Restrictive versus Liberal Rate of Extracorporeal Volume Removal Evaluation in Acute Kidney Injury (RELIEVE-AKI): A Pilot Clinical Trial Protocol

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for the

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Supplement 1

Figure S1: Study Organization

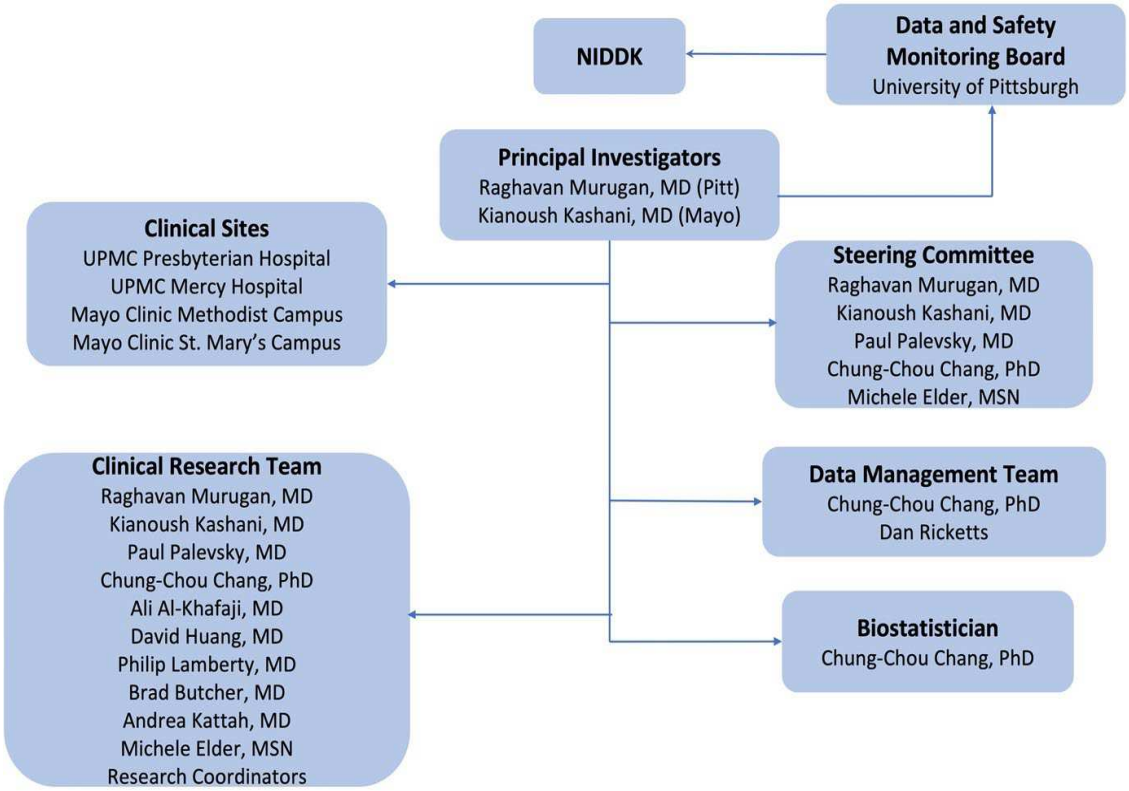

Figure S2: Study Flow Chart

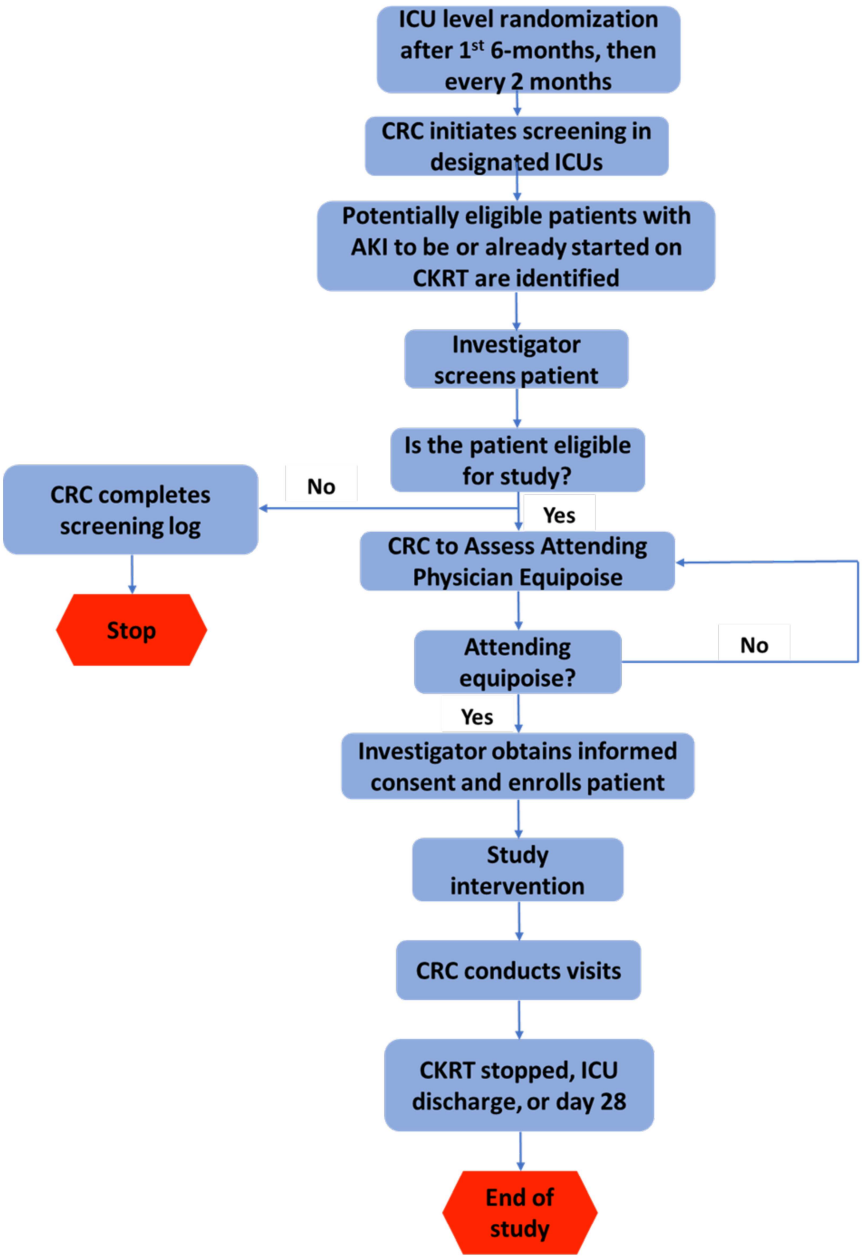

Figure S3: Study Brochure

RELIEVE-AKI

RELIEVE-AKI

Clinical Trial

Brochure

UPMC University of Pittsburgh Medical Center

MAYO CLINIC

RELIEVE-AKI

What is CRRT?

CRRT (continuous renal replacement therapy) is a slower and continuous form of dialysis used in patients whose kidneys do not work properly.

The patient's blood passes through a filter that removes extra fluid and waste materials from the blood.

This machine works continuously during the day and night. This helps patients with low blood pressure to better tolerate this form of dialysis.

RELIEVE-AKI

What is the RELIEVE-AKI clinical trial?

In this research study, we enroll patients undergoing CRRT by their doctors.
This study is comparing two different methods of fluid removal during CRRT. Therefore, if you or your loved one voluntarily participates in this study, we will randomly assign you to one of the two following methods:

Liberal method

Fluid removal will be started slowly and gradually increased to a higher level as tolerated by the patient.

Restrictive method

Fluid removal will be started slowly and gradually increased to a level that is lower than the liberal method.

RELIEVE-AKI

Liberal method

When the CRRT machine removes extra fluid from your body at a slightly faster speed, the body will get rid of fluid overload quickly and decrease body swelling which helps body organs (such as the kidneys) to work properly.

However, you **may** experience some symptoms:

- Low blood pressure
- Irregular heartbeats
- Abnormal levels of blood minerals, such as sodium, potassium, calcium

Rarely, this method **may** cause a clot in the vessels, anemia, low platelets, and cardiac arrest.

There may be other risks that we do not know about yet.

You will be monitored closely by the ICU team and if any risks happen, we will stop this method of fluid removal.

If you do not take part in this study, it will not affect your medical care. Your doctors will plan to remove extra fluids from your body at a speed based on their decision. The risks and benefits mentioned above may still be present.

RELIEVE-AKI

Restrictive method

When the CRRT machine removes extra fluid from your body slowly, you may tolerate it better without the risk of low blood pressure.

However, it **may** build up excess fluid and body swelling, which can affect function of body organs. Other risks include:

- High blood pressure
- Irregular heartbeats
- Persistence of body swelling

Rarely, this method **may** cause impaired wound healing, new infections, breathing difficulties and cardiac arrest.

There may be other risks that we do not know about yet.

You will be monitored closely by the ICU team and if any risks happen, we will stop this method of fluid removal.

If you do not take part in this study, it will not affect your medical care. Your doctors will plan to remove extra fluids from your body at a speed based on their decision. The risks and benefits mentioned above may still be present.

RELIEVE-AKI

If you have questions about RELIEVE-AKI at University of Pittsburgh Medical Center please contact:
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Table S1: Sample Size Analysis

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

Table S2: Time Events Schedule

A. 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[ϕΨ*]		X	X	X	X	X	X	X	X	X	X	X
CKRT parameters[ϕΨ$]		X	X	X	X	X	X	X	X	X	X	X
ABG[*]		A	A	A	A	A	A	A	A	A	A	A
Fluids (intake/output)[*]		X	X	X	X	X	X	X	X	X	X	X
MAP[*]		X	X	X	X	X	X	X	X	X	X	X
CVP, CI, PPV, SVV, and other hemodynamic data[*]		A	A	A	A	A	A	A	A	A	A	A
Hypotensive & Hypertensive episodes[$%]		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

Measurement/Event	Screening	Baseline/ Day 0@	1	2	3	4	5	6	7	8-14	15-21	22-28
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 β*	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
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
$= 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

B. CKRT DATA COLLECTION

Measurement/ Event	Initiation of KRT	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

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

Box S1: Intervention Start-up Procedures

- Ensure mean arterial pressure (MAP) ≥65 mmHg.
- Ensure that the CKRT is operational.
- 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 systolic blood pressure >90 mmHg, no fluid bolus has been administered, no new vasopressor has been started, or the dose of vasopressor increased in the last hour.
- The study investigator or designee following discussion with the attending physician will ensure there are no emergency indications for fluid removal.
- In both arms, UF_{NET} will be initiated within 24 hours of study enrollment.
- 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.
- In the liberal UF_{NET} rate arm, UF_{NET} will be initiated at 0.5 mL/kg/h and gradually increased by 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.
- In both the study arms, the UF_{NET} rate can be decreased or stopped at the discretion of clinicians for hypotension. Following the resolution of hypotension, the UF_{NET} rate can be restarted and increased as tolerated as per the assigned treatment arm.
- 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 the patient).

Box S2: Assessment and Management of Hemodynamic Instability

Hemodynamic Assessment

If hemodynamic instability develops after the initiation of study treatment, we will check the following:

- The patient, the arterial tracing, and heart rate and rhythm are on the monitor to ensure correct reading.
- The UF_{NET} rate on the CKRT machine to ensure that the rate is set correctly.
- The alarms on the CKRT machines.
- The patient does not have obvious bleeding.
- That no new sedative or other medications that cause hypotension has been administered or the existing sedation dose increased in the previous 30 minutes.
- Follow the recommendations for hemodynamic management.

Hemodynamic Instability Management

- Completely stop UF_{NET} (*i.e.,* no net fluid removal)
- Stop or reduce the dose of sedative medication infusion
- Stop or reduce the dose of any medication that is known to cause hypotension
- 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

Box S3: 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. This protocol is recommended for all enrolled patients, to be used until cessation of UF_{NET}.

- Discontinue all maintenance intravenous fluids.
- Double concentrate or use lowest possible volume for all carrier fluids for medications, if possible.
- Continue enteral nutrition and free water flushes.
- Manage electrolytes and blood products per usual practice. For shock, use any combination of fluid boluses and vasopressor(s) to achieve MAP ≥65 mmHg as fast as possible.
- 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.

Box S4: Criteria for Rapid Rescue Net Ultrafiltration

For emergent treatment of refractory hypoxia due to fluid overload or a patient requiring massive volume infusion that requires control of fluid overload, rescue UF_{NET} beyond the study intervention arms is allowed.

- Severe pulmonary edema with PaO2/FiO2 <150 and positive end-expiratory pressure (PEEP) >5 cm H_2O due to fluid overload.
- Respiratory distress due to fluid overload.
- Ongoing hourly volume infusion at a rate higher than the assigned treatment group for more than 6 hours.
- Inability to close surgical wounds due to tissue edema.
- Failing spontaneous breathing trial due to fluid overload at the discretion of the attending intensivist.