT and transition the patient to IHD; iii.) the patient or surrogate decision-makers decide to withdraw life-sustaining treatment; iv.) the patient dies; or v.) day 28 after study enrollment, whichever occurs first.

7.4 COMMON STRATEGIES FOR ALL STUDY GROUPS

7.4.1 STUDY STARTUP PROCEDURES

In both the study groups, we will use the following standardized, stepwise, startup procedures. Close oversight of study initiation will be provided by an intensive care attending and/or designee.

1. Ensure MAP ≥65 mmHg.

2. Ensure that the CKRT is operational.

3. Before starting UF_{NET}, a study investigator or designee will determine hemodynamic appropriateness for UF_{NET} using the following as guidelines: MAP ≥65 mmHg or SBP >90 mmHg, no fluid bolus has been administered, no new vasopressor has been started, or dose of vasopressor increased in the last hour.

4. Study investigator or designee following discussion with the attending physician will ensure there are no emergency indications for fluid removal.

5. In both the arms, UF_{NET} will be initiated within 24 hours of study enrollment.

6. In the restrictive UF_{NET} rate arm, UF_{NET} will be started at 0.5 mL/kg/h and increased to a maximum of 1.5 mL/kg/h. The UF_{NET} rate can be titrated by clinicians between 0.5-1.5 mL/kg/h, as tolerated.

7. In the liberal UF_{NET} rate arm, UF_{NET} will be initiated at 0.5 mL/kg/h and gradually increased 0.5 mL/kg/h to a maximum of 5.0 mL/kg/h. The UF_{NET} rate can be titrated by clinicians between 2.0-5.0 mL/kg/h, as tolerated.

8. In both the study arms, UF_{NET} rate can be decreased or stopped at the discretion of clinicians for hypotension. Following resolution of hypotension, UF_{NET} rate can be restarted and increased as tolerated as per the assigned treatment arm.

9. In both the study arms, at any given day and time, the UF_{NET} rate as per study protocol can be held if the clinicians decide to use CKRT for maintaining euvolemia (*i.e.,* no net fluid removal from patient).

7.4.2 HEMODYNAMIC MANAGEMENT

7.4.2.1 Toleration of UF_{NET}

Toleration of UF_{NET} will be defined as the absence of hemodynamic instability following initiation of UF_{NET} since there are no clinically validated tolerance parameters. We have chosen this construct for tolerance because in current clinical practice, tolerance to UF_{NET} is based on maintaining hemodynamic stability using MAP, HR and SBP.

7.4.2.2 Definition of hemodynamic instability

Hemodynamic instability during UF_{NET} will be defined as a *new* mean arterial pressure (MAP) <65 mmHg, systolic blood pressure (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 with a goal to maintain (MAP) ≥65 mmHg, systolic blood pressure (SBP)

≥90mmHg or discontinuation of fluid removal during CKRT.[18,19] The reason for choosing increased need of vasopressors, fluid bolus or discontinuation of fluid removal is to account for clinically significant hypotension that required an intervention.[18]

7.4.2.3 Interventions for hemodynamic instability

If hemodynamic instability develops after initiation of study treatments, we will check (i) the patient, the arterial tracing and heart rate and rhythm on the monitor to ensure correct reading; (ii) the UF_{NET} rate on the CKRT machine to ensure that the rate is set correctly; (iii) the alarms on the CKRT machines; (iv) the patient does not have obvious bleeding; (v) that no new sedative or other medications that cause hypotension has been administered or existing sedation dose increased in the previous 30 minutes; and (vi) follow the recommendations in Table 3.

Table 3: Interventions for managing hemodynamic instability

1.	Completely stop UF_{NET} (*i.e.,* no fluid removal)
2.	Stop or reduce the dose of sedative medication infusion
3.	Stop or reduce the dose of any medication that is known to cause hypotension
4.	Administer Plasmalyte or Lactated Ringers fluid bolus of 250 mL (may repeat as needed) AND/OR Start or increase norepinephrine to maintain MAP ≥65 mmHg

7.4.2.4 Re-initiation of UF_{NET} following hemodynamic instability

Following resolution of hypotension and attending physician approval, the bedside clinician will ensure that MAP ≥65 mmHg. The UF_{NET} rate will be set at 0.5 mL/kg/h and increased as tolerated per the assigned treatment arm.

7.4.3 CKRT PROCEDURES

We will follow specific protocols for management of CKRT to ensure uniformity of treatment between the patient groups. We have chosen CKRT as the primary modality for UF_{NET} for this trial because (i) overall volume control is superior with CKRT compared with IHD,[33] (ii) better hemodynamic tolerance than IHD in critically ill patients,[20,21] (iii) more than 70% of critical care practitioners surveyed use CKRT for volume removal,[44] (iv) primary modality used for treatment in ICU patients with severe fluid overload and multisystem organ failure at the UPMC and the Mayo Clinic ICUs.

CKRT will be provided at the discretion of attending nephrologist (Appendix D). CKRT modality will either be CVVHDF, CVVHD, CVVH or SCUF. All hemofilters will be comprised of biocompatible synthetic hollow-fiber membranes and will be changed at least every 48-72 hours. The electrolyte composition of the dialysate and replacement fluids and dialysate and replacement fluid flow rates will be prescribed by the attending nephrologist. Dialysate will be bicarbonate-buffered. Choice and type of anticoagulation will be at the discretion of

the clinician. Effluent flow rate will be 20-30 mL/kg/h and prescribed by the attending nephrologist. All efforts will be made to minimize CKRT downtime and ensure that CKRT is functioning at least 20 hours per day. Patients would be transitioned from CKRT to IHD or no KRT as determined by the treating physicians.

7.4.4 VENTILATOR PROCEDURES

We will protocolize low tidal volume ventilation strategy and use a simplified version of the ARDS network 6-8 mL/kg PBW lung protective ventilation protocol. We will use a standardized PEEP protocols based on prior ARDS network studies. Both low tidal volume ventilation and standardized PEEP strategies are already in use at the UPMC and the Mayo Clinic ICUs.

7.4.5 CONSERVATIVE FLUID MANAGEMENT PROTOCOL

Fluid management during shock or treatment for hypotension will be unrestricted. However, in patients not in shock, a conservative fluid approach will be recommended for all patients enrolled in the study (Table 4). This protocol is recommended for all enrolled patients, to be used until cessation of UF_{NET}.

Table 4: Conservative fluid management protocol

1.	Discontinue all maintenance intravenous fluids.
2.	Double concentrate or use lowest possible volume for all carrier fluids for medications, if possible.
3.	Continue enteral nutrition and free water flushes
4.	Manage electrolytes and blood products per usual practice.
5.	For shock, use any combination of fluid boluses and vasopressor(s) to achieve MAP ≥65 mmHg as fast as possible.
6.	If the patient is on total parenteral nutrition (TPN), the TPN volume would be limited to provide the least volume required to administer the calories, protein, and lipids.

7.4.6 RESCUE PROCEDURES

Our goal is to respect clinician autonomy and protect patient safety, while preserving separation of treatment between arms. Thus, we will encourage higher UF_{NET} rates beyond that which is specified by the protocol at the discretion of treating physician for emergent treatment of refractory hypoxia due to fluid overload or patient requiring massive volume infusion that requires control of fluid overload in the opinion of treating clinician (Table 5). However, following the resolution of emergency indication for fluid overload, UF_{NET} rate will be resumed as per protocol as determined by the attending nephrologist/intensivist. Being a feasibility randomized trial, the use of rescue rates of UF_{NET} will be collected as secondary outcomes and will not constitute a protocol violation.

Table 5: Criteria for rapid rescue net ultrafiltration

1.	Severe pulmonary edema with PaO_2/FiO_2 <150 and PEEP >5 cm H_20 due to fluid overload
2.	Respiratory distress due to fluid overload
3.	Ongoing hourly volume infusion at a rate higher than the assigned treatment group for more than 6 hours
4.	Inability to close surgical wounds due to tissue edema
5.	Failing spontaneous breathing trial due to fluid overload at the discretion of attending intensivist

PaO_2, partial pressure of oxygen; FiO2, the fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

7.4.7 FACILITATING COMPLIANCE

We will use educational programs and academic detailing,[45] automated reminders,[46] selection of ICU staff that are local opinion leaders,[47] and regular audit with feedback.[48] Study coordinators will facilitate compliance in three key roles – background operational logistics, clinician in-servicing, and interventional logistics (*e.g.,* ensuring CKRT machine is operational; suggested UF_{NET} rate is followed etc.). We will provide clear instruction guides to each coordinator and standardize work across ICUs.

8 DATA VARIABLES

8.1 BACKGROUND ASSESSMENTS

1. Demographic and Admission Data (including age, sex, race and ethnicity, admission diagnosis including COVID status)
2. Pertinent Medical History and Physical Examination (including Elixhauser co-morbidity index score)
3. Premorbid body weight and serum creatinine (if available)
4. Time on CKRT prior to enrollment
5. Type and location of ICU admission
6. Risk factors for AKI (sepsis, ischemia, nephrotoxin, other)
7. Risk factors for fluid overload (sepsis, heart failure, shock, trauma, massive transfusion)

8.2 BASELINE ASSESSMENTS

The following information will be recorded during the 24-hour interval preceding study enrollment. If more than one value is available for this 24-hour period, the value closest to the time of study enrollment will be recorded. If no values are available from the 24 hours prior to enrollment, then values will be measured post enrollment but prior to initiation of study interventions. All values will be derived from clinically available data.

1. History and physical examination
   Vital signs: heart rate (beats/min), systemic systolic, diastolic, and mean arterial blood pressure (mmHg), body temperature (°C), central venous pressure (cm H_2O), and other hemodynamic data (e.g., pulse pressure variation, stroke volume

variation, if available). Measured height and actual weight of the patient. Arterial blood gas values, if available.

2. CKRT mode, prescribed and actual blood flow rate, replacement fluid type and rate, dialysate type and rate, rate of ultrafiltration, UF_{NET} rate, effluent fluid rate, venous access and inflow pressures, transmembrane pressure, hemofilter type, time of last change of filter.

3. Administration of the following medications and fluids
    a. Intravenous vasopressors and inotropes
    b. Intravenous or enteral corticosteroids
    c. Intravenous fluids and career fluids, enteral and parenteral nutrition

4. APACHE II score, including the acute physiology components and laboratory values

5. SOFA score: cardiovascular, kidney, respiratory, hepatic, and hematology organ function will be assessed using the SOFA methodology as described in Appendix E.

6. Fluid intake and output before study enrollment and prior to ICU admission, if available.

7. If receiving positive pressure ventilation, ventilator settings including set tidal volume, FiO2, and PEEP.

8.3 ASSESSMENTS DURING STUDY

8.3.1 HEMODYNAMIC MONITORING DURING STUDY STARTUP

We will record the baseline hemodynamics before initiation of UF_{NET}, time at which UF_{NET} is initiated, time at which target UF_{NET} rate is reached. We will also record any episodes of hypotension, cardiac arrhythmias, administration of fluid bolus, vasopressor use, or increase in vasopressor dose.

8.3.2 REFERENCE MEASUREMENTS

The following data will provide the basis for assessing protocol compliance and safety as well as between-group differences. Data for each of the variables will be recorded on the days shown in the Time-Events schedule (Appendix F) until death, discharge from the ICU, or day 28, whichever occurs first. Values will be derived from clinically available data.

1. UF_{NET} rate

    a. Restrictive UF_{NET} rate group
        i. Time and initial UF_{NET} rate
        ii. Time and target UF_{NET} rate
        iii. Time and hourly UF_{NET} rate

iv. Reason and duration of UF_{NET} hold (if any)
v. Total volume of UF_{NET} during the study
vi. Rescue UF_{NET} (YES/NO)

b. Liberal UF_{NET} rate group
i. Time and initial UF_{NET} rate
ii. Time and target UF_{NET} rate
iii. Time and hourly UF_{NET} rate
iv. Reason and duration of UF_{NET} hold (if any)
v. Total volume of UF_{NET} during the study
vi. Rescue UF_{NET} (YES/NO)

<u>Reference measurements (Daily)</u>

The following parameters will be measured and recorded between 4:00 A.M. and 10.00 A.M. using the values closest to 8.00 A.M. on the days specified in the Time-Events schedule. The following conditions will be ensured prior to measurements: no CKRT changes in the previous 30 minutes, no invasive procedures or ventilator changes for 30 minutes. All vascular pressures will be zero-referenced to the mid-axillary line.

1. If receiving CKRT: CKRT mode, blood flow rate, actual rate, replacement and dialysate flow rate, ultrafiltration rate, UF_{NET} rate, effluent flow rate.

2. If receiving positive pressure ventilation set tidal volume, FiO2, PEEP, and plateau pressures.

3. PaO_2, $PaCO_2$, pH, and SpO_2

4. Rescue procedures used
   a. Rescue UF_{NET} rates used beyond the assigned treatment arm
   b. Vasopressors used for hypotension including dose
   c. Fluid bolus used for hypotension including volume

5. Serum electrolytes

6. Administration of the following fluids and medication
   a. Enteral or intravenous corticosteroids
   b. Intravenous vasopressors

7. Was CKRT interrupted? (YES/NO)

8. Cardiovascular SOFA score

9. Fluid intake and output

9 STATISTICAL CONSIDERATIONS

NOTE: Detailed statistical analysis plan (SAP) will be a separate document

9.1 STATISTICAL METHODS

The primary feasibility outcomes are between-group difference in mean UF_{NET} rate, protocol adherence, and recruitment rate. The primary objective of this feasibility trial to measure a minimum of 0.53-0.57 mL/kg/h separation in the delivered patient mean UF_{NET} rates between the restrictive and liberal UF_{NET} rate groups. We estimated that, if each of the 10 ICUs enrolled a minimum of 0.93 patient per 2 months for 24 months, we would have a total of 111 patients. Using the sample size calculation for SW-CRT design, we estimated that 111 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 0.53-0.57 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 (Table 6). After accounting for a very small attrition rate, we plan to recruit from each of the 10 ICUs: 1 patient per 2 months for 24 months for a total of 112 subjects or 56 patients per group.

Table 6: Detectable difference in mean UF_{NET} rates

Difference	ICC	Alpha	Power	N
0.53	0.01	two-sided	0.8	111
0.57	0.1	two-sided	0.8	111
0.57	0.01	one-sided	0.8	126
0.63	0.1	one-sided	0.8	126

ICC, intra-cluster correlation coefficient

10 DATA COLLECTION AND SITE MONITORING

10.1 DATA COLLECTION

At the UPMC and the Mayo Clinic, the research staff will collect data and record it either on paper data sheets and/or enter in a secure web database. Once daily, coordinators will enter data that can be analyzed for consistency.

In this trial, we will define protocol deviation 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 UF_{NET} for MAP <65 mm Hg or increased rate for MAP ≥90 mm Hg).

We will also calculate "%-on target" value for each center for each of the monitored variables (# of dates on-target for a specific variable/# of opportunities to be on-target for that specific variable). Principle Investigators at each site will receive monthly reports of (1) % on-target for each of the specific variables in the most recent month; (2) % on-target for each of the variables since the beginning of a trial; and (3) a list of dates/times from the past month, the specific data that were entered for those dates/times, and determinations of on- or off-target.

Investigators will use these reports to identify aspects of protocol management that can be improved at their sites. The on-target performances of all ICUs will also be included, allowing investigators at each center to know how their ICU is performing related to other ICUs. On-target performances will be discussed during regular meetings of the Steering Committee.

10.2 SITE MONITORING

Data quality will be reviewed remotely using front end range and logic checks at the time of data entry and back-end monitoring of data using SAS reports. The site PIs at the two sites will perform random audits of up to 10% of eDCFs and verify source documents. A summary of the audits will be submitted to the IRB during annual renewal. Patient records and case report forms will be examined on a spot check basis to evaluate the accuracy of the data entered into the database and monitor for protocol compliance.

11 RISK ASSESSMENT

This study involves randomization to either restrictive UF_{NET} rate, or liberal UF_{NET} rate. Compared to not being part of the study, patients may have a higher, lower, or similar risk of adverse events.

11.1 RISKS OF RESTRICTIVE UF_{NET} RATE

Restrictive UF_{NET} rates between 0.5 to 1.5 mL/kg/h may theoretically increase the risk of fluid overload, increase dependence on ventilator as well as dependence on kidney replacement therapy by prolonging fluid overload. Myocardial edema may result in increased episodes of cardiac arrhythmias. Worsening oxygenation may result in increased use of rescue procedures. However, UF_{NET} rates used in the restrictive group are also frequently used in clinical practice and our observational studies showed a lower risk of cardiac arrhythmias than liberal UF_{NET} rates.

11.2 RISKS OF LIBERAL UF_{NET} RATE

Liberal UF_{NET} rates between 2.0-5.0 mL/kg/h may increase the risk of hypotensive episodes and cardiac arrhythmias requiring treatment similar to that encountered in current clinical practice. Ischemic kidney injury due to hypotension may result in impaired recovery of

kidney function and longer dependence on KRT. The UF_{NET} rates in liberal group is also widely used in clinical practice.

11.3 RISK OF ADVERSE EVENTS

It is possible that one treatment arm may lead to more adverse events, which will be monitored during the study. However, being a feasibility trial, the study is not powered to detect any statistically significant differences in adverse events. Many of the adverse events commonly occur during current clinical practice of fluid removal (Section 5.2.5; Table 1).

11.4 MINIMIZATION OF RISKS

Net ultrafiltration is currently used clinically in the treatment of patients with fluid overload during CKRT and hypotensive episodes occur in 19% to 97% of patients[18-20] with a mortality rate of more than 40%.[2,3,26,49] This trial will study two different approaches to fluid removal in order to minimize the risk of hypotension and ultimately to improve patient outcomes in a subsequent large multicenter randomized trial. There are several elements of study design inherent in the present protocol that ensures the minimization of risks greater than that provided during routine clinical care. Below we address the mitigation strategies used for each risk.

Risks of the release of information: The risk of inadvertent release of confidential information is unlikely due to the numerous protections in place. i.) All data will be collected and stored in secure files both at the participating clinical sites and at the CRISMA coordinating center. ii.) Each enrolled study participant will be assigned a study identification number, and the information to be collected and submitted to the coordinating center will not contain any personal identifiers (protected health information). iii.) We will enter all data collected by the site study coordinator using electronic data collection forms into a secure web-based study database, which will be password protected. Only the site study coordinators and the PI will have access to the password for the database. iv.) All study personnel with access to the study database will be required to complete training on the web-based data collection system and have the necessary CITI modules completed. v.) All study participant consent forms, research data, and linkage information will be stored in a secure manner with access limited to the study personnel. The linkage will be maintained by CRISMA's Biostatistics and Data Management Core's Data Manager only and is kept in a password protected location with access to no one else.

Risk of hypotension: i.) This protocol assesses attending physician equipoise to ensure safety before study enrollment. Subjects will not be enrolled in the study if the attending physician believes that fluid should not be removed due to severe hemodynamic instability. ii.) All patients will have continuous monitoring of blood pressure in the ICU via indwelling arterial line as per routine clinical care for early detection of hypotension. iii.) This protocol also mandates that UF_{NET} rates do not exceed greater than 5.0 mL/kg/h in the liberal group to ensure that subjects are not exposed to high UF_{NET} rates that are used in current clinical practice. iv.) This protocol mandates that fluid removal be completely stopped if a patient develops hemodynamic instability and provides a stepwise approach to management of

hemodynamic instability (Table 3). v.) Hypotensive episodes will be treated by slowing rate or completely stopping fluid removal. vi.) Fluid bolus and vasopressors will be administered, as needed. vii.) Fluid removal will only be restarted once the patient regains hemodynamic stability. viii.) all ICU clinicians will undergo training on study protocol and what to do when hypotension occurs.

Risk of hypertension: Hypertensive episodes related to severe fluid overload will be treated according to clinician discretion by increasing the rate of fluid removal and also with anti-hypertensive medications, as per clinician discretion.

Risk of prolonged exposure to fluid overload: i.) This protocol assesses attending physician equipoise to ensure safety before study enrollment. Subjects will not be enrolled in the study if the attending physician believes that fluid should be removed rapidly due to severe fluid overload. ii.) This protocol recommends conservative fluid management in both study arms to minimize unnecessary fluid administration (Table 4). We will recommend that all medications and infusions be double concentrated to reduce fluid volume. iii.) All patients will have daily monitoring of fluid input, output, and daily fluid balance in the ICU as part of routine clinical care. iv.) If severe fluid overload occurs, clinicians can increase the rate of fluid removal, as required, to treat fluid overload.

Risk of heart failure and pulmonary edema: If a patient develops respiratory distress due to fluid overload, this protocol provides for the option of using rapid and rescue UF_{NET} rates, as required per clinician discretion to treat fluid overload (Table 5).

Cardiac arrhythmias: i.) Cardiac arrhythmias due to severe fluid overload will be treated by increasing the fluid removal rate as per clinician discretion. Whereas arrhythmias due to rapid fluid removal will be treated by slowing the fluid removal rate, as needed. ii.) Clinically significant cardiac arrhythmias will be treated using anti-arrhythmic agents as per clinician discretion.

Risk of increased duration of mechanical ventilation, dialysis, ICU and hospital length of stay due to fluid overload will be treated by increasing fluid removal rate, as per clinician discretion.

Risk of surgical wound edema, bowel ischemia and anastomotic break down, and ileus, abnormal liver function, delirium, poor wound healing due to fluid overload will be treated by increasing fluid removal rate as clinically indicated to treat organ edema and dysfunction per discretion of treating clinicians.

Risk of wound infections and secondary infections: Patients will be monitored for wound infections due fluid overload. Wound infection will be treated using debridement or antibiotics as per clinician discretion.

Risk of hypophosphatemia, hypokalemia, hypocalcemia: Electrolytes will be monitored frequently as per ICU protocol. Severe hypophosphatemia, hypokalemia, and hypocalcemia will be treated by appropriate electrolyte replacement.

Risk of arterial and venous thrombosis: Patients will be monitored for arterial and venous thrombosis. Arterial and deep venous thrombosis will be treated with anticoagulation, as per the discretion of treating clinicians.

Risk of anemia, hemolysis, and thrombocytopenia: Hematology labs will be monitored daily in all patients. Clinically significant anemia, hemolysis, and thrombocytopenia will be treated with administration of blood products, as per the discretion of treating clinicians.

11.5 POTENTIAL BENEFITS

Study subjects may or may not receive any direct benefits from their participation in this study. Restrictive UF_{NET} rates have been found to reduce risk of cardiac arrhythmias as well as short- and long-term mortality and KRT dependence in observational studies.[6,22] Restrictive UF_{NET} rates may result in less hypotensive episodes and may result in overall net negative fluid balance and improved patient outcomes if risk of hypotension and subsequent fluid administration are reduced. The liberal UF_{NET} rates may also result in overall reduced exposure to fluid overload, earlier liberation from mechanical ventilation and lower complications from fluid overload.

The knowledge gained from this study may be of significant benefit to future critically ill patients undergoing treatment with CKRT with a restrictive or liberal UF_{NET} rate strategy. Understanding the UF_{NET} rate-outcome relationship in acutely ill patients is critical for four reasons: a) to ensure that the provision of current care is safe, b) to design interventions to reduce mortality, c) to develop evidence-based clinical practice guidelines, and d) to implement quality measures during treatment with CKRT.

11.6 RISKS IN RELATION TO ANTICIPATED BENEFITS

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. Faster and slower UF_{NET} rates are currently used in clinical practice. There is a potential for benefit to the society and individual patients should one of the UF_{NET} strategies reduce complications and improve outcomes in a subsequent large phase III trial. Should one of the UF_{NET} rate strategies, again consistent with clinical practice, prove to be harmful, the benefit will be in avoiding such therapies for future patients.

11.7 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The knowledge gained from this trial will be used to design a large multicenter phase III trial to examine alternative UF_{NET} rate strategies and its association with patient-centered clinical outcomes of 90-day mortality and dependence on KRT. We will also use the knowledge gained from this proposal to design other interventions to reduce the risks associated with UF_{NET}. Such knowledge may serve to take precautionary measures to mitigate risks and prevent adverse events during UF_{NET} in critically ill patients in the future.

This trial will also help us understand four key points, 1) whether it is feasible to maintain patients in the restrictive or liberal UF_{NET} rates throughout the study; 2) an assessment of protocol adherence, 3) the patient recruitment rates in each center for the current trial, and 4) the effects of alternate UF_{NET} rate strategies on patient's secondary clinical and safety outcomes. Thus, this study will enhance the scientific knowledge of understanding the UF_{NET} rate-outcome relationship in critically ill patients.

12 HUMAN SUBJECTS

Each study participant or a LAR must sign and date an informed consent form. Approval for this feasibility trial will be obtained from the University of Pittsburgh Human Research Protection Office (HRPO), which will serve as the single IRB, before any subject is entered into the study.

12.1 SELECTION OF SUBJECTS

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The ICUs at the UPMC and Mayo Clinic will be screened daily to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. No protocol-specific tests or procedures will be performed as part of the screening process. If any subject meet criteria for study enrollment, then the attending physician will be asked for permission to approach the patient or his/her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

12.2 JUSTIFICATION OF INCLUDING VULNERABLE SUBJECTS

The present research aims to investigate the feasibility of alternative UF_{NET} strategies for critically ill patients. Since the subjects enrolled in this clinical trial will have fluid overload and one or more organ system failure (*e.g.,* respiratory and renal failure) it is anticipated that most of these patients will have impaired decision-making capability. This study cannot be conducted if limited to enrolling only those subjects with retained decision-making capacity. Hence, subjects recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available.

12.3 INFORMED CONSENT

Federal regulations 45 CFR 46.111 (a) (5) require that informed consent be sought from each prospective subject or the subject's LAR. We anticipate almost all consents will be from the subject's LAR, and thus the remainder of this section will focus on LARs. The one obtaining consent is responsible for ensuring that the LAR understands the risks and benefits of participating in the study and answering any questions the LAR may have throughout the study and sharing any new information in a timely manner that may be

relevant to the LAR's willingness to permit the subject's continued participation in the trial. The consenter will make every effort to minimize coercion.

All study participants or their LARs will be informed of the objectives of the study and the potential risks. Prior to obtaining informed consent the patient and/or LAR will also be provided a study brochure. The informed consent document will be used to explain the risks and benefits of study participation to the LAR in simple terms before the patient is entered into the study, and to document that the LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each LAR. The process of informed consent between a study attending physician investigator or study resident/fellow physician and the patient or LAR may occur face-to-face either in-person or virtually via a remote electronic communications platform (*e.g.,* via ZOOM/Teams) due to restrictions because of hospital COVID-19 protocols. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures. In case of virtual consent with LAR, appropriate electronic signatures from LAR, witness, and/or attending physician investigator or study resident/fellow physician will be obtained via an approved electronic consent platform.

To obtain informed consent, the following information shall be provided to each patient or patient's LAR:

a. The name of the study.
b. The name of the Principal Investigator.
c. An explanation that the study involves research.
d. An explanation that the purpose of the study is to determine feasibility of maintaining slow or fast fluid removal, and whether a particular strategy of fluid removal is associated with less fluid overload and complications.
e. An explanation that the active treatment portion of the study will last up to 28 days from study enrollment.
f. A description of the restrictive and liberal UF_{NET} rate strategies
g. A description of benefits and risks associated with restrictive and liberal UF_{NET} strategies
h. A description of randomization at the ICU level.
i. A description that participation in the study may require longer or shorter times on dialysis treatment with fluid removal.
j. A description that the patient's medical record number will be used to identify records and to track the patient during hospital stay.
k. A description that the alternative to participation in this study will be to receive fluid removal during kidney replacement therapy (dialysis) as per clinician discretion and not as part of the study.
l. A description that all records will be kept confidential.
m. An explanation of whom to contact for answers to questions about the research and about research subject's rights.
n. An explanation of whom to contact in the event of research-related injury.

o. A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing to participate will involve no penalty, loss of benefits or reduction in access to medical care.
p. A statement that there will be no cost for the treatments provided as part of this study.
q. A statement that there will be no payment for participation in this study.

12.4 CONTINUING CONSENT

Subjects for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while still in hospital within the 28d post intervention period, will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR will reflect that such consent will be obtained.

12.5 WITHDRAWAL OF CONSENT

Patients may withdraw or be withdrawn (by the LAR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analyses unless consent to use their data has also been withdrawn. If a patient or LAR requests termination of the trial intervention during the treatment period, the intervention will be stopped but the patient will continue to be followed up as part of the trial. If a patient or LAR withdraws consent during the trial treatment, the trial intervention will be stopped but permission will be sought to access medical records for data related to the trial. If a patient or LAR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

12.6 IDENTIFICATION OF LEGALLY AUTHORIZED REPRESENTATIVES

Many of the patients approached for participation in this research protocol will invariably have limitations of decision-making abilities due to their critical illness. Hence, most patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the potential subject's LAR.
Regarding proxy consent, the existing federal research regulations ("the Common Rule") states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research….. unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (2) a legally authorized representative as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." The Office of Human Research Protections (OHRP) defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for subject participation in the research.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee [NBAC]), an investigator should accept a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place.[50] Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study.

In the state of Pennsylvania, the following individuals may be considered LARs of a potential research subject and capable of providing surrogate consent:

- A court-appointed guardian authorized in a current court order to consent to the subject's participation in the research.
- A health care agent appointed by the subject in a power of attorney.
- A "health care representative" when the individual cannot speak for his/herself and where there has been no guardian appointed by the court and no health care power of attorney designated (PA Act 169).
- Any of the following relatives, in descending order of priority, who is reasonably available, may also act as the subject's health care representative:
    a. The spouse (unless an action for divorce is pending).
    b. Adult children (18 years of age or older).
    c. A parent.
    d. An adult sibling.
    e. An adult grandchild.
    f. An adult who has knowledge of the potential research subject's preferences and values, including but not limited to religious and moral beliefs, who is able to assess how the patient would make decisions.

12.7 JUSTIFICATION OF SURROGATE CONSENT

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents greater than minimal risks. Commentators and research ethics commissions have held the view that it is permissible to include incapable subjects in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits similar to that available in the clinical setting.[51] Commentators and research ethics commissions have held the view that it is permissible to include incapable subjects in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits similar to that available in the clinical setting.[51]

Several U.S. tasks forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of

participation are not substantially greater than the risks of standard treatment".[52] Finally, NBAC stated than an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that "the potential subject's LAR gives permission…..".[50] Several U.S. tasks forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment".[52] Finally, NBAC stated than an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that "the potential subject's LAR gives permission…..".[50] Consistent with the above ethical sensibilities regarding the participation of decisional incapable subjects in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is similar to that available in the clinical setting.

12.8 ADDITIONAL SAFEGUARDS FOR VULNERABLE SUBJECTS

The present research will involve subjects who might be vulnerable to coercion or undue influence. As required in 45 CFR 46.111 (b), we will use additional safeguards to protect the rights and welfare of these subjects. Such safeguards might include but are not limited to: i.) assessment of the potential subject's capacity to provide informed consent; ii.) the availability of the LAR to monitor the subject's subsequent participation and withdrawal from the study; and iii.) augmented consent processes. The specific nature of the additional safeguards will be left to the discretion of the Human Research Protection Office.

12.9 CONFIDENTIALITY

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all evaluation forms, and reports will be identified only by a coded number. The coded number will be generated by a computer, and only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All computer entry and networking programs will be done with coded numbers only. All paper case report forms will be maintained inside a locked office. Study information will not be released without the written permission of the patient, except as necessary for monitoring by the institutional Data and Safety Monitoring Board.

13 SAFETY MONITORING

13.1 ADVERSE EVENTS

A clinical trial adverse event (AE) is defined as any untoward medical event temporally associated with the use of drug or study procedure in humans, whether or not it is considered related to a study intervention or study procedure. Assuring patient safety is an essential component of this protocol and the Principal Investigators have the primary responsibility for the safety of the individual participants. Thus, the Principal Investigators

will monitor for all AEs from study enrollment until ICU discharge or day 28, whichever occurs first.

Following study enrollment, AEs occurring after the patient received the study interventions will be evaluated at the two clinical sites by the Principal Investigators. Investigators will assess if there is a reasonable possibility that the study procedure caused the event, based on the criteria outlined in Appendix G1.

If a patient's study treatment is discontinued because of an AE, the study investigator must report the circumstances and data leading to discontinuation of treatment in the AE case report forms. AEs will be considered related or possibly related to study treatment only up to 24 hours following discontinuation of CKRT. AEs occurring after discontinuation of CKRT and after transition to IHD will not be considered related to study interventions.

Investigators will also consider if the event is unanticipated or unexplained given the patient's clinical course, previous medical conditions, and concomitant medications as outlined in Appendix G2. An adverse event is considered "unanticipated" if it is not listed in the study protocol (21 CFR 312.32(a)).

The following adverse events will be collected in the case report forms:

- Serious adverse events
- Non-serious adverse events that are considered by the investigator to be related to study intervention or study procedures or of uncertain relationship (Appendix G)
- New onset hypotensive and hypertensive episodes, cardiac arrhythmias, considered by the investigator to be related to rate of fluid removal during CKRT, or of uncertain relationship
- Emergent use of rescue UF_{NET} rates with rates higher than the assigned treatment arm
- Severe hypophosphatemia, hypokalemia, hypocalcemia
- CKRT system clotting, clogging, downtime, and discontinuation of fluid removal due to patient instability.
- Inability to close surgical wounds due to edema
- New organ dysfunction such as diastolic and systolic dysfunction on echocardiogram; pulmonary edema on chest X ray; ileus, bowel ischemia, anastomotic break down; wound infection, and pressure ulceration; arterial and venous thrombosis; severe anemia requiring red cell transfusions, and severe thrombocytopenia requiring platelet transfusions.
- New secondary infections

13.2 SERIOUS ADVERSE EVENTS

Serious adverse event (SAE) collection begins after the patient or surrogate has signed informed consent and has received the study intervention or undergone study procedures. If a patient experiences a SAE after consent, but prior to receiving the study intervention, the event will NOT be collected unless the Principal Investigator feels the event may have

been caused by a protocol procedure. SAEs will be collected after initiation of study intervention until ICU discharge or day 28, whichever occurs first, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were unanticipated and related to the study procedure. If a determination is made that a SAE has a reasonable possibility of having been caused by a study procedure, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unanticipated, it will be classified as a serious unanticipated suspected adverse reaction (SUSAR).

As per the FDA and NIH definitions, a SAE is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or rehospitalization

  As per https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (*e.g.,* life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- Persistent or significant disability/incapacity

  As per https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, *i.e.,* the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

13.3 IRB AND DSMB REPORTING

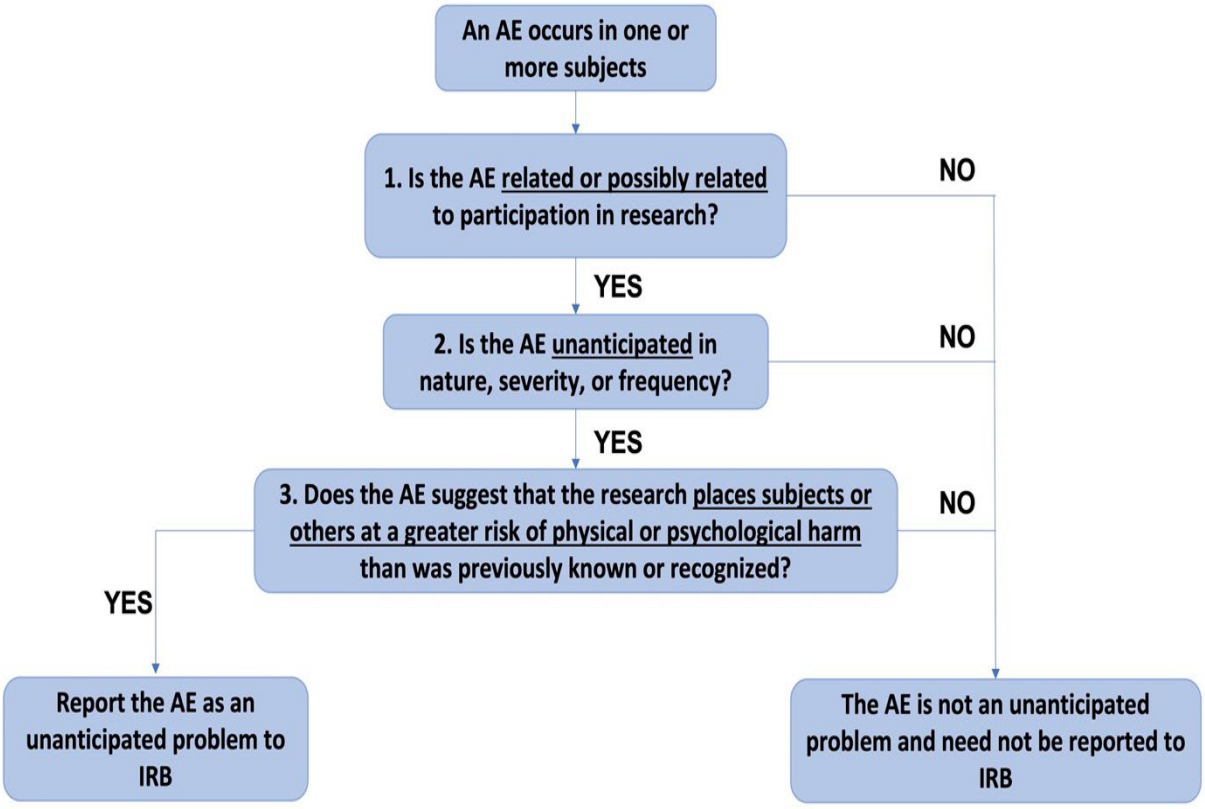
13.3.1 IRB REPORTING

An AE or SAE is judged to be reportable to University of Pittsburgh HRPO, if it meets ALL of the following: i.) unanticipated in terms of nature, severity, or frequency; ii.) related or possibly related to study intervention; iii.) places subjects or others at a greater risk of physical, psychological, economic or social harm than was previously known or recognized. If the AE is judged to be reportable to the IRB based on above criteria, then the study team at the University of Pittsburgh will report to the HRPO within 10 working days. If it is an SAE and meets the above criteria, the study team will report to the HRPO within 24 hours.

All SAEs that meet above criteria and occurring at Mayo Clinic must be reported to the study team at University of Pittsburgh within 24 hours. All AEs that meet above criteria and occurring at Mayo Clinic must be reported within 5 working days to the team at University of Pittsburgh. The study team at University of Pittsburgh will then report all AE and SAE to the University of Pittsburgh HRPO within timelines shown in Table 7. The AEs that comprise the safety outcomes will be included in outcome reporting and will not be reported a second time as AEs or SAE.

At both clinical sites the study personnel must alert the Principal Investigator of any serious and study procedure-related adverse event within 24 hours of investigator/coordinator awareness of the event. Please note that most AEs will not meet the definition of an Unanticipated Problem Involving Risk to Subjects or Others and need not be reported to the HRPO. Expected AEs or AEs which are determined by the investigator to be unrelated to the research intervention need not be reported to the IRB. The flow chart below provides an algorithm for determining whether an AE meets the definition of an unanticipated problem involving risk to subjects or others and whether it needs to be reported to HRPO.

Figure 9: Adjudication of AEs



13.3.2 DSMB REPORTING

All SAEs meeting the definition of unanticipated problem as stated in Section 13.3.1 will be reported to DSMB within 24-48 hours of investigator/coordinator awareness of the event. For all other AEs meeting the definition of unanticipated problem a written report will be sent to the DSMB within 10 working days. The DSMB will also review all AE and clinical outcomes during regularly scheduled meetings and at the final analyses, including frequency of rescue procedures and hypotension in all the study groups. If the DSMB determines that

the overall rate of adverse events is higher in any of the two intervention groups, University of Pittsburgh HRPO will be notified within 15 days of this determination. An AE table summarizing IRB and DSMB reporting timeline is provided below.

Table 7: Reporting timelines

Reporting organization	Fatal or life-threatening AE meeting definition of unanticipated problem	All other AEs meeting definition of unanticipated problem	AEs that are expected and listed as secondary or safety outcome
Co-ordinating center	24 hours	5 working days	No reporting
IRB	24 hours	10 working days	No reporting
DSMB	24-48 hours	10 working days	Reporting at the regular DSMB meeting

14 APPENDICES

A. CALCULATION OF NIH GENDER-SPECIFIC PREDICTED BODY WEIGHT

Predicted body weight (PBW) is calculated from gender and height (heel to crown) according to the following equations:

Males: PBW (Kilograms) = 50 + 2.3 [height (inches) – 60]

Females: PBW (Kilograms) = 45.5 + 2.3 [height (inches) – 60]

B. KDIGO CRITERIA FOR DIAGNOSING AND STAGING OF ACUTE KIDNEY INJURY

B1. DIAGNOSIS OF AKI

AKI will be diagnosed using as any of the following

- Increase in serum creatinine ≥0.3 mg/dL within 48 hours[a]

  OR
- Increase in serum creatinine ≥1.5 times baseline, which is known or presumed to have occurred within prior 7 days[a]

  OR
- Urine volume <0.5 mL/kg/h for 6 hours

  OR
- Increase in serum creatinine value ≥ the age, gender, and race corrected levels in Table B1

[a] *The increase in serum creatinine (absolute and relative) will be determined based on the lowest available serum creatinine value in the past 12 months. If no baseline value is available, AKI status will be determined using the age- and gender-corrected table below provided there is no past medical history of chronic kidney disease*

Table B1: Cut-off values for serum creatinine based on 1.5 times estimated normal values for age group

Age (years)	Black Male mg/dL	Other Male mg/dL	Black Female mg/dL	Other Female mg/dL
20-24	2.3	2.0	1.8	1.5
25-29	2.3	1.8	1.7	1.5
30-39	2.1	1.8	1.7	1.4
40-54	2.0	1.7	1.5	1.4
55-65	2.0	1.7	1.5	1.2
>65	1.8	1.5	1.4	1.2

B2 STAGING OF AKI

Table B2: Determination of the stage of AKI

Stage	Serum Creatinine	Urine Output
1	1.5 – 1.9 times baseline OR ≥0.3 mg/dl increase	<0.5 mL/kg/h for 6 – 12 hours
2	1.0 – 2.9 times baseline	<0.5 mL/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl OR Initiation of kidney replacement therapy	<0.3 mL/kg/h for 24 hours OR Anuria ≥12 hours

C. DEIDENTIFIED DATA ELEMENTS FOR SCREENED, NON-ENROLLED SUBJECTS

The following data elements will be collected on screened subjects who met the inclusion criteria but were not enrolled.

- Has CKRT been started?
- Was UF_{NET} commenced before screening?
- Was the attending intensivist/nephrologist intending to start CKRT for fluid removal?
- Month of year that patient met screening criteria (02-21)
- Gender
- Ethnicity
- Age (if age >89, 89 will be entered as age)
- Patient location (e.g., TICU, Medical ICU etc.) and if regularly screened
- Reason(s) patient excluded from study
- If not excluded, not enrolled, why?
- Cause of acute kidney injury

D. CONTINUOUS KIDNEY REPLACEMENT THERAPY (CKRT) MANAGEMENT PROCEDURES

General treatment parameters for the prescription of CKRT are summarized in the table below.

Modality	CVVHDF, CVVHD, CVVH, or SCUF
Treatment schedule	Continuous
Hemofilter	M100 or any synthetic hollow-fiber membranes
Blood flow rate	200 – 350 mL/min, prescribed by primary team
Effluent flow rate	20-30 mL/kg/h
Dialysate	Bicarbonate buffered; electrolyte composition prescribed by primary team
Dialysate flow rate	Prescribed by primary team
Post-filter replacement fluid	Bicarbonate buffered; electrolyte composition prescribed by primary team
Pre-filter replacement fluid	Bicarbonate buffered; electrolyte composition prescribed by primary team
Ultrafiltration rate	As per study protocol
Anticoagulation	Prescribed by primary team
System change	At least every 48-72 hours

To deliver the targeted dose of UF_{NET}, it is critical that periods of time during which the patient is off CKRT are kept as brief as possible. We recognize that patients will need to come off therapy for a variety of reasons, including CT scans, MRI scans, angiographic and surgical procedures. The ICU staff will be educated as to the importance of resuming treatment promptly upon the patients return to the ICU. Similarly, when systems need to be changed, either due to system clotting, or due to routine system changes, the time off therapy needs to be minimized.

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

F. TIME-EVENTS SCHEDULE

F1. GENERAL DATA COLLECTION

Measurement/Event	Screening	Baseline/ Day 0@	1	2	3	4	5	6	7	8-14	15-21	22-28
Serum Creatinine	X	X	X	X	X	X	X	X	X	X	X	X
Demographics, History and Physical		X										
AKI Cerner alerts	X	X										
Etiology of AKI		X										
APACHE II		X										
Weight*		X	X	X	X	X	X	X	X	X	X	X
Daily FB*		X	X	X	X	X	X	X	X	X	X	X
Restrictive UF_{NET}		X	X	X	X	X	X	X	X	X	X	X
Liberal UF_{NET}		X	X	X	X	X	X	X	X	X	X	X
Ventilator parameters$^{\phi\Psi*}$		X	X	X	X	X	X	X	X	X	X	X
CKRT parameters$^{\phi\Psi\$}$		X	X	X	X	X	X	X	X	X	X	X
ABG*		A	A	A	A	A	A	A	A	A	A	A
Fluids (intake/output)*		X	X	X	X	X	X	X	X	X	X	X
MAP*		X	X	X	X	X	X	X	X	X	X	X
CVP, CI, PPV, SVV, and other hemodynamic data*		A	A	A	A	A	A	A	A	A	A	A
Hypotensive & Hypertensive episodes$^{\$\%}$		X	X	X	X	X	X	X	X	X	X	X
Cardiac arrhythmias$^{\$\%}$		X	X	X	X	X	X	X	X	X	X	X
Use of rescue UF_{NET} rates$^{\$}$		X	X	X	X	X	X	X	X	X	X	X
Severe hypophosphatemia$^{\$}$		X	X	X	X	X	X	X	X	X	X	X
Severe hypokalemia$^{\$}$		X	X	X	X	X	X	X	X	X	X	X
Severe hypocalcemia		X	X	X	X	X	X	X	X	X	X	X
All lab data*		X	X	X	X	X	X	X	X	X	X	X
Vital signs and medications*		X	X	X	X	X	X	X	X	X	X	X
Inability to close surgical wounds		X	X	X	X	X	X	X	X	X	X	X
New organ dysfunction*		X	X	X	X	X	X	X	X	X	X	X
Secondary infections		X	X	X	X	X	X	X	X	X	X	X
SOFA score $^{\beta*}$	X	X	X	X	X	X	X	X	X	X	X	X
Vital status		X	X	X	X	X	X	X	X	X	X	X

Measurement/Event	Screening	Baseline/ Day 0[@]	1	2	3	4	5	6	7	8-14	15-21	22-28
KRT Status		X	X	X	X	X	X	X	X	X	X	X
IHD use			X	X	X	X	X	X	X	X	X	X

X= Required
A=When available
Ψ=Data gathered at times indicated or until 72 hours, whichever occurs first
β=Records clinically available creatinine, platelets, bilirubin, MAP, SBP, FiO2, fluid bolus and vasopressor use
ϕ=Measure during reference period (0600 -1000); other values may be obtained closest to 0800 on the specified calendar date
[*] = collected only if the patient is still in the ICU before day 28 and if available in the electronic health records
[$]= collected only if the patient is on CKRT upto 24 hours following discontinuation of CKRT
[%]=collected only if the patient is on IHD
[@] =Data collected before initiation of study intervention

F2. CKRT DATA COLLECTION

Measurement/ Event	Initiation of RRT	Baseline/Day 0[@]	1	2	3	4	5	6	7	8-14	15-21	22-28
Indication for KRT - Volume status - Serum potassium - Acid-base status - Symptoms - BUN - Hemodynamic status	X											
CKRT - Mode - Hemodiafilter - Blood flow rate - Dialysate flow rate - Replacement fluid rate - Ultrafiltration rate - Net Ultrafiltration rate - Hours of therapy - 24- hour effluent volume - Anticoagulation		X	X	X	X	X	X	X	X	X	X	X
Complications - Clogging - Clotting - Downtime		X	X	X	X	X	X	X	X	X	X	X

Measurement/ Event	Initiation of RRT	Baseline/Day 0[@]	1	2	3	4	5	6	7	8-14	15-21	22-28
- Discontinuation of UF_{NET} due to patient instability												
Indications for termination of KRT		X	X	X	X	X	X	X	X	X	X	X

[@]= Data collected before initiation of study intervention

G. ADVERSE EVENT REPORTING AND UNANTICIPATED PROBLEMS

G1. DETERMINING RELATIONSHIP OF ADVERSE EVENTS TO STUDY PROCEDURES

Investigators will be asked to grade the strength of the relationship of an adverse event to study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.

- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.

- Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.

- Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

G2. UNANTICIPATED PROBLEMS (UP)

Investigator will report Unanticipated Problems, regardless of severity, associated with the study procedures to University of Pittsburgh HRPO and DSMB. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the HRPO-approved research protocol and informed consent document; and the characteristics of the subject population being studied.

- Related or possibly related to participation in the research. Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

H. DATA AND SAFETY MONITORING BOARD

The principal role of the DSMB is to assure the safety of patients in this feasibility trial. They will regularly monitor the data from this trial, review and assess the performance of its operations, and make recommendations to the Principal Investigator with respect to:

- Review of adverse events
- Possible modifications in the clinical trial protocol

The Clinical and Translational Science Institute at the University of Pittsburgh will appoint a DSMB. The DSMB will consist of members with expertise in critical care medicine, nephrology, and biostatistics. Appointment of all members is contingent upon the absence of any conflicts of interest. The Principal Investigator will be responsible for the preparation of all DSMB and adverse event reports.

The DSMB will review the protocol and sample consent form during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB. When appropriate, face-to-face (*i.e.,* Teams/Zoom) meetings will be held. Recommendations to end, modify, or continue the trial will be prepared by the DSMB executive secretary. Recommendations for major changes, such as stopping, will be reviewed by the DSMB and communicated immediately. Other recommendations will be distributed to the RELIEVE-AKI steering committee.

I. COMMON REASONS FOR ACUTE KIDNEY INJURY, FLUID OVERLOAD AND RAPID UF_{NET}

I1. COMMON CAUSES FOR AKI AND FO

- Sepsis
- Massive hemorrhage
- Cardiac surgery
- Major trauma
- Acute pancreatitis

I2. COMMON REASONS FOR RAPID UF_{NET}

- Severe fluid overload with impending respiratory failure
- Acute heart failure with pulmonary edema and cardio-renal syndrome
- Refractory hypoxemia due to fluid overload and ARDS while on mechanical ventilation
- Severe fluid overload after massive septic shock resuscitation
- Chronic kidney disease and heart failure or COPD

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