CLINICAL TRIAL PROTOCOL

LoW Dose-Intensity vs. Standard Dose-Intensity COntinuous Renal ReplaceMent Therapy in Critically Ill Patients (WISDOM): A Pilot Randomized Trial

Short Protocol Title: WISDOM

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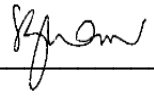
SPONSOR STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the International Council on Harmonisation Good Clinical Practice (ICH GCP) E6, the conditions of ethics committee approval at each participating site and the Tri-Council Policy Statement (TCPS) on Ethical Conduct for Research Involving Humans-2 (2022) (Available at: https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2022.html).

Name of Study Principal Investigator (Print): __*Sean M Bagshaw*__

Signature of Study Principal Investigator: 

Date: __25 September 2024__
<DD Month YYYY>

Name of Study Principal Investigator (Print): __*Ron Wald*__

Signature of Study Principal Investigator: 

Date: __25 September 2024__
<DD Month YYYY>

SITE STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with this protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) E6 and applicable local regulatory requirements. The Site Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Research Ethics Board (REB), except where necessary to eliminate (an) immediate hazard(s) to the trial participants.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Name of Site Principal Investigator (Print): _____

Signature of Site Principal Investigator: _____

Date: _____
<DD MMM YYYY>

Site: _____

ABBREVIATIONS

AAA	abdominal aortic aneurysm
ACT	Accelerating Clinical Trials
AE	adverse event
AHS	Alberta Health Services
AKI	acute kidney injury
Ca(+)	calcium
CI	confidence interval
CIHR	Canadian Institutes of Health Research
Co-PI	Co-Principal Investigator
CPG	Clinical Practice Guidelines
CRF	case report form
CRRT	continuous renal replacement therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
CV	curriculum vitae
CVVH	continuous veno-venous hemofiltration
CVVHD	continuous veno-venous hemodialysis
CVVHDF	continuous veno-venous hemodiafiltration
DW	Dialyzing Wisely
eCRF	electronic case report form
EDC	electronic data capture
GCP	Good Clinical Practice
GI	gastrointestinal
$HCO_3(-)$	bicarbonate
HDRN	Human Data Research Network
Hgb	hemoglobin
hr	hour
ICH	International Council of Harmonization
ICU	intensive care unit
IRRT	intermittent renal replacement therapy
K(+)	potassium
KDIGO	Kidney Disease: Improving Global Outcomes
Kg	kilogram
MAKE	major adverse kidney event
MG(+)	magnesium
mL	millilitre
MOP	manual of procedures
MRP	most responsible physician
NAS	Nursing Activities Score
PI	Principal Investigator
$PO_4(-)$	phosphate
PROBE	prospective, randomized, open-label, blinded endpoint
PWLE	people with lived experience
RBC	red blood cells
RCT	randomized controlled trial

REB	research ethics board
REDCap	Research Electronic Data Capture
RRT	renal replacement therapy
SAE	serious adverse event
SC	steering committee
SD	standard deviation
SDM	surrogate decision-maker
SID	strong ion difference
SIV	site initiation visit
$SOFA_{cv}$	Sequential Organ Failure Assessment (cardiovascular)
SOP	standard operating procedure
TCPS2	Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans – 2 (2022)
UF_{NET}	net ultrafiltration
VA/NIH	Veterans Affairs/National Institutes of Health
WCHRI	Women and Children's Health Research Institute

SUMMARY

Section	
Title:	**LoW Dose-Intensity vs. Standard Dose-Intensity COntinuous Renal ReplaceMent Therapy in Critically Ill Patients (WISDOM): A Pilot Randomized Trial**
Background:	An estimated 12-15% of critically ill patients receive RRT for acute kidney injury, the majority of whom initially receive continuous renal replacement therapy (CRRT). The 2012 *Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines (CPG) for* AKI recommend delivering a CRRT dose-intensity of 20-25 mL/kg/hr. This recommendation is derived from prior RCTs evaluating higher dose-intensity (35-40 mL/kg/hr vs. 20-25 mL/kg/hr) that have not shown any survival advantage. These findings translated to a dose-intensity of 20-25 mL/kg/hr becoming the *de facto* dose-intensity standard for patients receiving CRRT. In addition, because epidemiologic studies describing CRRT dose-intensity practices have consistently found that the "delivered" dose-intensity was often less than "prescribed" (only ~75-90%), usually due to therapy interruptions (i.e., circuit clotting; diagnostic imaging; minor surgical procedures), the 2012 KDIGO CPGs suggest that dose-intensity augmentation is required and that "*a higher prescription"* in the range of 25-30 mL/kg/hr is needed. The current practice, based on data from ICUs in Alberta, Canada and sites that participated in the international STARRT-AKI trial shows the range in median delivered CRRT dose-intensity is 26-30 mL/kg/hr. To date, no RCT has focused on evaluating or defining a minimally acceptable and safe CRRT dose-intensity threshold. Specifically, it is not clear whether a lower dose-intensity (10-15 mL/kg/hr) may be equally acceptable or even superior to the current guideline-directed standard (25-30 mL/kg/hr).
Objective:	The WISDOM research program aims to address whether a lower CRRT dose-intensity (10-15 mL/kg/hr) in critically ill patients with AKI is non-inferior for 90-day mortality compared to the current guideline-directed standard CRRT dose-intensity (25-30 mL/kg/hr) and will secondarily determine if lower CRRT dose-intensity can shorten RRT duration and improve kidney recovery versus the guideline-directed standard.
Study Design:	Multi-centre prospective, randomized, open-label, blinded endpoint (PROBE) pilot trial in adult ICU patients with AKI receiving CRRT.
Population:	ICU patients with AKI in whom the clinical team has decided to start CRRT or who are within 24 hours of having started CRRT will be potentially eligible. Each patient will fulfill all inclusion and have no exclusion criteria.
Eligibility:	Inclusion criteria:

	i) age ≥ 18 years, ii) patient weight ≥ 55 kg iii) plan to initiate CRRT or within 24 hours of having started CRRT for acute kidney injury (AKI) iv) expected to survive and receive CRRT for a duration of ≥ 48 hours v) able to consent or have an authorized representative consent after being informed on the details and risks of participation, unless a deferred consent process is approved by local REB. Exclusion criteria: i) indication for sustained higher dose-intensity CRRT as designated by the attending clinician(s) 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.
Intervention:	The *experimental arm* will be lower CRRT dose-intensity, defined as a delivered effluent flow rate of **10-15 mL/kg/hr**. The rationale for this lower dose-intensity is based on the observed lower threshold of dose-intensity currently delivered in clinical practice and observational data showing that this threshold may be acceptable, tolerated and safe. The *control arm* will be guideline-directed standard CRRT dose-intensity, defined as delivered effluent flow rate of **25-30 mL/kg/hr**. The standard dose-intensity is aligned with current practice and by recommendations from international CPGs.[5] The current standard of care for CRRT dose-intensity provided in ICUs in Alberta and across the sites that participated in STARRT-AKI (39 Canadian sites) ranges between 26-30 mL/kg/hr. The CRRT dose calculation will use measured or estimated actual body weight, as previously described and recommended by CPGs. All enrolled patients will receive an active run-in period of standard dose-intensity of up to 24 hours (minimum 12 hours) to ensure initial metabolic and azotemic stabilization.
Outcomes:	
Primary Endpoint	The primary feasibility endpoint is the difference (95% CI) in the total delivered effluent flow rate per patient between those in the lower and standard CRRT dose-intensity groups. The WISDOM pilot trial will target the detection of a minimum difference of 10 mL/kg/hr in average delivered dose-intensity between the groups.
Secondary Endpoints	The secondary feasibility endpoints are: i) Ability to enroll an average of two patients per site per month. ii) Consent rate for participation by patient or surrogate decision-maker (SDM).

	iii) Time from eligibility (e.g., starting RRT) to randomization. iv) Protocol adherence for allocated CRRT dose-intensity. v) Ability to capture delivered CRRT dose-intensity measures. vi) Ability to capture patient and kidney endpoints at 90-days.
Biochemical Endpoints	The secondary biochemical endpoints are: i) daily serum sodium, bicarbonate, base excess, strong ion difference (SID) and pH while receiving CRRT. ii) daily serum magnesium, potassium, and phosphate while receiving CRRT. iii) daily serum urea while receiving CRRT.
Process of Care Endpoints	The process of care measures are: i) The lowest/highest CRRT dose-intensity delivered for any given hour following randomization. ii) The proportion of hours of CRRT when the dose-intensity is in the target range following randomization. iii) The total treatment time per day while receiving CRRT following randomization. iv) The number of hemofilter/circuit replacements while receiving CRRT following randomization. v) The total volume of replacement/dialysate fluid used per day following randomization. vi) The number and cumulative dose of supplementary electrolytes, protein and vitamins administered while receiving CRRT. vii) modified daily bedside (nursing) activity score, as a measure of nursing bedside workload, while receiving CRRT following randomization. viii) The mean daily net ultrafiltration (UF_{NET}) delivery while receiving CRRT following randomization.
Safety	The safety endpoints are: i) occurrence of trial-related adverse and serious adverse events. ii) occurrence of adverse events and serious adverse events leading to discontinuation of the trial intervention.
Tertiary Endpoints	The trial will measure and describe selected outcomes, including: duration of RRT; transition from CRRT to IRRT; receipt of RRT at hospital discharge, 30-days and 90-days; RRT-free days at 90-days; ICU mortality; hospital mortality; 90-day mortality; a composite of major adverse kidney events (MAKE) at 30-days and 90-days; change in estimated glomerular filtration rate (baseline to 90-days), daily receipt of non-renal organ support, ICU duration of stay, hospital duration of stay and re-hospitalization within 90-days.

Sample Size Estimation:	The sample size for the WISDOM pilot trial will address the detection of a minimum difference in the delivered dose-intensity of CRRT between the groups. Based on the ability to detect a minimum difference of 10 mL/kg/hr in dose-intensity, assuming the delivery of 25 mL/kg/hr in the standard dose-intensity group and 15 mL/kg/hr in the lower dose-intensity group, with a conservative standard deviation (SD) of 15, 90% power, and an alpha of 0.05, a total sample of 96 patients is needed (48 patients per group). This will be inflated to 100 patients to account for any withdrawal or dropout.
Registration:	Clinicaltrials.gov: NCT06446739 (June 6, 2024)

1. ADMINISTRATIVE INFORMATION

1.1 Lay Title

Low vs. Standard Dose-Intensity CRRT in Critically Ill Patients: A protocol for a pilot, randomized controlled trial comparing lower dose-intensity to standard dose-intensity continuous renal replacement therapy (CRRT) in adult patients in the intensive care unit (ICU).

1.2 Trial Registration

The trial is registered on ClinicalTrials.gov (https://clinicaltrials.gov/) – NCT06446739 (June 6, 2024).

1.3 Protocol Version

Version 2.0

1.4 Funding

ACT/HDRN (CIHR). Additional applications for funding are in progress.

1.5 Roles and Responsibilities

1.5.1 Study Principal Investigators

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1.5.2 Steering Committee

The Steering Committee is responsible for providing overall oversight of the WISDOM trial. Its membership includes the study co-chairs and other individuals with specialized knowledge in critical care and experience in running, and oversight of, clinical trials.

The Steering Committee will be accountable for the:

- Design and conduct of the study;
- Preparation of the essential study documents, including the protocol, protocol amendments, manuals and data collection forms;

- Review of data collection practices and procedures;
- Monitoring recruitment and retention of study participants;
- Modifications in study procedures, as appropriate;
- Allocation of resources based on priorities of competing study demands;
- Review of study progress in reaching goals and appropriate actions to ensuring the likelihood of achieving those goals.

A list of the Steering Committee members will be maintained in the Manual of Procedures and updated as needed.

1.5.3 Trial Statistician

Statistician	Contact	Role
Fernando Zampieri	E: fzampier@ualberta.ca	Statistician

1.5.4 Project Manager

Project Manager	Contact	Role
Ellen Morrison	E: ejmorris@ualberta.ca	Project Manager

1.5.5 Coordinating and data management centre

The Clinical Trials Office (CTO), Faculty of Medicine and Dentistry, University of Alberta will act as the coordinating and data management centre for this phase of the trial.

2. INTRODUCTION – THE NEED FOR A TRIAL

2.1 Background - what is the problem to be addressed?

Acutely ill patients admitted to the intensive care unit (ICU) are frequently exposed to a spectrum of risk factors for development of acute kidney injury (AKI).[1, 2] In those patients with more severe AKI characterized by azotemic, metabolic, acid-base and fluid complications that are generally refractory to medical therapy, renal replacement therapy (RRT) is often initiated.[3] An estimated 12-15% of critically ill patients receive RRT; however, this can exceed 20% in those with septic or cardiogenic shock.[1] Across high- and middle-income countries, most critically ill patients (>70%) will initially receive acute RRT in the form of continuous renal replacement therapy (CRRT).[4]

CRRT has several important aims in the contect of AKI: i) achieve and maintain fluid, electrolyte, acid-base homeostasis; ii) achieve and maintain toxic/metabolic solute homeostasis; iii) facilitate life support interventions as indicated (e.g., nutrition, medications, transfusions); and iv) mitigate the hazards of severe complications attributable to AKI (i.e., hyperkalemia; acidemia, pulmonary edema).[5] RRT can also theoretically act as a broader platform to support multiple organs in critical illness, potentially mitigating the non-kidney organ dysfunction that may be exacerbated by severe persistent AKI and aid in facilitating weaning of organ support (e.g., invasive mechanical ventilation).[6]

To date, several aspects of acute RRT have been the focus of randomized controlled trials (RCTs), some having informed specific recommendations for acute RRT in the 2012 KDIGO clinical practice guidelines (CPGs) for AKI[7], and these include the optimal selection and timing of RRT initiation (early vs. delayed)[8-11], selection of RRT modality (continuous vs. intermittent)[12-14], regimens for anticoagulation (heparin vs. citrate)[15, 16], and delivered dose-intensity (standard vs. high-intensity).[17-22]

The 2012 KDIGO CPGs (Chapter 5.8) currently "recommend delivering an effluent volume of 20-25 mL/kg/hr for CRRT in AKI" (1A recommendation) and further suggest that "this will usually require a higher prescription of effluent volume" (not graded)[7]. Several small, single-center trials had variably suggested that higher dose-intensity of CRRT was associated with improved outcomes in critically ill patients with severe AKI.[19, 20, 22] In the landmark single centre RCT by Ronco and colleagues, survival at 15 days following CRRT discontinuation was compared among patients allocated to effluent flow rates of 20 mL/kg/hr, 35 mL/kg/hr and 45 mL/kg/hr, respectively.[22] Survival was found to be lowest among patients allocated to 20 mL/kg/hr. The publication of this RCT translated into widespread adoption of a minimum CRRT dose-intensity effluent rate of 35 mL/kg/hr.

However, this finding was not replicated in two large high-quality multicenter RCTs.[17, 18] In the VA/NIH ATN study, performed in centres in the US, CRRT was predominantly used in patients with hemodynamic instability.[18] Patients were randomized to pre-dilution continuous veno-venous hemo-diafiltration (CVVHDF) either dosed at an effluent flow rate of 20 mL/kg/hr in the lower dose-intensity arm or 35 mL/kg/hr in the higher dose-intensity arm. In the RENAL study, performed in centres across Australia and New Zealand, patients were randomized to CVVHDF either at an effluent flow rate of 25 mL/kg/hr in the less dose-intensive arm or 40 mL/kg/hr in the more dose-intensive arm.[17] In both dose-intensity groups, the delivered dose was split equally between dialysate and post-dilution hemofiltration. Neither study detected differences in survival or kidney recovery from the higher dose-intensity CRRT, including across several subgroup analyses (e.g., sepsis). Notably, both RCTs found that the delivered dose-intensity was often less than the prescribed dose-intensity. Based on the findings from these two rigorous RCTs, the 2012 KDIGO CPGs recommended a minimum CRRT dose-intensity of 20-25 mL/kg/hr.[7] Moreover, the finding that delivered dose-intensity was frequently below prescribed, contributed to further suggestions that careful attention should be given to ensuring that the target dose-intensity is monitored and actually delivered, while need to further augment the CRRT prescription to 25-30 mL/kg/hr is needed. This de facto threshold dose-intensity of 25-30 mL/kg/hr advocated by the KDIGO CPGs has not been the focus of rigorous evaluation in a RCT.[23]

2.2 Why is the trial needed now?

No RCT to date has specifically evaluated the lower dose-intensity threshold for critically ill patients receiving CRRT though two pilot trials are ongoing (Clinicaltrials.gov: NCT6021288 and NCT06014801).

Overall, there has been no specific evidence or guidance on the minimum dose-intensity targets for patients receiving CRRT. This is important for several reasons. First, CRRT is an invasive, resource intensive and expensive therapy.[6] As such, there should be a concerted effort to minimize time on RRT and facilitate early recovery and weaning. Second, abundant evidence derived from secondary analyses have suggested that higher CRRT dose-intensity can propagate oliguria, prolong the need for CRRT and disrupt and delay kidney recovery.[21, 24] This would imply that lower dose-intensity may facilitate kidney recovery and earlier weaning from RRT. Third, evidence has emerged that higher dose-intensity may have non-renal organ support implications, such as risk of cardiac arrhythmias and delayed weaning from invasive mechanical ventilation.[25] Fourth, evidence derived from observational registries has shown that lower CRRT dose-intensity (~10-18 mL/kg/hr), aligned with the lower CRRT dose-intensity proposed herein, can provide comparable efficacy for azotemic, metabolic and acid-base control.[26-28] Observational data have suggested a prescribed CRRT dose-intensity of 15 mL/kg/hr is not associated with worse outcomes compared with guideline directed dose-intensity.[27, 28] This is lower quality evidence, however, implies that lower dose-intensity may be acceptable and safe. Fifth, it is plausible that following a short period of metabolic stabilization with CRRT (~12-24 hours), the minimum CRRT dose-intensity threshold currently recommended is excessive and has the potential for unmeasurable harm (e.g., excess removal of electrolytes, micronutrients, and medications [antimicrobials; antiepileptics; etc.]). Patients receiving CRRT for sustained periods of time (>48 hours) routinely require supplementation to replace the loss of electrolytes, protein and vitamins. Finally, a lower CRRT dose-intensity may have a meaningful impact on reducing bedside nursing workload (e.g., fewer replacement solution bag changes; less need for supplementation); reducing avoidable waste (e.g., reduce carbon footprint) and reducing costs attributable to CRRT (e.g., reducing total volume of replacement/dialysate solutions; shortening total CRRT duration)..[29]

2.3 How will the results of this trial be used?

While this proposal outlines a pilot feasibility trial, it is aimed at performing a larger rigorous RCT that will generate generalizable and high-quality evidence to impact clinical practice. The findings of the main phase of the WISDOM trial program will provide clearer evidence to guide the prescription of a minimal dose-intensity for patients receiving CRRT. Current practice in Alberta for the prescription of CRRT is variable. Based on data from October 1, 2023 to December 31, 2023, there were 518 patients receiving CRRT

across Alberta (2,790 CRRT-days; average 5.4 days per patient) and an estimated 77% of these patients receiving CRRT fulfilled the criteria for AKI. Our team has implemented a provincial program, Dialyzing Wisely (DW), to monitor and report key performance and quality indicators of CRRT, aimed at implementing evidence-formed best practices and minimizing unnecessary variations in practice.[30] A key measure this program has implemented is the dose-intensity delivered to patients receiving CRRT. Currently estimates from this audit show a mean (SD) effluent rate of 27.7 mL/kg/hr (SD 15; min 11; max 91) for patients receiving CRRT. This would imply there are currently variations in practice and that a meaningful proportion of patients are receiving less than the current guideline directed recommended dose-intensity. The Dialyzing Wisely platform provides key infrastructure to implement, measure process and outcome data, and disseminate the findings from this trial. Moreover, the findings from this trial can be immediately implemented into clinical practice, including into provincial standardized CRRT order sets, and used to establish revised dose-intensity targets for reporting in the Dialyzing Wisely program. Furthermore, if the main phase trial establishes that lower dose-intensity is acceptable and safe with no clinically meaningful differences in patient-centred or health service outcomes, the lower dose-intensity would become the current default standard and inform clinical practice guidelines for CRRT management worldwide.

2.4 Are there any risks to the participants involved in the trial?

Critically ill patients with AKI who are started on CRRT and enrolled in this trial are unlikely to encounter incremental risk beyond that experienced in the ICU.[26, 27] This trial will measure adverse and serious adverse events to ensure patients are exposed to minimal risk in the trial.

2.5 Objectives

The overall WISDOM trial program will address whether a lower CRRT dose-intensity in critically ill patients with AKI is non-inferior to standard CRRT dose-intensity and will secondarily address whether lower CRRT dose intensity will shorten total CRRT duration and improve kidney recovery compared with standard CRRT dose-intensity. This pilot trial will specifically evaluate the feasibility of lower versus standard CRRT dose-intensity.

3. METHODS: PARTICIPANTS, INTERNVENTIONS, AND OUTCOMES

3.1 Trial Design

This LoW Dose-Intensity vs. Standard Dose-Intensity COntinuous Renal ReplaceMent Therapy in Critically Ill Patients (WISDOM) trial is a multicentre prospective, randomized, open-label, blinded endpoint (PROBE) pilot trial in adult ICU patients with AKI receiving CRRT.

3.2 Study Setting

The WISDOM pilot trial will take place at sites across Canada and internationally, most of which participated in the international STARRT-AKI trial.[10] These will include a spectrum of academic/teaching and community ICU sites.

3.3 Eligibility Criteria

Patients who are admitted to an ICU and are prescribed CRRT will be potentially eligible and will be identified through local site processes. Each patient will be further assessed for the presence of all inclusion and exclusion criteria. Those patients fulfilling eligibility will be approached (most often this will be an authorized representative or surrogate decision-maker [SDM]) by a member of the treating ICU team and/or a research coordinator to invite participation and obtain informed consent. Each patient or SDM will be provided an information sheet with details of the trial and a copy of the consent form. Consent will be sought from all patients for linkage to routinely collected administrative health data to measure long-term outcomes and to contact patients or SDMs for information related to the outcome of the trial.

3.3.1 Inclusion Criteria

Eligible patients will be admitted to an intensive care unit and fulfill the following inclusion criteria:

i) age ≥ 18 years
ii) patient weight ≥ 55 kg
iii) plan to initiate CRRT or within 24 hours of having started CRRT for AKI
iv) expected to survive and receive CRRT for a duration of ≥ 48 hours
v) able to provide informed consent or have an authorized representative provide consent after being informed of the details and risks of the trial unless a deferred consent process is approved by the local Research Ethics Board (REB).

3.3.2 Exclusion Criteria

At the time of screening, any of the following criteria will result in exclusion:

i) indication for sustained higher dose-intensity CRRT as designated by the attending clinician(s)
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

This trial does not restrict co-enrollment on other clinical trials unless the intervention in the other trial is perceived to interact with the WISDOM interventions. This will be determined by the PIs.

3.4 Interventions

3.4.1 Study Interventions

All enrolled patients will receive the standard dose-intensity for a maximum of 24 hours and a minimum of 12 hours from the time CRRT is started (not the time of enrollment and randomization) to ensure initial metabolic and azotemic stabilization.

The *experimental arm* will be lower CRRT dose-intensity, defined by a delivered effluent flow rate of **10-15 mL/kg/hr**. The rationale for this lower dose-intensity is based on the observed lower threshold currently delivered in clinical practice and observational data showing that this threshold is acceptable, tolerated and safe.[26-28] The *control arm* will be guideline-directed standard CRRT dose-intensity, defined by a delivered effluent flow rate of **25-30 mL/kg/hr**. The standard dose-intensity aligns with current practice and by recommendations from international CPGs.[31] The standard of care for CRRT dose-intensity provided in ICUs in Alberta in a recent audit and across participating sites in STARRT-AKI (39 Canadian sites) ranged between 26-30 mL/kg/hr. The dose calculation will utilize measured or estimated actual body weight.

3.4.2 Criteria for discontinuing or modifying allocated interventions

The duration of the intervention will be until CRRT is discontinued due to any of patient death, transition to intermittent RRT (IRRT) or due to kidney recovery with no further requirement for RRT. Transition to IRRT will align with current best practices and align with local standards of care. This will generally occur following hemodynamic stabilization and weaning of vasoactive support (i.e., $SOFA_{CV}$ score <2). Ultimate decisions about transitions to IRRT will be made by the local attending physicians. If during their ICU admission a patient has their CRRT temporarily interrupted (e.g., diagnostic imaging or other investigations; procedures or operations), once restarted, the CRRT will be prescribed according to their allocated dose-intensity. If a patient has prolonged CRRT interruption (>6 hours) (e.g., operative theatre), CRRT will be temporarily restarted at the standard dose-intensity for 6 hours to ensure a period of stabilization, then transitioned to their allocated CRRT dose-intensity, as applicable.

If patients are perceived by the treating ICU team to require a temporary increase in dose-intensity to augment acid-base/metabolic/azotemic control due to critical illness, the following actions should be followed in hierarchical order:

i) For patients with persistent hyperkalemia, defined as [K+] > 5.5 mmol/L at 24 hours after randomization, the treating ICU team can lower the potassium [K+] concentration in the replacement/dialysis solutions, as per ICU-specific protocols.

ii) For patients with persistent metabolic acidosis, defined as pH <7.25 and BE < -10 at 24 hours after randomization, the treating ICU team can add supplementary bicarbonate (HCO3) either as a continuous infusion or bicarbonate can be added to the replacement/dialysate solutions, as per ICU-specific protocols.

iii) For patients who are refractory to the above modifications to the prescribed CRRT or those who have persistent azotemia, defined as [urea] >30 mmol/L at 24 hours after randomization, the treating ICU team can adjust the dose-intensity to the upper limit of dose-intensity within the allocation. For example, in those patients allocated to the low dose-intensity group (target 10 mL/kg/hr), adjust the prescribed dose to 15 mL/kg/hr.

If patients have their CRRT dose-intensity prescription further modified outside their allocated dose-intensity (e.g., a patient allocated to 10-15 mL/kg/hr is increased to >15 mL/kg/hr) for reasons not specified above, this will be considered a protocol deviation. The reason for the dose-intensity modification must be documented and will be classified as: i) inadequate acid-base control; ii) inadequate electrolyte control; iii) inadequate azotemic/metabolic control; and iv) other (describe).

3.4.3 Strategies to improve protocol adherence

The study principal investigators and site principal investigators will be responsible for education about the trial and training clinicians and research staff. Trial interventions will utilize local standardized CRRT order sets.

3.4.4 Cointerventions

Additional aspects of CRRT, including timing, catheter insertion site, selection of clearance mode (e.g., CVVH, CVVHD, CVVHDF), anticoagulation strategy, and net ultrafiltration rate (e.g., total fluid removal rate) will be independent of the allocated intervention and based on the principles of standard best practices and at the discretion of the responsible clinical team.[31] These aspects of the delivery of CRRT will be recorded and reported, as applicable. The management of critical illness, including but not limited to hemodynamic support, ventilatory support, fluid resuscitation and therapy, nutrition, rehabilitation, and medications will also be at the discretion of the responsible clinical team.

3.5 Outcomes

3.5.1 Primary Endpoint

The primary feasibility endpoint is the difference (95% CI) in the total delivered effluent flow rate per patient between those in the lower and standard CRRT dose-intensity groups. The WISDOM pilot trial will target the detection of a minimum difference of 10

mL/kg/hr in average delivered dose-intensity between the groups. This will be an important proof-of-concept endpoint to inform the feasibility of a larger multi-centre trial.

3.5.2 Secondary Endpoints

The secondary feasibility endpoints are:

i) Ability to enroll an average of 2 patients per site per month. We believe a target of 2 per month is feasible across sites in Alberta given the number of patients starting CRRT per month (~32 new CRRT initiations per month) and accrual at sites during the STARRT-AKI trial.

ii) The ability to enroll >50% of fully eligible patients.

iii) Time from eligibility (e.g., starting RRT) to randomization with a target of >75% of eligible patients within 12 hours.

iv) Protocol adherence for allocated CRRT dose-intensity. We believe a target in-range dose-intensity of >80% to be adequate.

v) Ability to capture delivered CRRT dose-intensity measures. This is a process measure of trial implementation and fidelity. We believe a target of electronic capturing >95% of daily time-averaged CRRT dose-intensity data to be adequate. This will enable an assessment of difference in CRRT dose-intensity between groups.

vi) Ability to capture patient and kidney endpoints at 90-days from randomization. We believe a target of >95% ascertainment to be adequate.

3.5.3 Biochemical Endpoints

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

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).

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

iii) daily serum urea while receiving CRRT and number of (%) days without serum urea >35 mmol/L.

3.5.4 Process of Care Endpoints

The process of care measures will assess the tolerability of the intervention and are:

i) The lowest and highest CRRT dose-intensity delivered for any given hour following randomization.

ii) The proportion of hours of CRRT when the dose-intensity is in the target range following randomization.

iii) The total treatment time/day while receiving CRRT following randomization. This will be defined as time on treatment divided by 24-hours.

iv) The total number of hemofilter/circuit replacements during CRRT following randomization.

v) The total volume of replacement/dialysate fluid used per day and overall following randomization.
vi) The total number and cumulative doses of supplemental electrolytes (Mg+, K+, PO4-, HCO3-), protein and vitamins administered while receiving CRRT following randomization.
vii) The modified daily bedside (nursing) activity score, as a measure of nursing bedside workload, while receiving CRRT following randomization.
viii) The mean daily net ultrafiltration (UF_{NET}) delivery while receiving CRRT following randomization.

3.5.5 Safety

An adverse event (AE) is any untoward medical occurrence in a patient enrolled in the trial which does not necessarily have a causal relationship with the intervention. 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; other medically important event (is not immediately life-threatening or results in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes). Due to this trial being performed in critically ill patients, AEs and SAEs 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.[32] This includes a predefined list of AEs that will be considered potentially trial-related AEs and require reporting in the REDCap database. SAEs 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).[33] Information related to the trial-related SAEs will be captured on a dedicated form, shared with the study sponsor and submitted to the REB, as applicable (See the Manual of Procedures (MOP) for details of the predefined AEs and recording and reporting requirements for trial-related AEs and SAEs).

Table. Summary of predefined adverse events that will be considered potentially trial-related.

Adverse Event	Definition
Serum K+	<3.0 or >6.0 mmol/L
Serum Mg+	<0.5 or >1.5 mmol/L
Serum PO4+	<0.5 or >2.5 mmol/L
Serum Urea	>35 mmol (24 hour after randomization)
Serum pH	<7.20 or >7.60 mmol/L
Serum HCO3	<10 or >35 mmol/L
Serum Ionized Ca+	<0.80 or >1.50 mmol/L

Generalized Seizures	Occurrence of a generalized seizure
Arrhythmias	New atrial fibrillation or occurrence of ventricular tachycardia or fibrillation (As defined in STARRT-AKI)
Major bleeding	Major Bleeding will be classified as “major” if it was: • Life threatening bleeding due to hypovolemic shock (e.g., ruptured AAA or upper or lower GI hemorrhage); • Life threatening bleeding at a critical site (e.g., intracranial, retroperitoneal, pericardial); • Overt, clinically important bleeding associated with one of the following within 24 hours of the bleed: decrease in Hgb> 20g/L or transfusion >2 units of packed RBC; • Bleeding at other critical sites (e.g., epidural, intraocular or intraarticular); • Bleeding requiring an invasive intervention (e.g., re-operation).

The safety outcomes reported in REDCap will 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.

3.5.6 Tertiary Endpoints

The WISDOM pilot trial is not designed to detect differences in patient-centred, kidney-centred or health service-specific outcomes[34], however, the following endpoints will be described: duration of RRT; transition from CRRT to IRRT; receipt of RRT at hospital discharge, 30-days and 90-days; RRT-free days at 90-days; ICU mortality; hospital mortality; 90-day mortality; a composite of major adverse kidney events (MAKE) at 30-days and 90-days; change in estimated glomerular filtration rate (baseline to 90-days); daily receipt of non-renal organ support (e.g., invasive and non-invasive mechanical ventilation; vasoactive therapy), ICU duration of stay, hospital duration of stay and re-hospitalization within 90-days. The kidney-specific outcomes, duration of hospitalization, and rates of re-hospitalization are outcomes that have been informed through patient and family preferences and priorities during engagement in our Dialyzing Wisely program.[30] For the next phase trial, the preferable patient-centred primary non-inferiority outcome

will be 90-day mortality (from enrollment) and for superiority, will be RRT-free days at 90-days (from enrollment). These outcomes will aid in the design of a larger-scale trial.

3.6 Sample size calculation and recruitment

For the WISDOM pilot trial, our primary sample size consideration will address the detection of a minimum difference in the delivered dose-intensity of CRRT between the groups. For the WISDOM pilot trial, we are targeting a total sample size of 100 patients (50 patients per group). This is based on the ability to detect a minimum difference of 10 mL/kg/hr in dose-intensity, assuming delivery of 25 mL/kg/hr in the standard dose-intensity group and 15 mL/kg/hr in the lower dose-intensity group, with a conservative standard deviation (SD) of 15, 90% power, and an alpha of 0.05. This would translate into a sample of 96 patients (48 patients per group) that will be inflated to 100 to account for any withdrawal or dropout (See Table below).

Table. Sample Size Calculation Estimates.

Scenario	Difference in Dose Intensity	Standard Deviation	Power	Estimated Sample (Total)
1	10	5.0	0.9	12
2	10	7.5	0.9	24
3	10	10.0	0.9	44
4	10	12.5	0.9	66
5	**10**	**15.0**	**0.9**	**96**
6 (ATN Trial)	15	6.3*	0.9	18
7 (RENAL Trial)	15	15.3**	0.9	100

* From the ATN trial, based on average standard deviation for both groups of the aggregate total effluent flow rate delivered.[18]
** From the RENAL trial, based on average standard deviation for both groups of the aggregate total effluent flow rate delivered.[17]

For the WISDOM pilot trial, the total sample of 100 patients would translate into a target recruitment of 4 patients per week (50% of expected eligible) across 5-10 sites, thereby requiring an estimated 6-10 months to complete, if all sites are active.

We will further explore the practicality of identification of eligible patients, site-specific recruitment, protocol adherence, and data monitoring and ascertainment, that will inform the logistical planning and operations of a larger-scale multi-centre trial.[34]

All patients enrolled in the trial will be admitted to and monitored in an ICU setting. The primary and secondary feasibility endpoints, along with biochemical and process of care endpoints will be captured in local hospital medical records (either paper charts or electronic medical records) and data repositories. Data will be captured electronically where feasible, otherwise, standardized paper case report forms will be used. The expected rate of loss to follow-up will be low for ICU and hospital-specific outcomes

(<1%). Similarly, established processes for linkage to health administrative data ensure longer-term outcomes will be reliably captured.

The WISDOM pilot trial will maintain a screening log to record numbers of patients screened and those eligible and not randomized (e.g., missed, no consent, clinician exclusion), along with the reasons for exclusion. To monitor for selection bias, we will capture a minimal dataset on eligible not randomized patients, as permitted by local REB.[10, 35]

4. METHODS: ASSIGNMENT OF INTERVENTIONS

4.1 Randomization and Allocation Concealment

A web-based randomization system through REDCap maintained at the University of Alberta (Edmonton, Alberta) will be used to allocate treatment assignments for all participating sites. The randomization process will consist of a computer-generated random listing of the treatment allocations, stratified by site and using variable permuted blocks of 2, 4 and 6. All investigators, research staff and clinical personnel will be blinded to the allocation schedules.

4.2 Implementation

Patients will be identified and enrolled in the WISDOM trial by ICU physicians (attending physicians, fellows, residents) and research personnel. The allocated intervention will be communicated to the most responsible care team member, who will co-sign the trial-specific standardized order sets and prescribe the allocated intervention. The allocated intervention will be implemented by the bedside nursing personnel delivering the CRRT.

4.3 Blinding

The WISDOM pilot trial is designed as a prospective, randomized, open-label, blinded endpoint (PROBE) trial.[36] This approach is necessary given the impracticality of blinding the prescription and delivery of CRRT. PROBE trials produce comparable effect estimates to conventional double-blind trials, however, are more pragmatic and have greater similarly to standard clinical practice.[37] In this trial, process measures of performance and safety endpoints will be independently ascertained.

5. METHODS: ANALYSIS

5.1 Proposed analyses

Baseline characteristics will be summarized with descriptive statistics. The primary feasibility endpoint, the difference in mean (SD) CRRT dose-intensity between groups, will be reported as difference in means (with 95% confidence intervals [CI]). For secondary feasibility, physiological and biochemical, and process of care endpoints, all

continuous variables will describe the number of non-missing values [n], means, medians, standard deviation [SD], interquartile ranges, whereas all categorical variables, will describe frequency counts and percentages, as appropriate. Between group differences will be assessed using Chi-square or Fisher's exact tests for dichotomous outcomes and student t-tests or non-parametric methods for continuous outcomes, as appropriate. A mixed linear regression for repeated measures will be performed, adjusted for baseline variables and CRRT duration, to evaluate dose-intensity differences by allocated group. Safety endpoints will describe and compare the occurrence of AE, SAE and SAE leading to intervention discontinuation overall and by allocated CRRT dose-intensity.

The WISDOM pilot trial is not designed and will be inadequately powered to detect important differences in clinical outcomes and effect estimates may be inaccurate with large confidence intervals.[34]

5.2 Proposed frequency of analyses

Analyses for the primary, secondary, physiological, biochemical, process of care and safety endpoints will be performed upon completion of the trial. No interim analyses for the pilot trial will be performed due to the short recruitment period planned.

5.3 Planned Subgroup analyses

There are no pre-planned subgroup analyses proposed for this pilot trial.

5.4 Pilot study work

A provincial-scale implementation project, Dialyzing Wisely (DW), focused on key performance and quality indicator monitoring and reporting for acute RRT across all ICUs in Alberta led by our team has been successfully launched.[30] The DW project has established infrastructure and mechanisms to implement, capture and report key performance indicators related to CRRT, including dose-intensity, the primary intervention that is the focus of this trial. This platform, embedded into our shared provincial clinical information system (Connect Care™) will be used to rapidly identify potentially eligible patients for recruitment and will capture data on important process of care and endpoints measures for sites in Alberta.

6. TRIAL MANAGEMENT

6.1 Day to day management

The WISDOM pilot trial will have a dedicated project manager in the Clinical Trials Office (CTO) at the University of Alberta for daily management and coordination of clinical aspects of the trial. The project manager will liaise with coordinators at the trial sites to ensure compliance and provide guidance on the conduct of the trial. The project manager, in consultation with the co-principal investigators, will recruit a statistician to facilitate data

management, develop a detailed statistical analysis plan, and oversee the final analyses. The trial will be coordinated from the CTO at the University of Alberta and the Department of Critical Care Medicine, which have extensive experience in supporting investigator-initiated clinical trials.

6.1.1 Engagement and partnership of people with lived experience

The WISDOM Steering Committee will include people with lived experience (PWLE), including patients and family members, as in our prior work. The PWLE partners will be engaged to co-design and implement this pilot trial and to co-design the next phases, incorporating their perspectives within all activities of the trial, including selection of patient-centred endpoints that are perceived as priorities for patients and families, ensuring the results will be relevant to patients who are treated with CRRT while in the ICU.

6.1.2 Role of principal investigator, co-investigators, and collaborators

The co-principal investigators will assume overall responsibility for the trial. The SC for the trial will be composed of principal investigators, co-investigators, collaborators, and key stakeholders, including knowledge users and patient partners. The Co-PIs for the study and project manager will meet weekly during the start-up and initiation of the trial. Once the study has been activated, the SC committee will meet every two weeks until recruitment targets have been met for four consecutive weeks, and monthly thereafter and during the follow-up period after recruitment has been completed and during the analysis phase.

7. ETHICS AND DISSEMINATION

7.1 Research ethics approval

The WISDOM pilot trial protocol has been reviewed and approved by the Research Ethics Board at the University of Alberta and will be reviewed and approved by the local REB at each participating institution, as applicable, prior to commencement.

As part of the study activation process, study sites will submit a study-specific application to their respective REB for approval to perform the study. Study sites are responsible for adhering to the application requirements and for meeting the deadlines for submission specified by their respective REB.

7.2 Protocol amendments

Amendments to the protocol will be documented, dated, and will be updated on applicable clinical trial registries.

All amendments or administrative updates to the protocol must undergo review by the local REB as per local guidelines. Amendments and administrative updates will be circulated to all participating sites in a standard format. Amendments will be communicated by regular updates to site investigators and research personnel, per the communication plan outlined in the Manual of Procedures (MOP). Amendments will be reviewed and approved by the local REB prior to implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial participants. In this case, an Action Letter will be generated and amendments removing an immediate hazard will be provided for current study participants expeditiously.

7.3 Consent

Most patients eligible and enrolled in this trial will lack capacity to give informed consent at the time of enrolment due to the circumstances of their critical illness (e.g., acute illness [delirium], interventions to facilitate care [sedation]). Given this trial is evaluating the delivered CRRT dose-intensity within the broad boundaries of standards of care, the following consent options are considered acceptable, conditional on review and approval by an REB:

(i) A priori consent by the patient or a SDM;

(ii) deferred consent process in circumstances where a potential participant lacks capacity and the SDM is not available. In this case, the most responsible physician (MRP) signs assent for the patient to be enrolled, followed by regained capacity consent completed by the patient or the SDM signs consent as soon as available, as approved by the local REB;

(iii) consent provided by a research ethics board, Guardianship Board or other legal authority in circumstances where patient or SDM consent was not obtained prior to patient's discontinuation of study [death].

7.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may need to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP E6 (R2):

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in the source documents and reported in the participant database as soon as the study team is aware of the deviation. Protocol deviations must be sent to the local REB per their policies. The site investigator is responsible for knowing and adhering to the reviewing REB requirements.

Examples of protocol deviations which may occur (but are not limited to) include:

- Consent Procedures error: no consent/re-consent obtained (deferred, SDM/participant or regained capacity), incorrect consent form used, not all signatures obtained, etc
- Inclusion/Exclusion criteria not met
- Study Procedures: did not begin receiving study-prescribed CRRT within the protocol specified timelines, received incorrect CRRT prescription, CRRT dose escalated above the protocol-mandated dose-intensity target
- Confidentiality Breach
- SAE Reporting: Did not notify coordinating centre of SAE within 24 hours of becoming aware

There may be other types of deviations that occur as well. All deviations should be recorded in the REDCap participant database. Further details about the handling of protocol deviations are included in the MOP.

7.5 Regulatory Considerations

The Sponsor will collect documentation of REB approval. ‘Approved’ REB status must be maintained until the Sponsor informs the study site that it is no longer required. The study site will maintain REB compliance including renewal according to local requirements. REB renewal approval letters (typically provided annually) must be submitted to the Sponsor as soon as received from the REB.

If an REB refuses to approve this protocol (or amendment or administrative update to this protocol), the Sponsor must be notified immediately of the date of refusal and the reason(s) for the refusal.

During the study the following documents must be added to the REDCap regulatory database as they are received/created/updated for review by the study sponsor, prior to activation of the study or implementation of an amendment.

- Initial REB approval letter
- Annual REB study renewal letters
- REB approval letters for all amendments

- Documents required from site staff (Principal Investigator, Co-Investigators and Clinical Research Coordinators/Associates, pharmacists):
    - A signed and dated Curriculum Vitae (CV)
    - Medical License or Professional Certificates are required annually (if required for role)
    - TCPS2 and GCP certificates of training
    - Documentation of training on original protocol and all subsequent amendments
- Study Personnel Delegation Log and all updates during the trial
- Completed Protocol Statement of Compliance pages for all versions of protocol
- Other documents as requested by the Sponsor

Prior to activation the sponsor will conduct a Site Initiation Visit (SIV), either in person or virtually via video-conference, with each site, to provide study specific protocol and operational training for all study team members. The SIV will provide a time for the site teams to ask questions and confirm processes. Training on subsequent amendments will be done locally at each site and must be documented prior to implementing an amendment.

A task delegation log must be completed prior to site activation. Personnel assigned any research-related responsibilities or tasks not considered standard of care are required to be on the delegation log. All staff delegated significant study related duties must show evidence of education and training appropriate to the role to confirm they are qualified to perform the delegated task. Training on local SOPs for specific aspects of study related duties (e.g., consent discussions, data collection, maintenance of regulatory binders) must be documented. PI affirmation and delegation, by means of signature and date, must occur after the individual has completed GCP, TCPS2, SOP and study-specific training, and prior to conducting any research-related responsibilities. The PI should assign individual study training as required per the role of the personnel in the study, at study start-up, as new team members are added or when amendments are released.

7.6 Confidentiality and Data Protection

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The site Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Where the source data is not collected as part of the participant's medical record, paper

copies of the study visit CRFs may be used as source document worksheets for recording data for each participant enrolled in the study as long as they are signed and dated by an individual delegated the task of data collection. Data recorded in the REDCap electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Study data will be entered into REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. The WISDOM REDCap database is maintained by Women and Children's Health Research Institute (WCHRI), at the University of Alberta, in Edmonton, Alberta. The application and data are housed on servers provided by the University of Alberta.

The Site PI (and delegated study team members) will be given access to the online web-based EDC system REDCap. This system is specifically designed for collecting data in electronic format. Access and rights to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Site PI and authorized staff can enter data and make corrections in the eCRFs.

The eCRFs should be completed for each participant for whom a signed study-specific informed consent form was obtained, with the exception of those that may not have consented but are eligible but not randomized for whom a minimal data set will be entered, if permitted by the local REB approval. Data entry into the eCRFs for randomized participants should reflect the latest observations on the participant participating in the study. Data must be entered into REDCap no later than 2 weeks from the completion date of the patient's participation in the study except for the eCRFs required to confirm eligibility which must be completed and submitted in order to randomize the participant.

The investigator is responsible for ensuring that eCRFs and source documents are complete and accurate. The investigator will confirm the authenticity of all laboratory and clinical data recorded in the eCRFs by written or electronic signature.

The database will be locked once the final participant has completed the study and the data has been verified by the quality assurance/monitoring team.

7.7 Declaration of conflicts of interest

The principal investigators and steering committee members will declare any financial or other real or perceived conflicts of interest in relation to this trial.

7.8 Access to data

For the WISDOM pilot trial, the final dataset will be available to the study investigators. There will be no contractual agreements in place which limit access to trial data.

7.9 Dissemination and impact

The findings of the WISDOM pilot trial will be disseminated to institutional and provincial stakeholders and knowledge users, and as applicable, shared with national and international stakeholders. We will perform end-of-trial knowledge dissemination activities, including providing a summary report to funding organizations (as applicable). We will facilitate presentations at national and international meetings, along with submission for peer-reviewed publication. The trial will give full credit to all investigators, collaborators, research personnel and institutions, as applicable. Sponsoring institutions and funding organizations will be acknowledged in all presentations and publications.

If the WISDOM pilot trial is proven to be feasible, we will implement, scale, and expand the next phase to focus on the detection of minimally clinically important differences in outcomes that are important to patients and to our healthcare system.

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9. APPENDICES
9.1 Protocol Amendment History

Protocol Version	Date	Amendment Details
Version 1.0	February 19, 2024	This was the first protocol version.
Version 2.0	September 25, 2024	Title Page: Updates to version #, date, addition of NCT # and funding information; Addition of short title
		Pages 3 & 4: Addition of Sponsor and Site Statements of Compliance
		Page 5 & 6: Updated list of abbreviations
		Pages 7 – 10: Summary: Updates to the Background, Objective, study design, population, inclusion/exclusion criteria, intervention, primary endpoint, secondary endpoints, biochemical and process of care endpoints, tertiary endpoints, sample size estimation and registration Background: Fully revised. New text: An estimated 12-15% of critically ill patients receive RRT for acute kidney injury (AKI), the majority of whom initially receive continuous renal replacement therapy (CRRT). The 2012 *Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines (CPG) for* AKI recommend delivering a CRRT dose-intensity of 20-25 mL/kg/hr. This recommendation is derived from prior RCTs evaluating higher dose-intensity (35-40 mL/kg/hr vs. 20-25 mL/kg/hr) that have not shown any survival advantage. These findings translated to a dose-intensity of 20-25 mL/kg/hr becoming the *de facto* dose-intensity standard for patients receiving CRRT. In addition, because epidemiologic studies describing CRRT dose-intensity practices have consistently found that the "delivered" dose-intensity was often less than "prescribed" (only ~75-90%), usually due to therapy interruptions (i.e., circuit clotting; diagnostic imaging; minor surgical procedures), the 2012 KDIGO CPGs suggest that dose-intensity augmentation is required and that "*a higher prescription"* in the range of 25-30 mL/kg/hr is needed. The current practice, based on data from ICUs in Alberta, Canada and sites that participated in the international STARRT-AKI trial shows the range in median delivered CRRT dose-intensity is 26-30 mL/kg/hr. To date, no RCT has focused on evaluating or defining a minimally acceptable and safe CRRT dose-intensity threshold. Specifically, it is not clear whether a lower dose-intensity (10-15 mL/kg/hr) may be equally acceptable or even superior to the current guideline-directed standard (25-30 mL/kg/hr). Objective: Fully Revised. New text: The WISDOM research program aims to address whether a lower CRRT dose-intensity (10-15 mL/kg/hr) in critically ill patients with AKI is non-inferior for 90-day mortality compared to the current guideline-directed standard CRRT dose-intensity (25-30 mL/kg/hr) and will secondarily determine if lower CRRT dose-intensity can shorten RRT duration and improve kidney recovery versus the guideline-directed standard. Study Design: Fully revised.

		New text: Multi-centre prospective, randomized, open-label, blinded endpoint (PROBE) pilot trial in adult ICU patients with AKI receiving CRRT. Population: Fully revised. New text: ICU patients with AKI in whom the clinical team has decided to start CRRT or who are within 24 hours of having started CRRT will be potentially eligible. Each patient will fulfill all inclusion and have no exclusion criteria. Eligibility: Fully revised, new criteria added. New text: <u>Inclusion criteria</u>: i) age ≥ 18 years, ii) patient weight ≥ 55 kg iii) plan to initiate CRRT or within 24 hours of having started CRRT for acute kidney injury (AKI) iv) expected to survive and receive CRRT for a duration of ≥ 48 hours v) able to consent or have an authorized representative consent after being informed on the details and risks of participation, unless a waiver or deferred consent process is approved by local REB. <u>Exclusion criteria</u>: i) indication for sustained higher dose-intensity CRRT as designated by the attending clinician(s) 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. Intervention: Fully revised. New text: The *experimental arm* will be lower CRRT dose-intensity, defined as a delivered effluent flow rate of **10-15 mL/kg/hr**. The rationale for this lower dose-intensity is based on the observed lower threshold of dose-intensity currently delivered in clinical practice and observational data showing that this threshold may be acceptable, tolerated and safe. The *control arm* will be guideline-directed standard CRRT dose-intensity, defined as delivered effluent flow rate of **25-30 mL/kg/hr**. The standard dose-intensity is aligned with current practice and by recommendations from international CPGs.[5] The current standard of care for CRRT dose-intensity provided in ICUs in Alberta and across the sites that participated in STARRT-AKI (39 Canadian sites) ranges between 26-30 mL/kg/hr. The CRRT dose calculation will use measured or estimated actual body weight, as previously described and recommended by CPGs. All enrolled patients will receive an active run-in period of standard dose-intensity of up to 24 hours (minimum 12 hours) to ensure initial metabolic and azotemic stabilization. Primary Endpoint: Fully Revised. New text: The <u>primary feasibility endpoint</u> is the difference (95% CI) in the total delivered effluent flow rate per patient between those in the lower and standard CRRT dose-intensity groups. The WISDOM pilot trial will target the detection of a minimum difference of 10 mL/kg/hr in average delivered dose-intensity between the groups.

		Secondary Endpoints: New endpoint added: i) Ability to enroll an average of two patients per site per month. Biochemical Endpoints: Changed title from 'Physiological and Biochemical Endpoints' to 'Biochemical Endpoints' Removed chloride from i) Removed creatinine from iii) Process of Care Endpoints: In i), changed statement, 'the lowest and standard CRRT . . . 'to 'the lowest/highest CRRT. . .' Added two new measures: v) The total volume of replacement/dialysate fluid used per day following randomization. vii) modified daily bedside (nursing) activity score, as a measure of nursing bedside workload, while receiving CRRT following randomization. Modified measures: iv) The number of ~~planned and unplanned~~hemofilter/circuit replacements while receiving CRRT following randomization. vi) The number and cumulative dose of supplementary electrolytes, protein and vitamins administered while receiving CRRT ~~magnesium, potassium and phosphate supplementation following randomization~~ Safety: added 'trial-related' to i) Tertiary Endpoints: Revised (removed (single line through) and added (bold)). The trial will measure and describe selected outcomes, including: duration of RRT; transition from CRRT to IRRT~~HD~~; receipt of RRT at hospital discharge, 30-days and 90-days; RRT-free days at 90-days; ICU mortality; hospital mortality; 90-day mortality; a composite of major adverse kidney events (MAKE) at 30-days and 90-days; **change in estimated glomerular filtration rate (baseline to 90-days),** daily receipt of non-renal organ support, ICU duration of stay, hospital duration of stay and re-hospitalization within 90-days. ~~This pilot trial is not designed to detect differences in patient-centred, kidney-centred, or health service-specific outcomes.~~ Sample Size Estimation: Fully Revised. New text: The sample size for the WISDOM pilot trial will address the detection of a minimum difference in the delivered dose-intensity of CRRT between the groups. Based on the ability to detect a minimum difference of 10 mL/kg/hr in dose-intensity, assuming the delivery of 25 mL/kg/hr in the standard dose-intensity group and 15 mL/kg/hr in the lower dose-intensity group, with a conservative standard deviation (SD) of 15, 90% power, and an alpha of 0.05, a total sample of 96 patients is needed (48 patients per group). This will be inflated to 100 patients to account for any withdrawal or dropout. Registration: Text added. New text: Clinicaltrials.gov: NCT06446739 (June 6, 2024)
		Section 1.1 Title – changed to **Lay** Title

		Low vs. Standard Dose-Intensity CRRT in Critically Ill Patients: A protocol for a pilot, ~~feasibility,~~ randomized controlled trial comparing lower dose-intensity to standard dose-intensity continuous renal replacement therapy (CRRT) in adult patients in the intensive care unit (ICU).
		Section 1.2 Trial Registration. NCT information added The trial is ~~will be~~ registered on ClinicalTrials.gov (https://clinicaltrials.gov/) – NCT06446739 (June 6, 2024).~~prior to commencement.~~
		Section 1.3 Protocol Version Updated to version 2.0
		Section 1.4 Funding. Added text. New text: ACT/HDRN (CIHR). Additional applications for funding are in progress.
		Section 1.5.1 Study Principal Investigators Addition of second study PI **Name:** **Ron Wald, MDCM MPH FRCPC** **Title:** **Professor** **Address:** **Division of Nephrology, Department of Medicine, St Michael's Hospital, University of Toronto, 30 Bond Street, Toronto Ontario, Canada, M5B 1W8** **Telephone:** **416-867-3703** **Fax:** **416-593-6275** **Email:** **waldr@smh.ca**
		Section 1.5.2 Management Committee: Title changed to Steering Committee New text: The Steering Committee is responsible for providing overall oversight of the WISDOM trial. Its membership includes the study co-chairs and other individuals with specialized knowledge in critical care and experience in running, and oversight of, clinical trials. The Steering Committee will be accountable for the: • Design and conduct of the study; • Preparation of the essential study documents, including the protocol, protocol amendments, manuals and data collection forms; • Review of data collection practices and procedures; • Monitoring recruitment and retention of study participants; • Modifications in study procedures, as appropriate; • Allocation of resources based on priorities of competing study demands; • Review of study progress in reaching goals and appropriate actions to ensuring the likelihood of achieving those goals. A list of the Steering Committee members will be maintained in the Manual of Procedures and updated as needed.

		Section 1.5.4 Project Manager Section added. New Text: 1.5.4 Project Manager **Project Manager** | **Contact** | **Role** Ellen Morrison | E: ejmorris@ualberta.ca | Project Manager
		Section 1.5.5 Coordinating and data management centre Revised (removed (single line through) and added (bold)). The ~~Department of Critical Care Medicine~~ **Clinical Trials Office (CTO),** Faculty of Medicine and Dentistry, **University of Alberta** will act as the coordinating and data management centre for this phase of the trial.
		Section 2.1 Background – what is the problem to be addressed? Minor updates to wording for clarity
		Section 2.2 Why is this trial needed now? Revised text (removed (single line through) and added (bold)). No RCT to date has specifically evaluated the lower dose-intensity threshold for critically ill patients receiving CRRT **though two pilot trials are ongoing (Clinicaltrials.gov: NCT6021288 and NCT06014801).** ~~There are two ongoing pilot trials that propose to evaluate CRRT dose-intensity. The first is a small single centre pilot RCT in Europe led by Dr. Alexander Zarbock, who was the STARRT-AKI lead for Germany (Clinicaltrials.gov: NCT6021288). The second is a five-centre pilot RCT in Japan led by Dr. Tomoko Fujii, (Clinicaltrials.gov: NCT06014801). There is an *a priori* proposal for an individual patient data meta-analysis (IPDMA) to pool WISDOM pilot data with these pilot trials.~~
		Section 2.3 How will the results of this trial be used? Revised text (removed (single line through) and added (bold)). ~~While this may be an effluent dose of 20-25 mL/kg/hr, it is entirely plausible that this will be a lower dose-intensity. Moreover, c~~Current practice in Alberta for the prescription of CRRT is variable.
		Section 3.1Trial Design Revised text (removed (single line through) and added (bold)). This LoW Dose-Intensity vs. Standard Dose-Intensity COntinuous Renal ReplaceMent Therapy in Critically Ill Patients (WISDOM) trial **is a multicentre prospective, randomized, open-label, blinded endpoint (PROBE) trial in adult ICU patients with AKI receiving CRRT.**~~will be a multi-centre pilot randomized feasibility trial comparing lower dose-intensity to standard dose-intensity continuous renal replacement therapy (CRRT) in adult patients in the intensive care unit (ICU).~~
		Section 3.2 Study Setting: Revised text (removed (single line through) and added (bold)). The WISDOM pilot trial will ~~begin by being conducted in intensive care units (ICU) that provide CRRT across acute care hospitals in Alberta. This will be strategically expanded to include additional~~ **tale place at**

		sites across Canada and internationally ~~that~~ **most of which** participated in the international STARRT-AKI trial.[10] These will include a spectrum of academic/teaching and community ICU sites. ~~The Alberta sites all utilize Alberta Health Services' common electronic clinical information system (Connect Care™, Epic Systems) and critical care data repository (eCritical Alberta) that will enable identification of any patients prescribed CRRT, use of standardized order sets (configured for low or standard dose-intensity CRRT), and ascertainment of automated clinical, physiological, laboratory, CRRT machine data, and feasibility, process, and clinical outcomes. Based on data from October 1, 2023 to December 31, 2023, there were 518 patients who received CRRT across Alberta ICUs (2,790 CRRT-days; average 5.4 days per patient). We estimate 77% of these patients receiving CRRT fulfilled the criteria for AKI. From this, we could expect approximately 8 patients per week to fulfill the eligibility for the trial. This will ensure enough patients will be rapidly identified for the pilot trial prior to further scale and spread.~~
		3.3 Eligibility Criteria: Revised text. Patients who are admitted to an ICU and are prescribed CRRT will be potentially eligible **and will be identified through local site processes**. ~~In Alberta, patients will be identified electronically through surveillance of Connect Care™.~~
		3.3.1 Inclusion Criteria: Revised criteria (removed (single line through) and added (bold)). **i) age ≥ ~~>~~18 years** **ii) patient weight ≥ 55 kg** **iii) plan to initiate CRRT or within 24 hours of having started CRRT for AKI** ~~ii) clinical team decision to initiate CRRT associated with AKI~~ ~~iii) within 18 hours of commencement of CRRT~~ iv) expected to **survive and** receive CRRT for a duration of ≥ 48 hours v) able to provide informed consent or have an authorized representative provide consent after being informed ~~on~~ of the details and risks of the trial unless a ~~waiver of~~**deferred** consent process is approved by **the** local Research Ethics Board (REB).
		3.3.2 Exclusion Criteria: Revised criteria (removed (single line through) and added (bold)). i) **indication for sustained higher dose-intensity CRRT as designated by the attending clinician(s)** ~~absolute indication for higher dose CRRT~~ ii) end-stage kidney disease receiving maintenance dialysis **iii) receipt of intermittent RRT for AKI during the current hospitalization** ~~ii~~**v**) inability to comply with the requirements of the study protocol **This trial does not restrict co-enrollment on other clinical trials unless the intervention in the other trial is perceived to interact with the WISDOM interventions. This will be determined by the PIs.**
		Section 3.4.1 Study Interventions: Fully revised. New text:

		All enrolled patients will receive the standard dose-intensity for a maximum of 24 hours and a minimum of 12 hours from the time CRRT is started (not the time of enrollment and randomization) to ensure initial metabolic and azotemic stabilization. **The *experimental arm* will be lower CRRT dose-intensity, defined by a delivered effluent flow rate of 10-15 mL/kg/hr. The rationale for this lower dose-intensity is based on the observed lower threshold currently delivered in clinical practice and observational data showing that this threshold is acceptable, tolerated and safe.[26-28] The *control arm* will be guideline-directed standard CRRT dose-intensity, defined by a delivered effluent flow rate of 25-30 mL/kg/hr. The standard dose-intensity aligns with current practice and by recommendations from international CPGs.[31] The standard of care for CRRT dose-intensity provided in ICUs in Alberta in a recent audit and across participating sites in STARRT-AKI (39 Canadian sites) ranged between 26-30 mL/kg/hr. The dose calculation will utilize measured or estimated actual body weight.**
		3.4.2 Criteria for discontinuing or modifying allocated interventions Revised/added text: Intermittent ~~hemodialysis (IHD)~~ changed to Intermittent **RRT (IRRT)** **Ultimate decisions about transitions to IRRT will be made by the local attending physicians.** Revised sentence: If a patient has prolonged CRRT interruption (>6 hours) (e.g., operative theatre), CRRT will be temporarily restarted at the standard dose-intensity for 6 hours to ensure a period of stabilization, then transitioned to their allocated CRRT dose-intensity, as applicable. ~~If a patient has CRRT discontinued with the intent of liberation and requires re-initiation due to ongoing need (after a period of hours or days) while in the ICU, the CRRT will be prescribed according to their allocated dose-intensity.~~ If patients are perceived by the treating ICU team to require **a temporary increase in** ~~greater~~ dose-intensity to augment acid-base/metabolic/azotemic control due to critical illness, the following actions should be followed in hierarchical order: Additional text: ii) For patients with persistent metabolic acidosis, defined as pH <7.25 and BE < -10 at 24 hours after randomization, the treating ICU team can add supplementary bicarbonate (~~Na~~HCO3) **either as a continuous infusion or bicarbonate can be added** to the replacement/dialysate solutions, as per ICU-specific protocols.

		If patients have their CRRT dose-intensity prescription further modified outside their allocated dose-intensity (e.g., a patient allocated to 10-15 mL/kg/hr is increased to >15 mL/kg/hr) ~~or discontinued (i.e., withdrawn from the study)~~for reasons not specified above, this will be considered a protocol ~~violation~~**deviation**. The reason for the dose-intensity modification **must be documented and** ~~or~~will be classified as: i) inadequate acid-base control; ii) inadequate electrolyte control; iii) inadequate azotemic/metabolic control; and iv) other (describe).
		3.4.3 Strategies to improve protocol adherence Revised text: The study principal investigators and site principal investigators will be responsible for education about the trial and training clinicians **and research staff. Trial interventions will utilize local standardized CRRT order sets.** ~~prior to commencement. Each site will utilize trial specific standardized CRRT order sets adapted for the purpose of the trial.~~
		3.4.4 Cointerventions: Fully revised. **Additional aspects of CRRT, including timing, catheter insertion site, selection of clearance mode (e.g., CVVH, CVVHD, CVVHDF), anticoagulation strategy, and net ultrafiltration rate (e.g., total fluid removal rate) will be independent of the allocated intervention and based on the principles of standard best practices and at the discretion of the responsible clinical team.** ~~The additional parameters in the delivery of CRRT, including catheter insertion site, selection of mode (e.g., CVVH, CVVHD, CVVHDF), anticoagulation, and net ultrafiltration rate will be based on the principles of standard best practices and at the discretion of the responsible clinical team.~~[31] These aspects of the delivery of CRRT will be recorded and reported, as applicable. **The management of critical illness, including but not limited to hemodynamic support, ventilatory support, fluid resuscitation and therapy, nutrition, rehabilitation, and medications will also be at the discretion of the responsible clinical team.** ~~The management of critical illness, including but not limited to hemodynamic support, ventilatory support, fluid therapy, nutrition, and medications will also be at the discretion of the responsible clinical team.~~
		Section 3.5.1. Primary Endpoint – Fully revised. New text: The **<u>primary feasibility endpoint</u> is the difference (95% CI) in the total delivered effluent flow rate per patient between those in the lower and standard CRRT dose-intensity groups. The WISDOM pilot trial will target the detection of a minimum difference of 10 mL/kg/hr in average delivered dose-intensity between the groups. This will be an important proof-of-concept endpoint to inform the feasibility of a larger multi-centre trial.** ~~primary outcome will be assessment of feasibility for scaling to a large, multi-centre trial of lower versus standard dose-intensity CRRT. The primary feasibility endpoint will be the ability to enroll 2 patients per site per month.~~
		Section 3.5.2 Secondary Endpoints - Addition of secondary endpoint

		i) **Ability to enroll an average of 2 patients per site per month. We believe a target of 2 per month is feasible across sites in Alberta given the number of patients starting CRRT per month (~32 new CRRT initiations per month) and accrual at sites during the STARRT-AKI trial.** ii) ~~Consent rate for participation by patient or surrogate decision-maker (SDM). We believe a target of 60~~**>50**% ~~consent rate among patients or SDM approached would be adequate.~~ **The ability to enroll >50% of fully eligible patients.** iii) Time from eligibility (e.g., starting RRT) to randomization **with a target of >75% of eligible patients within 12 hours.** ~~We believe a target <18 hours from eligibility to enrollment and randomization to be adequate.~~ iv) Protocol adherence for allocated CRRT dose-intensity. We believe a target in-range dose-intensity of **>9**~~**8**~~0% to be adequate. v) Ability to capture delivered CRRT dose-intensity measures. This is a process measure of trial implementation and fidelity. We believe a target of electronic capturing >95% of daily time-averaged CRRT dose-intensity data to be adequate. This will enable an assessment of difference in CRRT dose-intensity between groups. vi) Ability to capture patient and kidney endpoints at 90 days **from randomization**. We believe a target of >9**5**~~0~~% ascertainment to be adequate.
		3.5.3 Physiological and Biochemical Outcomes – title changed to **Biochemical Endpoints** Text revised. The ~~physiologicial and~~ biochemical ~~outcomes~~ **endpoints** will assess the tolerability of the intervention and~~ include~~ **are**: 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). ii) daily serum magnesium, potassium, and phosphate while receiving CRRT and number **of** (%) days without hyperkalemia (K+ >5.5 mmol/L). iii) daily ~~in~~ serum urea ~~and creatinine~~ while receiving CRRT and number **of** (%) days without serum urea >35 mmol/L~~)~~.
		3.5.4 Process of care measures – title changes to **Process of Care Endpoints** Text revised. New endpoints added. i) The lowest and **highest** ~~higher~~ CRRT dose-intensity delivered for any given hour following randomization. ii) The proportion of hours of CRRT when the dose-intensity is in the target range following randomization. ~~This is a primary protocol adherence process measure and will provide evidence of between group differences in dose-intensity.~~ iii) The total treatment time/day while receiving CRRT following randomization. This will be defined as time on treatment divided by 24-hours.

iv) The total number of hemofilter/circuit replacements during CRRT following randomization.

v) The total volume of replacement/dialysate fluid used per day and overall following randomization.

vi) The total number and cumulative doses of supplemental electrolytes (Mg+, K+, PO4-, HCO3-), protein and vitamins administered while receiving CRRT following randomization.

vii) The modified daily bedside (nursing) activity score, as a measure of nursing bedside workload, while receiving CRRT following randomization.

v**iii**) The mean daily net ultrafiltration (UF_{NET}) delivery while receiving CRRT following randomization.

~~vi) The number and cumulative dose of magnesium, potassium and phosphate supplementation following randomization.~~

3.5.5 Safety – Fully revised

An adverse event (AE) is any untoward medical occurrence in a patient **enrolled in the trial which does not necessarily have a causal relationship with the intervention.** ~~administered a medicinal product and which does not necessarily have a causal relationship with this treatment.~~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; other medically important event (is not immediately life-threatening or results in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes). Due to this trial being performed in critically ill patients, **AEs and SAEs** 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.[32] **This includes a predefined list of AEs that will be considered potentially trial-related AEs and require reporting in the REDCap database.** SAEs 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).[33] Information related to the **trial-related** SAE**s** will be captured on a dedicated form, shared with the ~~PI~~ **study sponsor** and submitted to the REB, as applicable **(See the Manual of Procedures (MOP) for details of the predefined AEs and recording and reporting requirements for trial-related AEs and SAEs).**

Table. Summary of predefined adverse events that will be considered potentially trial-related.

Adverse Event	Definition
Serum K+	**<3.0 or >6.0 mmol/L**
Serum Mg+	**<0.5 or >1.5 mmol/L**
Serum PO4+	**<0.5 or >2.5 mmol/L**
Serum Urea	**>35 mmol (24 hour after randomization)**
Serum pH	**<7.20 or >7.60 mmol/L**

		Serum HCO3	**<10 or >35 mmol/L**
		Serum Ionized Ca+	**<0.80 or >1.50 mmol/L**
		Generalized Seizures	**Occurrence of a generalized seizure**
		Arrhythmias	**New atrial fibrillation or occurrence of ventricular tachycardia or fibrillation (As defined in STARRT-AKI)**
		Major bleeding	**Major Bleeding will be classified as "major" if it was:** • **Life threatening bleeding due to hypovolemic shock (e.g., ruptured AAA or upper or lower GI hemorrhage);** • **Life threatening bleeding at a critical site (e.g., intracranial, retroperitoneal, pericardial);** • **Overt, clinically important bleeding associated with one of the following within 24 hours of the bleed: decrease in Hgb> 20g/L or transfusion >2 units of packed RBC;** • **Bleeding at other critical sites (e.g., epidural, intraocular or intraarticular);** • **Bleeding requiring an invasive intervention (e.g., re-operation).**
		The safety outcomes **reported in REDCap** will 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.	
		Section 3.5.6 Tertiary Endpoints: Revised: The WISDOM pilot trial is not designed to detect differences in patient-centred, kidney-centred or health service-specific outcomes[34], however, ~~we will measure and describe~~ the following **endpoints will be described**~~outcomes~~: duration of RRT; transition from CRRT to **IRRT**~~HD~~; receipt of RRT at hospital discharge, 30-days and 90-days; RRT-free days at 90-days; ICU mortality; hospital mortality; 90-day mortality; a composite of major adverse kidney events (MAKE) at 30-days and 90-days; **change in estimated glomerular filtration rate (baseline to 90-days);** For the next phase trial, the preferable patient-centred primary **non-inferiority outcome will be 90-day mortality (from enrollment) and for superiority,** ~~outcome~~ will be RRT-free days at 90-days **(from enrollment).**	
		Section 3.6. Sample Size calculation and recruitment: Fully revised.	

For the WISDOM pilot trial, our primary sample size consideration will address the detection of a minimum difference in the delivered dose-intensity of CRRT between the groups. For the WISDOM pilot trial, we are targeting a total sample size of 100 patients (50 patients per group). This is based on the ability to detect a minimum difference of 10 mL/kg/hr in dose-intensity, assuming delivery of 25 mL/kg/hr in the standard dose-intensity group and 15 mL/kg/hr in the lower dose-intensity group, with a conservative standard deviation (SD) of 15, 90% power, and an alpha of 0.05. This would translate into a sample of 96 patients (48 patients per group) that will be inflated to 100 to account for any withdrawal or dropout (See Table below).

Table. Sample Size Calculation Estimates.

Scenario	Difference in Dose Intensity	Standard Deviation	Power	Estimated Sample (Total)
1	10	5.0	0.9	12
2	10	7.5	0.9	24
3	10	10.0	0.9	44
4	10	12.5	0.9	66
5	10	15.0	0.9	96
6 (ATN Trial)	15	6.3*	0.9	18
7 (RENAL Trial)	15	15.3**	0.9	100
* From the ATN trial, based on average standard deviation for both groups of the aggregate total effluent flow rate delivered.[18] ** From the RENAL trial, based on average standard deviation for both groups of the aggregate total effluent flow rate delivered.[17]				

For the WISDOM pilot trial, the total sample of 100 patients would translate into a target recruitment of 4 patients per week (50% of expected eligible) across 5-10 sites, thereby requiring an estimated 6-10 months to complete, if all sites are active.

We will further explore the practicality of identification of eligible patients, site-specific recruitment, protocol adherence, and data monitoring and ascertainment, that will inform the logistical planning and operations of a larger-scale multi-centre trial.[34]

All patients enrolled in the trial will be admitted to and monitored in an ICU setting. The primary and secondary feasibility endpoints, along with ~~physiologic~~ biochemical and process of care endpoints will be captured ~~by our provincial information system and data repository (Connect Care™ and eCrticia/Tracer)~~in local hospital medical records (either paper charts or electronic medical records) and data repositories. Data will be captured electronically where feasible, otherwise, standardized ~~care~~paper case report forms will be used. The expected rate of loss to follow-up will be low for ICU and hospital-specific outcomes ~~will be low~~(<1%).

		Section 5.1 Proposed Analyses: Revised and added text. The primary feasibility endpoint, **the difference in mean (SD) CRRT dose-intensity between groups, will be reported as difference in means (with 95% confidence intervals [CI]).**~~the mean number of patients enrolled per site per month over the duration of the trial, will be reported using descriptive statistics (with 95% confidence intervals [CI]).~~ **A mixed linear regression for repeated measures will be performed, adjusted for baseline variables and CRRT duration, to evaluate dose-intensity differences by allocated group.** ~~As such, to minimize inappropriate interpretation of this pilot trial, we will give priority to reporting differences in delivered dose-intensity, duration of RRT, receipt of RRT at hospital discharge, hospital mortality, and receipt of non-renal organ dysfunction among enrolled patients.~~
		6.1 Day to day management New text: The WISDOM pilot trial will ~~recruit~~**have** a dedicated project manager **in the Clinical Trials Office (CTO) at the University of Alberta** for daily management and coordination of clinical aspects of the trial. The ~~trial~~ **project manager** will liaise with coordinators at ~~additional~~**the trial** sites **to ensure compliance and provide guidance on the conduct of the trial.** ~~and recruit part time coordinators.~~The project manager, in consultation with the **co-**principal investigators, will recruit a statistician to facilitate data management, develop ~~of~~a detailed statistical analysis plan, and oversee the final analyses. The trial will be coordinated from the **CTO at the University of Alberta and the** Department of Critical Care Medicine, which ~~has~~**have** extensive experience in supporting investigator-initiated clinical trials.
		6.1.1 Engagement and partnership of people with lived experience Revised text: The WISDOM ~~pilot trial team~~**Steering Committee** will include people with lived experience (PWLE), including patients and family members, as in our prior work. ~~We will invite PWLE to serve on the steering committee (SC) for the trial. We will engage our~~ **The** PWLE partners **will be engaged to co-design and** implement this pilot trial and to co-design the next phases, incorporating their perspectives within all activities of the trial, including selection of patient-centred endpoints that are perceived as priorities for patients and families ~~for the next phase~~, ensuring the results will be relevant to patients who are treated with CRRT while in the ICU.
		6.1.2 Role of principal investigator, co-investigators and collaborators Revised text: The **co-**principal investigator**s** will assume overall responsibility for the trial. The SC for the trial will be composed of principal investigator**s**, co-investigators, collaborators, and key stakeholders, including knowledge users and patient partners. The ~~SC~~**Co-PIs for the study and project manager** will meet ~~monthly to prepare and prior to implementation, and~~ weekly during the **start-up and** initiation of the

		trial. **Once the study has been activated, the** SC committee ~~meeting~~ **will meet** ~~subsequently occur regularly~~every two weeks until recruitment targets have been met for four consecutive weeks, and monthly thereafter and during the follow-up period after recruitment has been completed and during the analysis phase.
		7.1 Research ethics approval Minor rewording for clarity. Added statement **As part of the study activation process, study sites will submit a study-specific application to their respective REB for approval to perform the study. Study sites are responsible for adhering to the application requirements and for meeting the deadlines for submission specified by their respective REB.**
		7.2 Protocol Amendments. Revised text: Amendments to the protocol will be documented, dated, and will be updated on applicable clinical trial registries. ~~Amendments will be communicated by regular updates to the site investigators and research personnel as applicable.~~ **All amendments or administrative updates to the protocol must undergo review by the local REB as per local guidelines. Amendments and administrative updates will be circulated to all participating sites in a standard format. Amendments will be communicated by regular updates to site investigators and research personnel, per the communication plan outlined in the Manual of Procedures (MOP). Amendments will be reviewed and approved by the local REB prior to implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial participants. In this case, an Action Letter will be generated and amendments removing an immediate hazard will be provided for current study participants expeditiously.**
		7.3 Consent. Text revised: (i) A priori consent by the patient or a SDM; (ii) deferred consent **process in circumstances where a potential participant lacks capacity and the SDM is not available; in this case the most responsible physician (MRP) signs assent for the patient to be enrolled, followed by regained capacity consent completed by the patient or the SDM signs consent as soon as available, as approved by the local REB;** ~~(iii) waiver of consent with or without the option of opt out~~ (**ii**~~i~~**v**) consent provided by a research ethics board, Guardianship Board or other legal authority in circumstances where patient or SDM consent was not obtained **prior to patient's discontinuation of study [death].**
		7.4 Protocol Deviations – new section added **A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP)**

		requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may need to be developed by the site and implemented promptly. **These practices are consistent with ICH GCP E6 (R2):** • **4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3** • **5.1 Quality Assurance and Quality Control, section 5.1.1** • **5.20 Noncompliance, sections 5.20.1, and 5.20.2.** **It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in the source documents and reported in the participant database as soon as the study team is aware of the deviation. Protocol deviations must be sent to the local REB per their policies. The site investigator is responsible for knowing and adhering to the reviewing REB requirements.** **Examples of protocol deviations which may occur (but are not limited to) include:** • **Consent Procedures error: no consent/re-consent obtained (deferred, SDM/participant or regained capacity), incorrect consent form used, not all signatures obtained, etc** • **Inclusion/Exclusion criteria not met** • **Study Procedures: did not begin receiving study-prescribed CRRT within the protocol specified timelines, received incorrect CRRT prescription, CRRT dose escalated above the protocol-mandated dose-intensity target** • **Confidentiality Breach** • **SAE Reporting: Did not notify coordinating centre of SAE within 24 hours of becoming aware** **There may be other types of deviations that occur as well. All deviations should be recorded in the participant database. Further details about the handling of protocol deviations are included in the MOP.**
		7.5 Regulatory Considerations – new section added **The Sponsor will collect documentation of REB approval. 'Approved' REB status must be maintained until the Sponsor informs the study site that it is no longer required. The study site will maintain REB compliance including renewal according to local requirements. REB renewal approval letters (typically provided annually) must be submitted to the Sponsor as soon as received from the REB.**

		If an REB refuses to approve this protocol (or amendment or administrative update to this protocol), the Sponsor must be notified immediately of the date of refusal and the reason(s) for the refusal.
		
		During the study the following documents must be added to the REDCap regulatory database as they are received/created/updated for review by the study sponsor, prior to activation of the study or implementation of an amendment.
		• **Initial REB approval letter**
		• **Annual REB study renewal letters**
		• **REB approval letters for all amendments**
		• **Documents required from site staff (Principal Investigator, Co-Investigators and Clinical Research Coordinators/Associates, pharmacists):**
		  ○ **A signed and dated Curriculum Vitae (CV)**
		  ○ **Medical License or Professional Certificates are required annually (if required for role)**
		  ○ **TCPS2 and GCP certificates of training**
		  ○ **Documentation of training on original protocol and all subsequent amendments**
		• **Study Personnel Delegation Log and all updates during the trial**
		• **Completed Protocol Statement of Compliance pages for all versions of protocol**
		• **Other documents as requested by the Sponsor**
		
		Prior to activation the sponsor will conduct a Site Initiation Visit (SIV), either in person or virtually via video-conference, with each site, to provide study specific protocol and operational training for all study team members. The SIV will provide a time for the site teams to ask questions and confirm processes. Training on subsequent amendments will be done locally at each site and must be documented prior to implementing an amendment.
		
		A task delegation log must be completed prior to site activation. Personnel assigned any research-related responsibilities or tasks not considered standard of care are required to be on the delegation log. All staff delegated significant study related duties must show evidence of education and training appropriate to the role to confirm they are qualified to perform the delegated task. Training on local SOPs for specific aspects of study related duties (e.g., consent discussions, data collection, maintenance of regulatory binders) must be documented. PI affirmation and delegation, by means of signature and date, must occur <u>after</u> the individual has completed GCP, TCPS2, SOP and study-specific training, and <u>prior to</u> conducting any research-related

		responsibilities. The PI should assign individual study training as required per the role of the personnel in the study, at study start-up, as new team members are added or when amendments are released.
		7.6 Confidentiality and Data Protection – new section added **Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The site Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.** **All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.** **Where the source data is not collected as part of the participant's medical record, paper copies of the study visit CRFs may be used as source document worksheets for recording data for each participant enrolled in the study as long as they are signed and dated by an individual delegated the task of data collection. Data recorded in the REDCap electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.** **Study data will be entered into REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. The WISDOM REDCap database is maintained by Women and Children's Health Research Institute (WCHRI), at the University of Alberta, in Edmonton, Alberta. The application and data are housed on servers provided by the University of Alberta.** **The Site PI (and delegated study team members) will be given access to the online web-based EDC system REDCap. This system is specifically designed for collecting data in electronic format. Access and rights to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Site PI and authorized staff can enter data and make corrections in the eCRFs.** **The eCRFs should be completed for each participant for whom a signed study-specific informed consent form was obtained, with the exception of those that may not have consented but are eligible but not randomized for whom a minimal data set will be entered, if permitted by the local REB approval. Data entry into the eCRFs for randomized participants should reflect the latest observations on the participant participating in the study. Data must be entered into REDCap no later than 2 weeks from the completion date of the patient's participation in the study.**

		The investigator is responsible for ensuring that eCRFs and source documents are complete and accurate. The investigator will confirm the authenticity of all laboratory and clinical data recorded in the eCRFs by written or electronic signature. **The database will be locked once the final participant has completed the study and the data has been verified by the quality assurance/monitoring team.**
		7.7 Declaration of conflicts of interest – Revised text. ~~All trial investigators, collaborators and research personnel~~**The principal investigators and steering committee members** will declare any financial or other real or perceived conflicts of interest in relation to this trial.
		7.9 Dissemination and impact Removed text. We will perform en-of-trial knowledge dissemination activities, including providing a summary report to funding organizations (as applicable)~~, the Criticial Care Strategic Clinical Network™ and to AHS~~. ~~The WISDOM pilot trial is already benefitting from the extensive infrastructure offered through a provincially integrated clinical information system (Connect Care™), a critical care specific data repository (eCritical/TRACER), established mechanisms for linkage to health administrative data, and the implementation of key performance and quality indicators necessary to evaluate the proposed intervention, changes in CRRT dose-intensity. The WISDOM pilot trial will apply and evaluate innovative patient recruitment and data capture methods and be immediately scalable to the 14 ICUs across Alberta that currently provide acute CRRT to critically ill patients.~~
		Section 9. APPENDICES, Section 9.1 Protocol Amendment History added