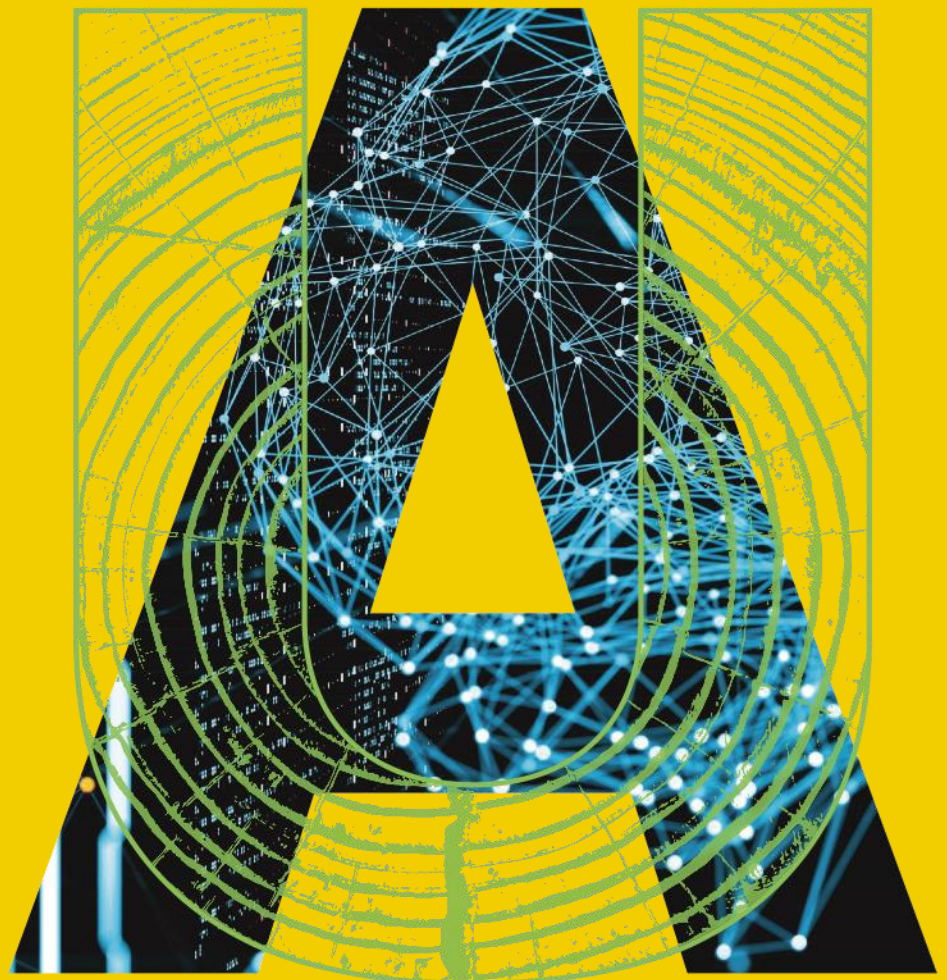
LOW DOSE-INTENSITY VS. STANDARD DOSE-INTENSITY CONTINUOUS RENAL REPLACEMENT THERAPY IN CRITICALLY ILL PATIENTS (WISDOM): A PILOT RANDOMIZED TRIAL

SITE INITIATION AND PROTOCOL TRAINING PRESENTATION



UNIVERSITY OF ALBERTA

Alberta Health Services

ST. MICHAEL'S UNITY HEALTH TORONTO

Outline

1. Introduction – Background, Rationale and Design
2. Screening and Eligibility
3. Good Clinical Practice and Consent Process
4. Randomization
5. CRRT Prescription
6. Endpoints
7. Adverse Events
8. Data collection and Follow-Up

Background

- An estimated 10-15% of critically ill patients with receive renal-replacement therapy (RRT).
- The majority initially receive continuous renal replacement therapy (CRRT).
- The "**dose-intensity**" of CRRT prescribed and delivered to critically ill patients is an important quality indicator and performance measure.

What is CRRT Dose-Intensity?

- Dose-intensity is based solely on the clearance of small solutes in the blood (e.g., urea, potassium, phosphate).
- Dose-intensity for CRRT is a function of the **total effluent flow rate delivered**, defined as the sum of ultrafiltrate +/- spent dialysate, and reported as effluent flow rate in mL per kg of body weight per hour (**mL/kg/hr**).

Dose-Intensity in CRRT

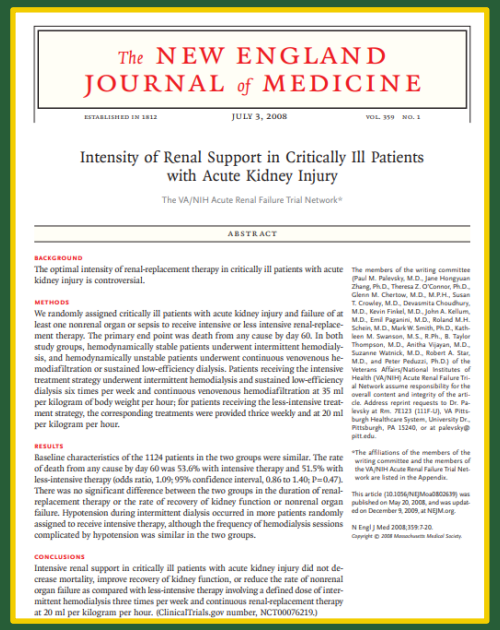
- The "**dose-intensity**" of CRRT is based on **total effluent flow (mL/kg/hr)** and is calculated by:

$$K_{Cr} = \frac{(Q_R^{PRE} + Q_D + Q_{UF}^{NET} + Q_R^{POST})}{B.W.} \cdot \frac{Q_B}{Q_B + Q_R^{PRE}}$$

- Where K_{Cr} = current dose; Q_R = replacement flow rate (pre + post-filter); Q_D = dialysate flow rate; $Q_{NET\ UF}$ = net ultrafiltration); BW = body weight (kg); Q_B = blood flow rate.

What is the Evidence?

ATN/RENAL trials found high dose (**35-40 mL/kg/hr**) did not improve survival relative to low dose (**20-25 mL/kg/hr**)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 3, 2008 VOL. 359 NO. 1

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

ABSTRACT

BACKGROUND

The optimal intensity of renal-replacement therapy in critically ill patients with acute kidney injury is controversial.

METHODS

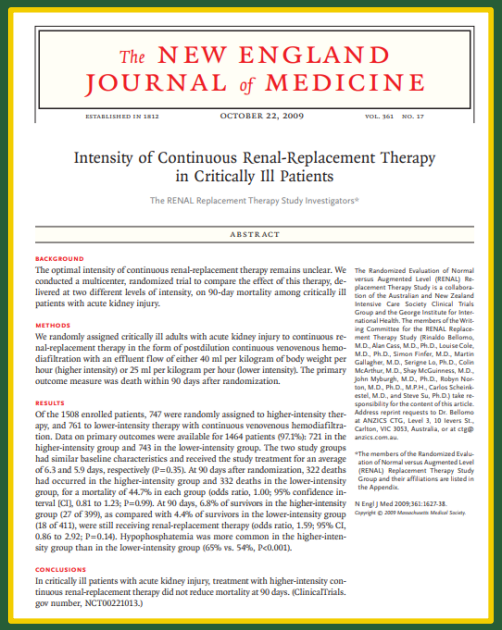
We randomly assigned critically ill patients with acute kidney injury and failure of at least one nonrenal organ or sepsis to receive intensive or less intensive renal-replacement therapy. The primary end point was death from any cause by day 60. In both study groups, hemodynamically stable patients underwent intermittent hemodialysis, and hemodynamically unstable patients underwent continuous venovenous hemodiafiltration or sustained low-efficiency dialysis. Patients receiving the intensive treatment strategy underwent intermittent hemodialysis and sustained low-efficiency dialysis six times per week and continuous venovenous hemodiafiltration at 35 ml per kilogram of body weight per hour; for patients receiving the less-intensive treatment strategy, the corresponding treatments were provided thrice weekly and at 20 ml per kilogram per hour.

RESULTS

Baseline characteristics of the 1124 patients in the two groups were similar. The rate of death from any cause by day 60 was 53.6% with intensive therapy and 51.5% with less-intensive therapy (odds ratio, 1.09; 95% confidence interval, 0.86 to 1.40; P=0.47). There was no significant difference between the two groups in the duration of renal-replacement therapy or the rate of recovery of kidney function or nonrenal organ failure. Hypotension during intermittent dialysis occurred in more patients randomly assigned to receive intensive therapy, although the frequency of hemodialysis sessions complicated by hypotension was similar in the two groups.

CONCLUSIONS

Intensive renal support in critically ill patients with acute kidney injury did not decrease mortality, improve recovery of kidney function, or reduce the rate of nonrenal organ failure as compared with less-intensive therapy involving a defined dose of intermittent hemodialysis three times per week and continuous renal-replacement therapy at 20 ml per kilogram per hour. (ClinicalTrials.gov number, NCT00076219.)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

ABSTRACT

BACKGROUND

The optimal intensity of continuous renal-replacement therapy remains unclear. We conducted a multicenter, randomized trial to compare the effect of this therapy, delivered at two different levels of intensity, on 90-day mortality among critically ill patients with acute kidney injury.

METHODS

We randomly assigned critically ill adults with acute kidney injury to continuous renal-replacement therapy in the form of postdilution continuous venovenous hemodiafiltration with an effluent flow of either 40 ml per kilogram of body weight per hour (higher intensity) or 25 ml per kilogram per hour (lower intensity). The primary outcome measure was death within 90 days after randomization.

RESULTS

Of the 1508 enrolled patients, 747 were randomly assigned to higher-intensity therapy, and 761 to lower-intensity therapy with continuous venovenous hemodiafiltration. Data on primary outcomes were available for 1464 patients (97.1%): 721 in the higher-intensity group and 743 in the lower-intensity group. The two study groups had similar baseline characteristics and received the study treatment for an average of 6.3 and 5.9 days, respectively (P=0.35). At 90 days after randomization, 322 deaths had occurred in the higher-intensity group and 332 deaths in the lower-intensity group, for a mortality of 44.7% in each group (odds ratio, 1.00; 95% confidence interval [CI], 0.81 to 1.23; P=0.99). At 90 days, 6.8% of survivors in the higher-intensity group (27 of 399), as compared with 4.4% of survivors in the lower-intensity group (18 of 411), were still receiving renal-replacement therapy (odds ratio, 1.59; 95% CI, 0.86 to 2.92; P=0.14). Hypophosphatemia was more common in the higher-intensity group than in the lower-intensity group (65% vs. 54%, P<0.001).

CONCLUSIONS

In critically ill patients with acute kidney injury, treatment with higher-intensity continuous renal-replacement therapy did not reduce mortality at 90 days. (ClinicalTrials.gov number, NCT00221013.)

These findings translated to 20-25 mL/kg/hr becoming the *de facto* standard dose-intensity for CRRT.

Renal replacement therapy intensity for acute kidney injury and recovery to dialysis independence: a systematic review and individual patient data meta-analysis

- This IPDMA found no clinically significant differences on mortality or kidney recovery for high vs. with standard dose-intensity RRT.
- However, high dose-intensity RRT had longer RRT duration during the first 28 days of therapy.

Wang Y et al NDT 2018; 33:1017

KDIGO Clinical Practice Guideline for Acute Kidney Injury

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI *(1A)*. This will usually require a higher prescription of effluent volume. *(Not Graded)*

…this would imply that dose-intensity be augmented and that "*a higher prescription*" in the range of **25-30 mL/kg/hr** is needed

https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf

What is Current Practice?

Audit Data from 13 ICUs in Alberta (2023; n=518) and the STARRT-AKI trial (~70% of patients received CRRT) show the range in median delivered CRRT dose-intensity of **26-30 mL/kg/hr** (total effluent flow rate).

Low-dose continuous renal replacement therapy for acute kidney injury

- **Design:** Retrospective cohort study.
- **Setting:** Two academic medical centres from 2007-2010.
- **Population:** 131 adults with AKI receiving CRRT (CVVHDF).
- **Exposure:** CRRT dose-intensity (median).
- **Endpoint:** Hospital and ICU mortality, kidney recovery.

TABLE I - BASELINE CHARACTERISTICS OF THE STUDY POPULATIONS

	Total	Lower-dose	Higher-dose
Number of patients	131	69	62
Male	87 (66%)	52 (75%)	35 (56%)
Age (yrs)	60 (49- 74)	56 (43-74)	63 (53-74)
Body weight (kg)	60.0 (53.0-70.0)	69.8 (60.0-75.6)	55.5 (50-59.4)
APACHE II at ICU admission	26.0 (21.0-34.5)	26.0 (20.7-36.5)	25.0 (21.0-33.5)
Predicted mortality	56% (34-86)	63% (29-89)	56% (34-80)
Presence of sepsis	74 (55%)	41 (59%)	33 (53%)
Post-surgical admission	32 (24%)	18 (26%)	14 (22%)
BUN at CRRT initiation (mg/dl)	39 (30-60)	40 (31-56)	36 (30-63)
Creatinine at CRRT initiation (mg/dl)	2.47 (1.44-3.65)	2.47 (1.52-4.44)	2.48 (1.21-3.33)
Total effluent rate (ml/kg/hr)	16.7 (14.2-20.0)	14.2 (13.0-16.6)	20.0 (18.1-23.0)
Duration of CRRT (days)	4 (2-9)	5 (3-11)	3 (2-9)

The median CRRT dose-intensity delivered was 16.7 mL/kg/hr.

Fugii T et al IJAO 2012;35(7):525-530

TABLE II - PRIMARY AND SECONDARY OUTCOMES

	Total	Lower-dose	Higher-dose	*P values*
Primary outcome				
Hospital mortality	58 (44%)	25 (36%)	33 (53%)	0.055
Secondary outcomes				
ICU mortality	51 (38%)	24 (34%)	27 (43%)	0.37
28-day ICU free days	0 (0-18)	0 (0-12)	0 (0-21)	0.16
Dialysis dependence among survivors	4 (3.0%)	2 (1.5%)	2 (1.5%)	>0.99

TABLE III - MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS FOR HOSPITAL MORTALITY

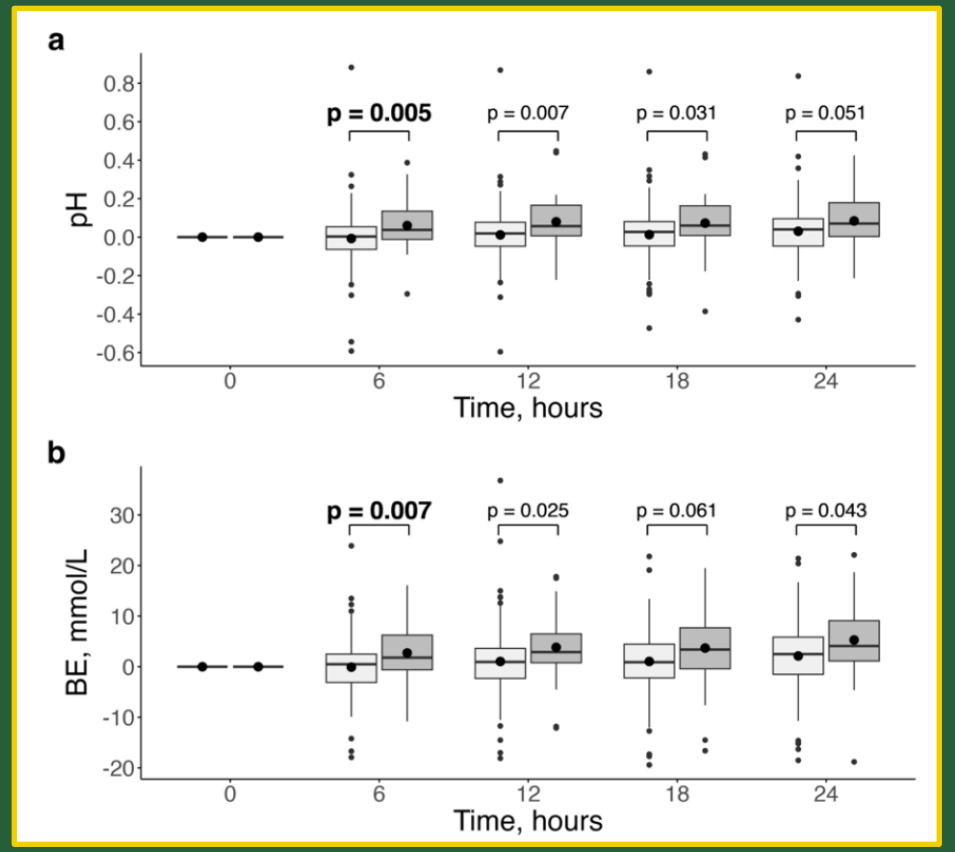
Independent variables	Odds ratios	*P* values
Sex (male)	1.012 (0.458 – 2.233)	0.977
Creatinine, mg/dl	1.018 (0.862 – 1.201)	0.837
BUN, mg/dl	0.982 (0.966 – 0.999)	0.036
APACHE II, per point	0.994 (0.953 – 1.038)	0.798
Emergency operation	0.711 (0.292 – 1.729)	0.452
Dose, ml/kg per hr	1.081 (1.002 – 1.165)	0.043

Fugii T et al IJAO 2012;35(7):525-530

The effects of early-phase, low- or standard- intensity continuous renal replacement therapy on acid-base control and clinical outcomes: An observational study

Yagi K, Fujii T, Kageyama A, Takagi T, Ikeda J, Uezono S

- **Design:** Single-centre, retrospective cohort
- **Setting:** Academic hospital
- **Population:** 194 adult patients receiving acute CRRT.
- **Exposure:** Low-intensity (10-19 mL/kg/hr) or Standard-intensity (> 20 mL/kg/hr) CRRT.
- **Endpoint:** changes in pH, BE and SID, adjusted for acuity, through 24 hr.



Yagi K et al Blood Purification 2024 (DOI: 10.1159/000539810)

WISDOM: What is the Rationale?

1. CRRT is invasive and resource intensive.
2. Higher CRRT dose can prolong oliguria, RRT treatment time and disrupt/delay kidney recovery (i.e., dialytrauma).
3. Higher CRRT dose may worsen non-renal organ support.
4. Lower CRRT dose (14-18 mL/kg/hr) has not shown worse outcomes compared with the guideline-directed standard.
5. Plausibly, after a period of stabilization, the current CRRT dose may be excessive and contribute to unmeasurable harm.
6. Lower CRRT dose may reduce bedside workload; waste and costs.

WISDOM: Primary Study Question

- The WISDOM trial aims to determine, among critically ill patients with AKI receiving CRRT, whether a lower dose-intensity, compared with standard dose-intensity is:
  1. Primarily non-inferior with respect to 90-day all-cause mortality.
  2. Secondarily superior with respect to reducing CRRT duration and improving kidney recovery.
- This pilot phase will specifically evaluate the feasibility of lower versus standard CRRT dose-intensity.

WISDOM Pilot Trial: Design

- **Design:** Pilot, randomized, open-label, parallel-group, blinded-endpoint (PROBE) clinical trial of low vs. standard CRRT dose-intensity.
- **Setting:** 10+ hospitals in Canada, US and UK.
- **Target Sample:** 100 patients.

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Eligibility Criteria - Inclusion

- Eligible patients will be admitted to an ICU and fulfill the following **inclusion criteria**:

  i. Age ≥ 18 years.
  ii. Patient weight ≥ 55 kg.
  iii. Plan to start CRRT or within 24 hours of having started CRRT for AKI.
  iv. Expected to survive and receive CRRT for a duration of ≥ 48 hours.

Eligibility Criteria - Exclusion

- Eligible patients will be admitted to an ICU and have none of the following **exclusion criteria**:

  i. Indication for sustained higher CRRT dose-intensity. (hyperammonemia; TLS; rhabdomyolysis).
  ii. End-stage kidney disease receiving maintenance dialysis.
  iii. Receipt of any RRT for AKI during the current hospitalization.
  iv. Inability to comply with the requirements of the study protocol.

Eligibility Criteria

- In the presence of all **inclusion criteria** and no **exclusion criteria**:

The patient is eligible for participation in WISDOM.

Eligibility Not Enrolled (Form 2)

- An understanding of the reasons that **eligible but not enrolled** patients are excluded can provide important information on equipoise, feasibility and generalizability.
- CRF Form 2 is a minimal dataset to be captured on **eligible but not enrolled** patients.
- Data captured will be non-identifying and include:
  - Age, sex, receipt of IMV; receipt of vasoactive therapy, SOFA score (within 24 hours of eligibility), death in ICU/hospital; receipt of RRT at ICU/hospital discharge; and reasons for exclusion.
  - Reasons for exclusion may include: no consent; clinician refusal (reasons); and missed.

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Good Clinical Practice (GCP)

What is Good Clinical Practice?

"…the ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve participation of human subjects"

Why is it needed?

- Protect participants: *rights, safety* and *well-being*
- Protect clinical trial: *credibility and integrity of data*

All clinical researchers should be familiar with GCP guidance:

- **Consolidated Guideline International Conference on Harmonization (ICH) GCP Topic E6** http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php
- **GCP training** https://gcp.nihtraining.com/

Site Responsibilities

- Protocol compliance.
- Conduct the study under ICH Guidelines for GCP.
- Comply with participant recruitment and protocol timeline expectations.
- Ensure proper and timely Case Report Form (CRF) completion, database entry and proper study documentation (e.g., source documents).
- Maintain up-to-date trial documents as specified in Section 8 of ICH Guideline for GCP - E6 (and per applicable regulatory requirements)

Site Investigator Responsibilities

- Overall responsibility of study conduct at the site:
  - Ensure adequate resources and facilities, and that study personnel are qualified & trained (formally documented on delegation log, availability of up-to-date CVs).
  - Retain study essential documents for 5 years (or longer per institutional REB requirement).
- Protect the safety and well-being of participants:
  - Patients receive proper medical care, confidentiality is maintained.
  - Following proper consenting procedures (i.e., consent SOP).
  - Reporting of SAEs to the sponsor and to local REB.

Data Collection & Source Documentation

Source Document: a document in which data collected for a clinical trial is first recorded. This data is usually later entered in the CRF. The ICH Guideline for GCP (E6 - 1.51 and 1.52) define source documents as "*original documents or certified copies, data, and records*".

All data entered into REDCap must have supporting source documentation.

Proper Source Documentation:

- Accurate, complete, legible, and recorded in a timely manner.
- All changes/corrections are initialed and dated by study team member.
- Corresponds to the data entered in REDCap. Discrepancies can be explained in the source document.

GCP and Informed Consent

ICH Guideline for Good Clinical Practice - E6:

2.9 - Freely given informed consent should be obtained from every subject prior to clinical trial participation

Proper consenting procedures include:

- Use of the current REB-approved version of the consent form
- Consenting prior to procedures (unless otherwise accepted by your REB) with adequate time to review and no coercion.
- Provide signed copy to patients/SDM, original form to be filed.
- Patient/SDM is free to withdraw at anytime.
- Document the informed consent process.

Consent Models for WISDOM

1. Participant has capacity to provide consent.

2. Participant does not have capacity, but a substitute decision maker (SDM) or legally authorized representative (LAR) is available to provide consent.

3. Participant does not have capacity and SDM/LAR is not available → deferred consent process may be used, if approved by the local REB.

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Timeline - After CRRT Initiated…

- From the time of starting CRRT, there are a total of **24 hours** to:

  i. Confirm eligibility,
  ii. Obtain informed consent from the patient or SDM/LAR or documentation of the process of deferred consent (as applicable),
  iii. Randomize the patient, and,
  iv. Start patient on allocated dose-intensity treatment.

Randomization and Data Management

- Patients must be randomized within 24 hours of starting CRRT.
- Randomization will be performed online using a validated web-based randomization system (**REDCap**)
- Randomization will be 1:1 (permuted blocks), stratified by site.
- **Clinical Trials Office (CTO)** at **UAlberta** will serve as the data management and coordinating centre.
- **REDCap** database will also be used for data capture and regulatory essential documents management (WCHRI; UAlberta)

Intervention

Randomization stratified by site

Patients receive a minimum CRRT dose-intensity 25-30 mL/kg/hr x 12 hours

Lower Intensity CRRT
- Target total effluent flow rate of 10-15 mL/kg/hr

Standard Intensity CRRT
- Target total effluent flow rate of 25-30 mL/kg/hr

CRRT continued until death (or WLST), transition to intermittent RRT or kidney recovery (no longer required).

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CRRT Prescription

- All patients will receive a **minimum of 12 hours of standard CRRT (total effluent flow rate ~ 25-30 mL/kg/hr)** prior to commencing allocated CRRT dose-intensity.

- Additional parameters of CRRT prescription/delivery (e.g., catheter site; catheter type; mode [CVVH; CVVHD; CVVHDF]; anticoagulation; ultrafiltration) are based on current best practice and at the discretion of the treating team.

STANDARD Dose-Intensity

- The **Standard** arm will receive a CRRT dose-intensity of **25-30 mL/kg/hr** (total effluent flow rate).
- The Standard CRRT dose-intensity is based on data describing current practice showing this in the range of 26-30 mL/kg/hr.
- This CRRT dose-intensity aligns with current contemporaneous practice and with recommendations in international clinical practice guidelines.

LOWER Dose-Intensity

- The **Lower** arm will receive a CRRT dose-intensity of **10-15 mL/kg/hr** (total effluent flow rate).*

- This Lower CRRT dose-intensity threshold is based on the evidence that 10-15 mL/kg/hr is the lower range of CRRT dose-intensity delivered in clinical practice and has been shown in observational data to be tolerated and safe.

LOWER Dose-Intensity - Mitigation

- If patients are perceived to require a temporary increase in dose-intensity, the following actions are proposed:
  - For persistent hyperkalemia, defined as [K+] > 5.5 mmol/L → lower [K+] in replacement/dialysate solutions.
  - For persistent metabolic acidosis, define as pH <7.25 and/or BE < -10 → add supplementary [HCO3] to replacement/dialysate solutions.
  - For refractoriness to the above or persistent azotemia, defined as sustained (not declining) [urea] > 30 mmol/L → adjust CRRT dose-intensity to the upper limit of dose-intensity (e.g., 15 mL/kg/hr).
- Further increases may be instituted at the discretion of the treating ICU team.
  - Decisions to further modify dose-intensity will be documented as deviations and clinicians will be asked to report the reason.

Trial Discontinuation

- The duration of the trial will continue until any one of the following events occurs:
  - Death
  - Transition to intermittent RRT therapy (e.g., SLED, IHD)
  - Kidney recovery and CRRT weaned

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Primary (Feasibility) Endpoint

- The primary feasibility outcome will be the **difference in delivered effluent flow rate per patient** between the low and standard CRRT dose-intensity groups.
- The pilot trial will **target detection of a minimum difference of 10 mL/kg/hr** in average delivered dose-intensity.
- This will be an important proof-of-concept endpoint for scaling to a larger multi-centre trial.

Secondary Feasibility Endpoints

i. Enrollment rate (target 2 patients/site/month).
ii. Consent rate (target 50% of fully eligible).
iii. Time to randomization (target >75% within 12 hours).
iv. Protocol adherence (target >80% time in allocated dose-intensity range).
v. Capture of delivered CRRT dose-intensity measures (target >95% of daily time-averaged CRRT dose-intensity).
vi. Capture of patient and kidney endpoints at 90-days (target of >95% ascertainment).

Biochemical Endpoints

The biochemical endpoints will assess the tolerability of the intervention and include:

i. Daily serum sodium, bicarbonate, base excess, strong ion difference (SID) and pH while receiving CRRT and number (%) of days without severe acidemia (pH <7.25) (excluding day of randomization).

ii. Daily serum magnesium, potassium, and phosphate while receiving CRRT and number (%) of days without hyperkalemia (K+ >5.5 mmol/L) (excluding day of randomization).

iii. Daily in serum urea while receiving CRRT and number of (%) days without serum urea >35 mmol/L (excluding day of randomization).

Process of Care Endpoints

The process of care measures will assess the fidelity of the intervention and include:

i. Daily lowest/highest CRRT dose-intensity delivered for any given hour.

ii. Total treatment time/day while receiving CRRT. This will be defined as time on treatment divided by 24 hours.

iii. Number of hemofilter/circuit replacements while receiving CRRT.

iv. Total volume of replacement/dialysate fluid used per day and overall.

v. Total number and cumulative doses of supplements given while receiving CRRT.

vi. Mean daily net ultrafiltration (UF_{NET}) delivery while receiving CRRT.

Safety Endpoints

The safety outcomes include:

i. Occurrence of trial-related adverse and serious adverse events.
ii. Occurrence of trial-related adverse events and serious adverse events leading to discontinuation of the trial intervention.

Tertiary Endpoints

The WISDOM pilot trial is not designed to detect differences in patient-centred, kidney-centred or health service-specific outcomes. However, it will measure and describe the following outcomes:

i. Duration of RRT; transition from CRRT to IRRT;

ii. Receipt of RRT at hospital discharge, 30-days and 90-days; and RRT-free days;

iii. ICU mortality; hospital mortality; 90-day mortality;

iv. Major adverse kidney events (MAKE) at 30-days and 90-days;

v. Daily receipt of non-renal organ support (e.g., invasive and non-invasive mechanical ventilation; vasoactive therapy),

vi. Change in estimated glomerular filtration rate (baseline to 90-days),

vii. ICU duration of stay, hospital duration of stay; re-hospitalization.

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Adverse Events (AEs)

- An **adverse event (AE)** is any untoward medical occurrence in a patient administered a "medicinal product" and which does not necessarily have a causal relationship with this treatment.

- Due to this trial being performed in critically ill patients, serious adverse events and death are expected to occur frequently, as such, AE and SAE reporting will follow recommendations set out for trials in this population by Cook and colleagues.

Serious Adverse Events (SAEs)

- A **serious adverse event (SAE)** is defined as any untoward medical occurrence that results in death, is life-threatening, requires hospitalization (overnight or longer), causes prolongation of existing hospitalization, results in persistent or significant disability or incapacity; results in congenital anomaly or birth defect; or other medically important event (is not immediately life-threatening or results in death or hospitalization, but may jeopardize the patient or require intervention to prevent one of the above outcomes).

- SAE will be graded based on **Common Terminology Criteria for Adverse Events (CTCAE) (grade 1-5)** and assigned causality with the intervention **(definite, probable, possible or unlikely related)**.

What to Report

- **Below are the safety events (AEs and SAEs) that should be reported:**
  - Events related to trial participation.
  - Events related to the allocated CRRT dose-intensity.
- **For the WISDOM pilot trial, the SAE definition must be met and also be considered:**
  - An atypical event, defined as clinically significant and unexpected in the context of critical illness, AKI and associated with receiving CRRT, AND;
  - An event that is at least possibly related to study procedures.
- Information related to the AE/SAE are to be captured on a dedicated CRF form.

Reporting Serious Adverse Events

- Collect safety data from **randomization through to CRRT discontinuation, death or the patient is discharged from ICU**, whichever time point occurs first.
  - Report all SAEs **within 1 business day of becoming aware of the SAE** using AE form in eCRF, and document in source.
  - Notify REB as per local requirements.
  - Follow-up for fatal/life-threatening events should happen within 7 calendar days.
  - Follow-up the outcome of SAEs until clinical recovery is complete and laboratory results have returned to baseline (if applicable), or until progression has been stabilized.
  - Follow-up will continue for the duration of the patient's study participation.

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Electronic CRF (REDCap)

- **REDCap (UAlberta, WCHRI, CTO)** will be used for data capture.
- Some advantages of using an eCRF:
  - Randomization automatically generated
  - Reduce data entry time and chances for error (automated checks for errors and omissions)
  - Facilitate data analysis, report data in real or near real time
  - Audit trail is automatically generated
- A **Manual of Procedures (MOP)** has been developed.
  - Detail trial-related data definitions, guidance for data entry

WISDOM Pilot Trial: Team

PI: Sean Bagshaw (bagshaw@ualberta.ca)

PI: Ron Wald (Ron.Wald@unityhealth.to)

Project Manager: Ellen Morrison (ejmorris@ualberta.ca)

Statistician: Fernando Zampieri

Data Management and Coordinating: Clinical Trials Office (UAlberta)

Steering (Management) Committee: First meeting complete.

Patient Partner: D'Arcy Duquette

International Advisors: Dr. Eric Hoste (Belgium), Dr. Antoine Schneider (Switzerland).

UNIVERSITY OF ALBERTA

WISDOM Pilot Trial: Status

- **Trial Status:**
  - Research Ethics Board review (UofA) - approved (Apr 24, 2024 – File # Pro00140224)
  - AHS Administrative review - approved.
  - ClinicalTrials.gov – NCT06446739 – June 6, 2024.
  - Funding – ACT and CIHR (2024 Fall Project) grants
  - Enrollment active (5 sites) – 46 patients enrolled (February 12, 2026).

THANK YOU FOR YOUR ATTENTION!

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Dose-Intensity Trials: VA/NIH ATN & RENAL

	VA/NIH ATN (n=1124)		RENAL (n=1465)	
Dose-Intensity	More	Less	More	Less
Received CRRT, n(%)	397 (70.5)	386 (68.8)	722 (100)	743 (100)
Delivered Dose, mL/kg/hr (mean [SD])	35.8 (6.4)	22.0 (6.1)	33.4 (12.8)	22.0 (17.8)
RRT Duration, days (mean [SD])	7.8 (6.4)	7.3 (5.9)	13.0 (20.8)	11.5 (18.0)
Primary Outcome:				
Death at 60/90-days, n(%)	302 (53.6)	289 (51.5)	322 (44.7)	332 (44.7)
Renal Recovery:				
RRT Dependent at 60/90 days, n(%)	85 (15.4)	102 (18.4)	27 (6.8)	18 (4.4)
RRT-free days, days (mean [SD])	6.0 (0.4)	7.0 (0.4)	-	-
Adverse events, n(%)				
Hypophosphatemia	99 (17.6)	61 (10.9)	461 (65.1)	396 (54.0)
Hypotension (requiring vasopressors)	81 (14.4)	56 (10.0)	-	-

1. Participant Informed Consent

- The modified Aid to Capacity Evaluation (ACE) is recommended as a guideline to assess participant capacity.

- Includes a hierarchy of questions starting with *"Is the patient able to communicate?"* and leading up to *"Does the patient have the ability to make a decision that is not substantially based upon hallucinations, delusions, or cognitive signs of depression?"*

- A consent checklist can be used to confirm the participant understands what participation in the research study entails and to document the process (i.e., consent SOP).

2. SDM/LAR Consent

- Consent may be sought from an SDM/LAR if a participant is incapacitated.
- The consent SOP can again be used to confirm that the SDM clearly understands what is being asked of them.
- When enrolment is based on SDM consent, the participant's capacity should be reassessed every 72 hours at a minimum and documented on the consent log → the participant should be consented once capacity is regained, as applicable by local REB.

3. Deferred Consent Process

- Deferred consent must be approved by the local REB (may not be approved at all sites).
- Re-evaluate participant capacity at least every 72 hours and further attempts should be made to contact an SDM/LAR, both of which should be documented on the consent log.
- Even if an SDM/LAR authorizes continuation in the trial after initial deferred consent, participant consent should ideally still be sought once capacity is regained, as applicable by local REB.