Protocol and statistical analysis plan for the REstricted fluid therapy VERsus Standard trEatment in Acute Kidney Injury – REVERSE-AKI randomized controlled pilot trial

Protocol Supplement

1. Study definitions

Intention-to-treat population

All randomized patients with consent to use data in the analysis

Per-protocol population

Intention-to-treat population excluding

1. patients with protocol violations
2. patients discharged from ICU within 48 hrs from randomization

Protocol violation

1. Violated inclusion criteria
2. Violated exclusion criteria
3. Violated stratification variables
4. Use of maintenance fluid (5% glucose-based or crystalloid solutions more than 20 mL/h) in the experimental arm without contraindications for iv/po nutrition

Baseline creatinine

The last outpatient recording within 7-356 days preceding current episode of critical illness. If not available, the lowest creatinine during current hospitalization.

Fluid balance

Total fluid output (urine output, losses to drains, losses from gastrointestinal tract, ultrafiltration by renal replacement therapy) subtracted from total fluid input (intravenous and per oral). Insensible losses will not be considered.

Study day

24-hour period starting from randomization. For example, if patient was randomized on October 17th at 13:00 (1 pm), the first study day is from Oct 17th 13:00 to Oct 18th 13:00 (1 pm).

2. Stratification variables

Randomization will be stratified according to:

#	Criterion	Detailed definition
1.	Presence of fluid overload (YES/NO) a. Peripheral pitting edema AND/OR b. Positive fluid balance AND P/F ratio less than 200 mmHg (26.7kPa)	a or b or both to be present a. mentioned in medical records/ask clinician/check the patient b. the reading from ICU admission at the time of randomization is positive. P/F ratio based on last available data.
2.	Severity of AKI (stage 1 vs. stage 2-3) a. Baseline Cr b. Last Cr before randomization c. Lowest Cr within 48 hrs before randomization d. Urine output less than 0.5ml/kg/h has lasted over 12 hrs	a. **Baseline Cr:** The last outpatient recording within 7-356 days preceding current episode of critical illness. If not available, the lowest Cr during current hospitalization. b. Last obtained value c. This may be the same value as in point b. d. urine output less than 6ml/kg for the previous 12h (with urine catheter in place for the period).

3. Inclusion and exclusion criteria with definitions

3.1 Inclusion criteria

#	Criterion	Detailed definition
1.	18-years or older and admitted to a critical care unit with an arterial line in place	Age on the day of randomization. Critical care unit: a unit where respiratory support (invasive or non-invasive) and haemodynamic support can be provided
2.	The patient has been in critical care for at least 12 hours but no more than 72 hours	Randomization must occur within these time limits
3.	The patient has AKI but is not receiving acute renal replacement therapy (RRT): For the purpose of the study AKI is defined by the following criteria: a. Increase in serum creatinine over 1.5-times above baseline without a decline of 27 umol/l or more from the last preceding measurement (at least 12 hours apart) AND/OR b. Overall urine output less than 0.5ml/kg/h (or 6ml/kg) for the previous 12h (with urine catheter in place for the period)	Either a or b or both must be fulfilled. a. The patient must have at least two available creatinine values. b. Based on the weight recorded at ICU admission preferably by weighting the patient.
4.	The patient is judged by the treating clinician not to be intravascularly hypovolemic	The attending clinician's opinion to be asked before randomization. If necessary, please refer to the site-specific decision algorithm.
5.	The patient is likely to remain in critical care for 48 hours after randomization	The attending clinician's opinion to be asked before randomization.

3.2 Exclusion criteria

Criteria 4, 7, and 11 are dynamic, and, if these change, patient can be reconsidered to be enrolled in the trial given that patient is still otherwise eligible and study randomization window is still open (from 12 to 72 hrs from ICU admission).

#	Criterion	Detailed definition
1.	Active bleeding necessitating transfusion	Clinical signs of active bleeding, patient is transfused, or red cells have been ordered. Patients with a previous bleeding episode that has resolved should not be excluded.
2.	Maintenance fluid therapy is necessary due to diabetic ketoacidosis, non-ketotic coma, severe burns or other clinical reason determined by the medical staff	The attending clinician's opinion to be asked before randomization. Other clinical reasons include post-liver transplant protocols in some institutions.
3.	Need for RRT due to intoxication of a dialyzable toxin	The clinical team is planning (recorded in the medical records or asked directly from the team) commencing RRT any time to remove a dialyzable toxin such as lithium or myoglobin
4.	Commencement of RRT is expected in the next 6 hours	The clinical team is planning (recorded in the medical records or asked directly from the team) commencing RRT within the next 6 hrs from the time of screening. If plans change, and the patient did not commence RRT, patient may be reconsidered for randomization within the study randomization window (12 to 72 hrs from ICU admission) given other eligibility criteria are still ok.
5.	On chronic RRT (maintenance dialysis or renal transplant)	Mentioned in the medical records
6.	Presence or a strong clinical suspicion of parenchymal AKI (for example glomerulonephritis, vasculitis, acute interstitial nephritis) or post-renal obstruction	Mentioned in the medical records or the clinical team has expressed concerns about it. Patients who are admitted post-nephrectomy (within the previous 7 days) are excluded based on this criterion.
7.	Severe hyponatremia (Na <125mmol/L) or hypernatremia (Na >155mmol/L)	The last value before screening. If this resolves during the randomization window (from 12 to 72 hrs from ICU admission), patient may be randomized given that all other criteria are still ok.
8.	Need for extracorporeal membrane oxygenation or molecular absorbent recirculating system (MARS-therapy)	In place or planned
9.	Pregnant or lactating	Condition is known

10.	Patients who are not to receive full active treatment	Limitation of treatment orders that restrict the intensity of interventions are in place
11.	No baseline creatinine available	The patient has only one Cr measurement during the current hospitalization. Later with more Cr measurements, the patient may be reconsidered for randomization within the study randomization window (12 to 72 hrs from ICU admission) given other eligibility criteria are ok.
12.	Lack of consent	Obtaining the approval to randomize the patient that is locally required will not be possible for this patient.

4. Safety issues in the trial

Critically ill patients with AKI will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless the event requires significant intervention or are considered to be of concern in the investigator's clinical judgment.

The potential safety issues related to restricted fluid therapy regimen are likely to stem from too conservative fluid therapy which may potentially result in impaired peripheral and/or organ perfusion and organ ischemia. Restricting fluid input may also lead to higher doses of vasoactive agents, typically noradrenaline. Additionally, interventions used at the discretion of the treating clinician to achieve the fluid balance target in the intervention arm may include increased use of diuretics (typically frusemide) or RRT and ultrafiltration. However, RRT is only commenced if treating clinician perceives it feasible in the clinical context, and accepting that patient cannot achieve the targeted fluid balance is included as an option in the trial intervention.

If fluid management is overzealous, it may lead to increased peripheral, pulmonary and other organ edema, and subsequent organ dysfunction. It may also induce hemodilution that may necessitate transfusion.

4.1 Definitions

Serious adverse event (SAE):
Any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

Serious adverse reaction (SAR):
Any adverse reaction that:

- Results in death
- Is life- threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.

4.2 Reporting

SAEs will be captured in the daily data collection of outcome measures and in the daily SOFA scoring. Patient charts will contain daily registrations of clinical data, which can be obtained on request from the medical authorities.

For this study, a reportable SAE must meet the definition noted above and also be considered:

- an atypical event, defined as clinically significant and unexpected in the context of critical illness secondary to AKI,
  AND
- an event that is at least possibly related to study procedures.

For reportable SAEs that occur from the time of patient enrollment until ICU discharge, the following reporting procedure applies:

- Report using the Adverse Event Form of the eCRF without undue delay of becoming aware of the event.
- Document in source records.

The coordinating center is responsible for reporting the SAEs to health authorities within 7 days at latest the report has been received and performing adequate follow-up.

Local reporting requirements may differ from those of the trial. The local investigator will be responsible for reporting SAEs to their Ethics Board as per institutional requirements.

4.3 Recording

Adverse events related to study interventions are recorded daily during the intervention period as specified in the study safety outcomes. Additionally, the following will be recorded regarding the use of RRT and diuretics (typically frusemide):

Adverse events related to RRT:

1. RRT-associated hypotension
2. Severe hypophosphatemia (<0.5 mmol/L)
3. Severe hypokalemia (<3.0 mmol/L)
4. Severe hypocalcemia (Ionized calcium <0.90 mmol/L)
5. Allergic reaction to RRT
6. Arrhythmia during RRT
7. Seizure
8. Major Bleeding
9. Complication related to central venous access

Serious adverse reactions to frusemide:

1. Loss of hearing
2. Severe disturbances in electrolytes (hypokalemia <3.0 mmol/L, ionized calcium <0.90 mmol/L, hyponatremia <125mmol/L)
3. Severe thrombocytopenia (<50 x 10^9/L)
4. Agranulocytosis
5. Allergic reactions (Rash, anaphylaxis or anything that raises clinical suspicion of an allergic reaction)

4.4 Detailed definitions of safety outcomes

4.2.1 General

1.	Ventricular tachycardia/fibrillation	Requiring interventions
2.	New-onset atrial fibrillation	Requiring medication/defibrillation
3a.	Acute myocardial infarction	acute myocardial infarction (ST-elevation myocardial infarction and non-ST elevation myocardial infarction) OR unstable angina pectoris, according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischaemic signs on ECG, clinical presence) AND the patient receives treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) or initiation/increased antithrombotic drug treatment).
3b.	Cerebral ischemia	verified by CT scan or MRI
3c.	Intestinal ischemia	Verified by endoscopy or open surgery
3d.	Acute peripheral limb ischemia	Clinical signs AND use of open/percutaneous vascular intervention, amputation or initiation/increased antithrombotic treatment.
4.	Radiologically diagnosed pulmonary edema	As stated in the chest x-ray report.
5.	Other safety event	Please describe.

4.2.2 Adverse events associated to RRT

RRT-associated hypotension	Defined as a drop in blood pressure requiring one of: initiation of a vasopressor during RRT session or need to escalate dose of a vasopressor during the session OR premature discontinuation of the RRT session
New-onset arrhythmia during RRT	New ventricular or atrial tachyarrhytmias that develop during RRT
Allergic reaction to RRT	Defined as clinician suspicion of allergic reaction to one or more of the components of the RRT machine
Seizure verified by the clinician related to RRT	

Major bleeding related to RRT	**Bleeding is related to RRT:** patient was receiving systemic anticoagulation and/or there was a major problem with the RRT circuit or vascular access that resulted in major bleeding. **Major bleeding** is defined as any of these: a. Life threatening bleeding and hypovolemic shock (such as ruptured abdominal aortic aneurysm, gastrointestinal bleeding) b. Life threatening bleeding at a critical site (intracranial, pericardial, retroperitoneal for example) c. Clinically important, overt bleeding with one of the following within 24 hrs of the bleed: decrease in hemoglobin > 20 g/l or transfusion of more than 2 packed red cells d. Bleeding at other critical sites such as epidural, intraocular, intra-articular. e. Bleeding requiring an invasive intervention f. (surgery, angiography).
Complication related to **dialysis catheter** - hemorrhage at the insertion site - CVC-associated bloodstream infection - confirmed thrombus related to CVC - pneumothorax related to insertion - hemothorax related to insertion - arterial puncture at the time of insertion - other (please specify) Please only consider double lumen RRT catheter inserted the purpose of RRT (not other lines for other purposes).	-Hemorrhage at the insertion site: Bleeding associated with the insertion of the dialysis catheter that necessitates transfusion of one or more packed red cells OR surgical intervention or repair within 12 hrs of insertion. -CVC-associated blood stream infection: Bacteraemia in 2 culture sets (one from the catheter and one from other site) with no proven alternative source of bacteremia. - confirmed thrombus related to CVC: Ultrasonographically confirmed occlusive or non-occlusive thrombus in the vein where CVC was placed/remains in place, further qualified by embolism as a result of thrombus in further vasculature where the vein is drained. -Pneumothorax related to catheter insertion: Air in pleural space on routine chest xray following the CVC insertion and chest tube placement is necessary. -Arterial puncture at time of dialysis catheter insertion: Described as the clinician and leads to serious complications (such as major bleeding, need for surgery).

5. Data collection

5.1 Baseline data

Demographics:

- Age, sex, race
- Height and weight
- Pre-existing comorbidities
- Chronic medications

Current admission:

- Hospital admission date and time
- Critical care/ICU admission date and time
- Critical care/ICU admission diagnosis (according to APACHE II)
- Variables needed to calculate SAPS II and SOFA scores 24h pre-randomization
- Cumulative fluid balance from ICU admission to randomization
- Cumulative fluid balance pre-ICU (if available)
- Suspected etiology of AKI

5.2 At randomization (the last value within last 2h)

- Hemodynamics (heart rate, mean arterial pressure, central venous pressure, cardiac output)
- Doses of vasoactive drugs
- Acid-base balance and electrolytes (pH, HCO3, lactate, K, Na) and Hb
- Presence of sepsis according to sepsis-3 definition

5.3 Daily data (from randomization to Day 7)

- Severity of AKI
- Hemodynamics (highest heart rate, lowest mean arterial pressure, highest central venous pressure, lowest cardiac output)
- Respiratory variables (respiratory rate, respiratory support, highest PEEP)
- Highest doses of vasoactive drugs (that were administered for at least 1 hour)
- Highest and lowest values of acid-base balance and electrolytes (pH, HCO3, lactate, Hb, hematocrit, K, Na)
- Variables for SOFA score (those not covered above)
- Administered fluids and blood products
- Administered diuretics (various agents, iv and po)
- Use of renal replacement therapy (and if started, indications specified)
- Urine output (mL)
- Ultrafiltation (mL)
- Fluid balance
- Weight
- Clinical signs of fluid accumulation
- Serious adverse events and reactions as specified in Safety outcomes
- Reasons for protocol suspension if any

5.4 Outcomes

- Mechanical ventilation -free days alive (truncated at 14 days)
- Vasopressor-free days alive (truncated at 14 days)
- ICU discharge time and status (dead/alive)
- Date of last dialysis (truncated at 90 days)
- 90-day dialysis dependence
- Time of death (truncated at 90 day

6. Biological samples

Plasma samples will be drawn (from the pre-existing arterial or central venous catheter without need for extra punctures and discomfort for the patient) as soon as possible after randomization, and at 72 hours from randomization. These will be used for later explorative analyses of patient-related changes in biomarkers indicating endothelial damage (such as syndecan-1, angiopoietin-2), AKI and renal recovery that will help to understand the mechanisms of this potentially beneficial intervention. Patients who are discharged earlier, the 72-hour sample may be substituted by a sample taken at ICU discharge. Collected samples will be aliquoted and transferred to Helsinki University Hospital for storage and later analysis.