Manual of Procedures

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

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Section 1: Introduction

1.1 Study Overview

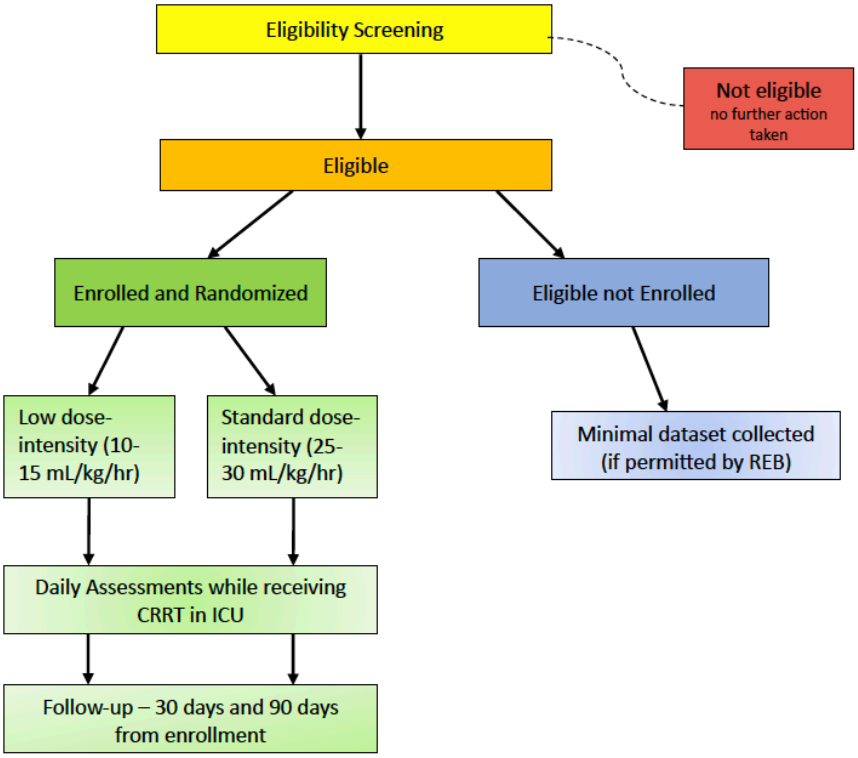
The WISDOM Pilot Trial is a multicentre, prospective, randomized, open-label, blinded endpoint (PROBE) trial. The trial will enroll 100 participants (50 in each arm) over multiple clinical sites (8-15) to receive either the standard dose-intensity (25-30 mL/kg/hr) or the low dose-intensity (10-15 mL/kg/hr) treatment for the duration of their continuous renal replacement therapy (CRRT). Participants with acute kidney injury (AKI) will be assessed daily while receiving CRRT in the intensive care unit (ICU). Participants will be followed for outcomes 30 days and 90 days after enrollment.

This Manual of Procedures (MOP) was developed to serve as a reference to all research team members involved in the conduct of the WISDOM trial. The MOP provides guidance by outlining the various procedures and processes required to ensure compliance with the study protocol, TCPS2 and GCP requirements. Each process involved in the conduct of this study has instructions detailing the steps required to perform each procedure, acting as a “How To” manual for research team members.

These guidelines ensure that participant safety and scientific integrity are thoroughly maintained. The study’s conduct and operations are detailed including the study’s organization, study personnel training, recruitment, screening, enrollment with follow-up procedures and data collection methods.

Any modifications in the study procedures as outlined in the MOP will be communicated to study sites following review and update of this manual by the sponsor. It will be the study sites’ responsibility to incorporate the changes outlined in the MOP into their procedures. All study team members listed on the study delegation log must be trained on the current version of the MOP. During the site initiation visit, questions will be addressed, and completion of training will be documented.

Figure 1: Study Schema



1.2 Glossary of Terms

AAA	abdominal aortic aneurysm
ACE	Aid to Capacity Evaluation
ACS	acute coronary syndrome
ABG	arterial blood gas
AE	adverse event
AKI	acute kidney injury
APACHE	Acute Physiology and Chronic Health Evaluation
A-V	arteriovenous
BiPAP	bilevel positive airway pressure
CAPA	corrective and preventative action
CFS	Clinical Frailty Scale
Cl^-	chloride
Co-I	co-investigator
COPD	chronic obstructive pulmonary disease
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 (resume)
CVC	central venous catheter
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
CPAP	continuous positive airway pressure
DMCC	Data Management and Coordination Centre
eCRF	electronic case report form
EMR	electronic medical record
FFP	fresh frozen plasma
FiO2	fraction of inspired oxygen
GCP	good clinical practices
GCS	Glasgow Coma Scale
GFR	glomerular filtration rate
GI	gastrointestinal
HCO_3	bicarbonate
HFO_2	high flow oxygen
HREB	human research ethics board
ICF	informed consent form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
ID	identification
IHD	intermittent hemodialysis
ILD	interstitial lung disease
IMV	invasive mechanical ventilation
IRRT	intermittent renal replacement therapy (includes IHD and SLED)
K^+	potassium
KDIGO	Kidney Disease Improving Global Outcomes
LAR	legally authorized representative
MAP	mean arterial pressure; mean airway pressure
Mg^+	magnesium
MI	myocardial infarction
MOP	manual of procedures
MRP	most responsible physician
Na^+	sodium
NIV	non-invasive ventilation
NTF	Note-to-file
PaO2	partial pressure of oxygen
PCO2	partial pressure of carbon dioxide
PO2	partial pressure of oxygen
PD	protocol deviation
PEEP	positive end-expiratory pressure
PI	principal investigator
PHI	personal health information

Plt	platelets
PMV	periodic monitoring visit
PO_4^-	phosphate
PPlat	plateau pressure
PROBE	prospective, randomized, open-label, blinded endpoint
RBC	red blood cells
RCA	root cause analysis
REB	research ethics board
REDCap	Research Electronic Data Capture
RN	registered nurse
RRT	renal replacement therapy
SAE	serious adverse event
SaO2	oxygen saturation of arterial blood
SAPS	Simplified Acute Physiology Score
SCr	serum creatinine
SDV	source data verification
SIV	site initiation visit
SDM	substitute decision maker
SLED	sustained low-efficiency dialysis
SOFA	Sequential Organ Failure Assessment
SOP	standard operating procedure
TCPS2 (2022)	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans
TDL	task delegation log
TIA	transient ischemic attack
UAH	University of Alberta Hospital
V-A	veno-arterial
V-V	veno-venous
WBC	white blood cell
WCHRI	Women and Children's Health Research Institute

Section 2: General Information

2.1 Co-Principal Investigators

Name and Institution	Address, Phone, Email
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Ron Wald, MDCM MPH FRCPC Division of Nephrology Department of Medicine St Michael's Hospital University of Toronto	30 Bond Street Toronto, Ontario, M5B 1W8 CANADA T: 416.867.3703 F: 416.593.6275 M: 416-258-6540 E: waldr@smh.ca

2.2 WISDOM 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 membership of the steering committee may change during the trial. Updates to the membership list below will be made when other updates to the MOP are also needed.

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;

Steering Committee Members:

Member	Contact	Role
Sean Bagshaw	E: bagshaw@ualberta.ca	Co-PI
Ron Wald	E: Ron.Wald@unityhealth.to	Co-PI
Ellen Morrison	E: ejmorris@ualberta.ca	Project Manager
D'Arcy Duquette	E: dvcduquette@shaw.ca	Patient Partner
Fernando Zampieri	E: fzampier@ualberta.ca	Co-Investigator

Ken Parhar	E: Ken.Parhar@albertahealthservices.ca	Co-Investigator
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Ellen Reil	E: Ellen.Reil@albertahealthservices.ca	Collaborator
Rachel Jeong	E: rachel.jeong@ucalgary.ca	Trainee
Zahraa Habeeb	E: zahraa@ualberta.ca	Trainee

2.3 Data Management and Coordinating Centre (DMCC)

The University of Alberta Clinical Trials Office (CTO) will serve as the Data Management and Coordinating Centre for the WISDOM trial. Participant data and regulatory documents will be deposited and maintained in REDCap databases hosted at the Women and Children's Health Research Institute (WCHRI) on secure servers at the University of Alberta in Edmonton, Alberta.

For questions about study operations please contact:
Ellen Morrison, Project Manager
Clinical Trials Office
University of Alberta
Suite 400, College Plaza
8215 112 Street
Edmonton, AB T6G 2C8
ejmorris@ualberta.ca

2.4 Study Sites and Site Principal Investigators

The current participating sites and site Principal Investigators' (PIs) contact information are listed below. The Site Principal Investigator must update the sponsor on any changes to the site name, mailing address, or site team members (name, role, email, phone contact) after site initiation. Such changes should be submitted by email to the Project Manager (ejmorris@ualberta.ca) in advance of any change and as soon as the site is aware of the changes.

List of Canadian Sites and PIs

Site Code	Site name	PI	PI Contact
UAH	University of Alberta	Sean Bagshaw	bagshaw@ualberta.ca
MAZ	Mazankowski Alberta Heart Institute	Sean van Diepen	sv9@ualberta.ca
RAH	Royal Alexandra Hospital	Jim Kutsogiannis	djk3@ualberta.ca
GNH	Grey Nuns Hospital	Janek Senaratne	janeks@ualberta.ca
FMC	Foothills Medical Centre	Ken Parhar	Ken.Parhar@ahs.ca
SCH	Sturgeon Community Hospital	Oleksa Rewa	rewa@ualberta.ca
RGH	Regina General Hospital	Bhanu Prasad	bprasad@sasktel.net
SHC	Sunnybrook Health Sciences Centre	Neill Adhikari	Neill.Adhikari@sunnybrook.ca
SMH	St Michael's Hospital	Ron Wald	Ron.Wald@unityhealth.to
SJH	St Joseph's Hospital	Ron Wald	Ron.Wald@unityhealth.to
CRH	Chinook Regional Hospital	Sean Spence	Sean.Spence@ahs.ca
KGH	Kingston General Hospital	Samuel Silver	samuel.silver@queensu.ca

The study sites are responsible for:

- Compliance with protocol, MOP, local Research Ethics Board (REB) policies and procedures and ICH Good Clinical Practice (GCP) guidelines
- Maintenance of study databases
- Recruitment, screening, and enrollment of participants
- Protection of participants' rights
- Data collection and participant follow-up through study completion
- Transfer of data to the Coordinating Center and resolution of all queries in a timely manner
- Compliance with and accountability of administration of study intervention
- Retention of specific records
- Communication of questions, concerns, and/or observations to the Coordinating Center

2.5 Communication Plan

2.5.1 Communication Between Sites and Sponsor/Coordinating Center

To ensure study progress and to address emerging study issues, the coordinating center will manage ongoing communication with study site investigators, study teams and members of the study committees.

The sponsor/coordinating centre will notify sites of any issues or new information that is identified during the conduct of the study by memo. All memos will be sent to all site PIs and site study coordinators as attachments to emails and should be filed in the site regulatory database upon receipt and reported to the local REB, as applicable.

A newsletter will be provided to the sites by the coordinating center on a monthly basis. This newsletter will include pertinent information, such as an update on the active or soon to be activated sites, number

of participants recruited, study reminders and most common adverse events encountered by all participants in the trial.

A monthly meeting for site investigators and study coordinators will occur to discuss the status of the study, any updates and issues with all the participating sites. All site investigators and study team members will be invited to attend. It will be required that at least the PI (or their designate) or the lead coordinator at each site attend these meetings. Site teams will be able to ask questions and share information during these meetings. Meeting minutes will be sent via email following the meeting to summarize the discussion.

2.5.2 Site Activation

Once the study site has received or is soon to receive the local ethics approval for the study and the subsite agreement is in signatures or finalized, the coordinating center will schedule a Site Initiation Visit (SIV). SIVs will most often be performed remotely via webinar. This SIV Meeting will provide protocol and operational training for the study. The site PI and site coordinator, at minimum, will be required to attend.

Once all the regulatory, contractual and training requirements have been completed by the study site, the coordinating center will issue an Activation Notice electronically to the participating site PI and site coordinator indicating that they may proceed with patient accrual.

2.5.3 Amendments

The Coordinating Centre/project manager will send a notification to all participating sites regarding any changes/amendments to the study protocol documents and procedures. It is the responsibility of the coordinating center/sponsor to:

- Provide all amended documents to the participating sites;
- Collect all approved study documents and site consent forms along with local ethics approval from the participating sites through the REDCap regulatory database.

If a participating site requests a modification to the study procedures, the following should occur:

- Protocol amendment: Notify the study co-PIs and the project manager indicating that a change is requested and explaining the reason why. This request will be reviewed by the steering committee and a decision as to whether a change to the protocol will be made, will be communicated to the site PI in writing.
- Consent Amendments: If a consent amendment is required by a participating site, the site must submit a highlighted/ tracked change version of the consent to the coordinating center for review. The coordinating center will provide written communication regarding approval of the revised site consents.
- Site PI Change: If the site PI needs to be changed, the site must notify the coordinating center and study co-chairs in writing prior to the date of the change in PI. The project manager will provide the procedure for the change in PI and template regulatory documents to be completed, if applicable. Contractual agreements will also be modified accordingly.

2.5.4 Study Documents

Site ethics annual approval letters, protocol compliance signature pages, approved study documents and consent forms should be uploaded to the REDCap regulatory database. The regulatory database will be reviewed by the project manager regularly for updates. If documents are unavailable for review, they will be requested by the project manager. Additional details regarding the REDCap regulatory database are provided in Section 10.

Section 3: Study Training Plan

3.1 Protocol Specific Training

An initial study specific training session will be conducted during the site initiation visit, including details about the protocol and operational training. Training on subsequent protocol amendments will be completed locally at each site. The coordinating center will provide updated training slides for each protocol amendment. Completion of training requirements must be documented and uploaded to the REDCap regulatory database for all study team members prior to activation or implementation of an amendment. Sites may use their own local training log template to document all training completed for this study or they may use the training log templates provided by the DMCC. If using a local site training log template, it must include the protocol number and title, version date and version # of the protocol, details of other documents reviewed with version date and # included, format of the training (group session, SIV, self-training (read and review)), the date of training, printed name of the individuals and signatures of the individuals who completed the training.

All study team members listed on the delegation log must complete the relevant training according to their responsibilities. At a minimum, the site PI and lead site coordinator must complete training on all protocol amendments. Local site SOPs for training requirements may be followed regarding decisions made by the site PI for when certain individuals do not require protocol amendment training. The decision on who needs training on each amendment should be documented (and signed by the site PI) and uploaded to the REDCap regulatory database prior to implementation of the protocol amendment.

3.2 General Clinical Trial Training Requirements

In addition to the study specific training, the study sites will have to upload to the regulatory database general clinical trial training documentation. This will be reviewed by the project manager for completeness prior to activation. The following table summarizes the requirements:

General clinical trial training requirements

Local site training requirements	**Documentation expected**
CVs (signed and dated)	CV - Everyone must be qualified to perform the role as delegated.
Copy of license/registration	license, practice permit - Required yearly for the principal and sub-investigators
GCP	Certificate of training completion, must be renewed every 3 years
Institutional SOPs	N2 SOPs (version 10) or local institutional SOPs training with training log/certificate must be completed at a frequency as required according to site policy.
Tri-Council Policy Statement (TCPS2 2022)	Certificate of training completion must be obtained. There is no expiry for this certificate.

As the WISDOM trial is a non-regulated trial, Health Canada Division 5 certification is not required.

3.3 REDCap Training

All site study staff who will be using the REDCap data entry system, including site PIs and coordinators, must complete and document training on REDCap prior to being granted access. The following REDCap training videos must be reviewed prior to signing off on the Training Log for new users who do not previously have a REDCap username and password for the University of Alberta WCHRI REDCap system.

i. **Detailed Overview of REDCap** (14 minutes): This video provides an overview of basic functions and features within a REDCap project. It will serve as a starting point for learning about the basic concepts of REDCap, what REDCap projects are, how to create them, and how to use them. A General Overview of REDCap (vanderbilt.edu)

ii. **Data Entry Overview** (19 minutes): A focused exploration of basic data entry workflow. Suitable for training data entry staff. An Overview of Basic Data Entry in REDCap (vanderbilt.edu)

iii. **Data Resolution Workflow- Data Queries Module** (5 minutes): This advanced tool enables a powerful data query management system. Data Resolution Workflow (vanderbilt.edu)

Sites may use their own local training log or one can be provided by the DMCC. The training log must include the REDCap module training details, the date of training, printed name of the individuals and signatures of the individuals who completed the training.

If any individuals at your site have already completed these REDCap training modules, the training does not need to be repeated. Documentation of the original REDCap training for those individuals who have previously completed the training or an attestation from the individual that they have previously be trained on the REDCap system must be maintained in the REDCap regulatory database with all other documents for this study.

Section 4: Task Delegation Log

4.1 Completion of a Task Delegation Log

A Task Delegation Log (TDL) is required to fulfill the following requirements:

- ICH GCP E6 (R2) Section 4.1.5 "the Investigator should maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related duties" and to document study-specific roles and responsibilities assigned to the study team by the Principal Investigator (PI).
- ICH GCP E6 (R2) Section 8.3.24 "signature sheet" to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs, clinic notes, etc.

Personnel assigned any research-related responsibilities or tasks not considered standard of care are required to be on the delegation log. The intention of the TDL is not to capture every task that an individual may perform, but to list the study personnel and the key study duties/tasks they are delegated. **This should include any duty/task that could impact participant safety, protocol conduct and compliance, collection of key study data, the quality and integrity of the study data**. A list of study tasks is included on the template TDL provided for this study. Additional tasks may also be added under the "Other" section. It is important to work with the sponsor to define additional study specific tasks and add them to the 'Other' section on the log.

The site PI retains the overall responsibility for the conduct of the clinical trial, including delegated duties/ tasks. The PI is responsible for providing adequate supervision and training to those to whom tasks are delegated. The evaluation of whether study personnel are performing functions within the scope of their professional licensure depends on the scope of their licensure, local regulations and institutional guidelines. The PI should be aware of the local requirements for licensed study personnel.

All staff delegated study-related tasks 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, assessment of AEs/SAEs, data collection, maintenance of regulatory binders) must be documented.

Prior to signing the Delegation Log, staff must have GCP, SOP and study-specific training. All personnel on the delegation log are required to have up-to-date GCP training, per their institutional and sponsor guidelines. Study-specific training must be current to the most recent approved amendment. Once training is completed, an individual can be added to the delegation log with responsibilities assigned by the PI. The delegated personnel should then sign the log indicating they understand and agree to the responsibilities/delegated tasks.

PI affirmation and delegation, by means of signature and date on the delegation log, must occur <u>after</u> the individual has completed GCP, 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.

A TDL must be completed prior to site activation, once training has been completed by the study team. The completed TDL must be added to the REDCap regulatory database in the appropriate instrument. Updates to the TDL (addition of new team members, changes in delegated tasks, removal of staff no longer participating in the conduct of the trial) should be made in real-time and the updated TDL added to the regulatory database each time a change occurs. At the end of the study, an end date for all individuals should be added and the final delegation log uploaded to the REDCap regulatory database.

Electronic signatures/initials on the TDL are permitted as long as the addition of these does not obscure any other information on the page. In addition, the signatures and initials must be the actual representation of the person's signature/initials. The signature/initials cannot be computer-generated fonts.

A study-specific TDL is provided for the WISDOM trial. Sites may use their own site template TDL with prior approval from the coordinating centre.

Section 5: Screening

5.1 Pre-Screening

Sites are encouraged to pre-screen patients in the ICU on a daily basis. The clinical status of these patients is dynamic and may change throughout the day. Ideally, pre-screening should occur in the morning and again in the afternoon. Theoretically, there is no limit on the frequency or number of times a patient may be re-screened. You may re-screen patients who are not initially eligible for the trial as several conditions for eligibility are inherently dynamic. For example, as the patient's clinical course continues CRRT may be considered later in their critical care course and not initially. If CRRT is considered or initiated at any time during their clinical course, the patient should be screened as they may be eligible. Patients that are not initially eligible because of anticipated withdrawal of life support within 24 hours whose prognosis subsequently improves may become eligible for inclusion in the study.

5.2 Screening Log

Patients should be screened for the first three inclusion criteria as outlined in the protocol (and below):

1. Age $\geq$ 18 years
2. Patient weight $\geq$ 55 kg
3. Plan to initiate CRRT or within 24 hours of having started CRRT for Acute Kidney Injury (AKI), (See Section 6.2 for details of the definition of AKI)

Screened patients who meet the first three criteria for inclusion (as listed above) should be entered in the screening log excel spreadsheet. If a patient does not meet all of the first three inclusion criteria, the patient should not be entered in the screening log.

Individuals should not be assigned more than one screening number. Patients that do not initially meet eligibility and that will be rescreened should not be entered in the screening log twice.

Clearly document the reasons patients are not meeting criteria and reasons eligible patients are not enrolled. This information is important for the Sponsor to make informed protocol revisions and assist sites with recruitment initiatives.

The Screening Log is an Excel spreadsheet provided by the sponsor to each site. The entries for the screening log have pre-assigned Screening IDs listed in the left-hand column of the spreadsheet. Patients should be entered consecutively in the list and no Screening ID should be skipped. This Screening ID will need to be entered on the top of the paper Eligibility CRF.

The Screen Date entered should be the last date screened, entered as dd/mmm/yyyy. The inclusion and exclusion criteria are listed across the top of the spreadsheet. Fill in the spreadsheet for all criteria by selecting Yes or No from the dropdown menu for each criterion.

If the patient is co-enrolled on another study, confirm that they do not need to be excluded from the

WISDOM study due to the co-enrollment. (Note: the WISDOM study does not restrict co-enrollment but other studies may not allow co-enrollment). Select Yes or No from the dropdown menu to indicate if the patient is being excluded from the WISDOM study due to a co-enrollment. If the patient is excluded because they are already enrolled on another study, enter the short name of the study in the appropriate cell.

Once all inclusion/exclusion criteria have been documented in the screening log spreadsheet, indicate by selecting Yes or No from the dropdown menu under the 'Eligible' column. If eligible, enter the date and time fully eligible in the appropriate columns. Enter the date in dd/mmm/yyyy format and the time in 24-hr clock HH:MM. If the patient is not eligible, enter N/A in the date and time columns.

For the Informed Consent at Time of Screening column, select from the dropdown menu the option that applies. If the option 'No – other' is selected in the Informed Consent at Time of Screening, please enter an explanatory comment in the Additional Comments column.

If the patient is eligible, then complete the 'Inclusion Exclusion and Enrollment' eCRF in REDCap and enter the Participant ID number that is created in REDCap in the last column for the Screening Log spreadsheet. (See Section 10.3.2.2 for details on assignment of Participant ID numbers in REDCap).

The screening log spreadsheet should be on-going and cumulative and include all screened patients from site activation to end of accrual. The current screening log should be uploaded into the site-specific REDCap 'Screening & Enrollment Log' instrument in the site's REDCap regulatory database on the FIRST business day of each month. Save the document as a new file each month using "Save As" and name the document "WISDOM-<3-letter site code> - <yyyy-mmm>. The month in the filename should be the month in which patients were screened (i.e. if uploading the document on May 1st, 2024, the filename would be WISDOM-<3-letter site code> - 2024Apr).

5.3 Informed Consent and Enrollment Log

Once the participant has met all inclusion criteria, signed a consent form (or a deferred consent process has been initiated) and been assigned a study participant ID, the details should be entered in the Informed Consent and Enrollment Log. The participant ID assigned after completion of the 'Inclusion Exclusion and Enrolment' eCRF in REDCap should be entered in the Participant ID column. The date the consent was signed, the type of consent obtained, the version & date of the ICF signed should be entered in the appropriate columns. Check the appropriate box to indicate if the participant was enrolled and randomized and provide the date of enrollment/randomization or the reason they were not enrolled/randomized, as appropriate. The person recording these details must initial and date the entry in the right-hand column. If entering the information electronically, typing the name or initials of the recorder in the last column is sufficient. Once the page is completed, it should be saved as a pdf and filed in the REDCap regulatory database under the 'Screening & Enrollment Log' instrument.

If the participant is enrolled in the study with deferred consent or SDM consent, additional entries on the Informed Consent and Enrollment Log for SDM/participant consent and regained capacity consent are required to be entered when the additional consents are completed.

5.4 Master ID Log

The site should maintain a Master ID log which links the participant's PHI with the study ID. This should not be uploaded to the REDCap regulatory database and should be kept in a secure area by the site study team. A Master ID Log Template can be provided upon request. Sites may also use their own Master ID Log template, with agreement from the sponsor.

Section 6: Eligibility Criteria

6.1 Overview of Eligibility Criteria

Part of the screening process will include gathering information and results from treating physicians and medical records, since the patients may not be physically able to answer questions. These pieces of information will help assess suitability and determine eligibility to participate in the trial. All patients entering the ICU should be assessed for eligibility for the WISDOM trial, including patients who are re-admitted into the ICU who did not previously meet eligibility criteria. Only after all inclusion criteria have been met, and all exclusion criteria have not, will the participant be considered eligible to participate in the trial. Eligible patients should then be reviewed with the attending physician(s) caring for the patient (i.e., the ICU physician). Enrollment of a patient rests on the non-objection of the attending physician(s) to the patient's participation in the trial.

6.2 Eligibility Criteria

Inclusion Criteria

1. Age $\geq$ 18 years
   - Patient's age on the day of eligibility screening
2. Patient Weight $\geq$ 55 kg
   - Current weight if was collected when admitted, or if not collected at the time of admission, a weight collected within the last 365 days, if available in the medical chart, or an estimated weight if not known/previously documented in the medical chart.
3. Plan to initiate CRRT or within 24 hours of having started CRRT for Acute Kidney Injury (AKI)
   - Diagnosis of AKI should meet the KDIGO CPGs consensus definition for eligibility on this trial:
     - AKI is defined as any of the following (Not Graded):
       - Increase in SCr by $\geq$ 0.3 mg/dL ($\geq$ 26.5 µmol/L) within 48 hours; or
       - Increase in SCr to $\geq$ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
       - Urine volume <0.5 mL/kg/hr for 6 hours.
4. Expected to survive and receive CRRT for a duration of $\geq$ 48 hours
   - Per the treating physician's judgement
5. 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 local REB

Exclusion Criteria

1. Indication for sustained higher dose-intensity CRRT as designated by the attending clinician(s)
   - For example (but not limited to), hyperammonemia in acute liver failure; hyperuricemia in tumor lysis syndrome; hyperkalemia in rhabdomyolysis, etc.
   - Per the treating physician's judgement
2. End-stage kidney disease receiving maintenance dialysis
3. Receipt of any RRT for AKI during the current hospitalization
4. Inability to comply with the requirements of the study protocol.

IF THE PATIENT MEETS ALL OF THE ABOVE INCLUSION CRITERIA AND NONE OF THE EXCLUSIONS, THEN THE PATIENT IS DEEMED ELIGIBLE AND THE TREATING PHYCISIAN SHOULD THEN BE APPROACHED BY THE RESEARCH TEAM TO CONFIRM THEIR AGREEMENT WITH TRIAL ENROLLMENT.

6.3 Documentation of Eligibility

Use the CRF Form "Form 1: Eligibility and Enrollment" in the paper CRF package to document the assessment of eligibility. For all eligibility criteria, source documents (either paper or electronic) must exist in either the participant's clinical chart or the study file. Examples of relevant source documents may include medical history note, hospital intake notes, progress notes and discussions with the SDM or MRP regarding medical history.

The paper Eligibility CRF should be signed by the site PI/Co-I prior to randomization. Signature/date and time on the paper eligibility CRF must be completed. Electronic signature or wet ink signature is acceptable. If a signature is not able to be provided on the paper CRF prior to randomization, then additional documentation (EMR note, email, text) must be available to document the date and time that the PI/Co-I reviewed and approved the eligibility prior to randomization. All documentation (CRF, EMR note, emails, texts, etc) confirming PI/Co-I approval of eligibility must be filed in the participant's research chart.

If your site's process differs from ICH GCP requirements, please describe your process for eligibility review in a Note to File or Standard Operating Procedure (SOP) and notify the project manager. File the documents that explain the eligibility review process in your REDCap regulatory file.

If a contraindication to eligibility occurs between the signing of the ICF and enrollment through REDCap, the participant must be deemed ineligible and not enrolled into the study.

Eligibility will not be re-assessed throughout the study – meaning that the participant does not need to continue to meet all the initial eligibility criteria throughout the length of the study. If at any time during the study, a participant no longer meets study inclusion/exclusion criteria due to a change in medication or due to the development of a new medical condition, this should be noted in the chart and CRFs, and the participant will be allowed to continue participation at the discretion of the PI.

Section 7: Informed Consent

7.1 Informed Consent Process

Informed consent is an ongoing process that must be obtained and maintained for each participant throughout the study. Consent to participate in the study **must** be obtained from the participant or their Substitute Decision Maker (SDM) prior to any study procedures taking place unless the use of a deferred consent process is approved by the local REB. Consent should be maintained by providing participants or their Substitute Decision Maker (SDM) with opportunities to ask questions throughout the duration of the study. Only ICFs and updates that have been approved by the local research ethics board may be used.

The individual obtaining informed consent must be a research team member that has been trained in the consent process and delegated this responsibility as recorded on the Task Delegation Log (TDL).

7.2 Substitute Decision Maker (SDM) Determination

As some potential study participants may be intubated or sedated and thus lack the capacity to consent, an SDM may be needed to consent on their behalf prior to enrollment. The site will need to refer to local regulations and policies to determine who can be an SDM. Any questions regarding the appropriateness of a potential SDM should be directed to the site's local REB. Additionally, if the emergency contact person listed on the participant file is not a direct family member (e.g., employer, friend, etc.), sites are encouraged to get in touch with their REB before contacting the emergency contact person, even if the purpose of contacting them is to collect SDM information. File any REB correspondence in the REDCap regulatory file and participant research file.

7.3 Obtaining Consent

Initiating the consent process

POLICIES REGARDING CONSENT MECHANISMS MAY DIFFER BETWEEN STUDY SITES. PLEASE FOLLOW BOTH REGULATORY REQUIREMENTS AND LOCAL POLICIES AS APPROVED BY THE LOCAL REB.

Patients and/or their SDM will be approached by the PI or Research Nurse/Coordinator. Ideally, a member of the clinical treating team for the patient will provide a brief introduction to the study prior to the patient/SDM being approached by the research personnel.

One or more study investigators may be involved in the clinical care of some prospective participants. In this scenario and whenever possible, the investigator(s) must excuse him/herself from involvement in the consent process in order to avoid an impression of a conflict of interest or undue influence.

Prior to initial contact with the patient, the study team should ensure that the patient/SDM has been informed regarding the patient's clinical condition and diagnoses and potential eligibility for a research study by the attending team (MRP/RN).

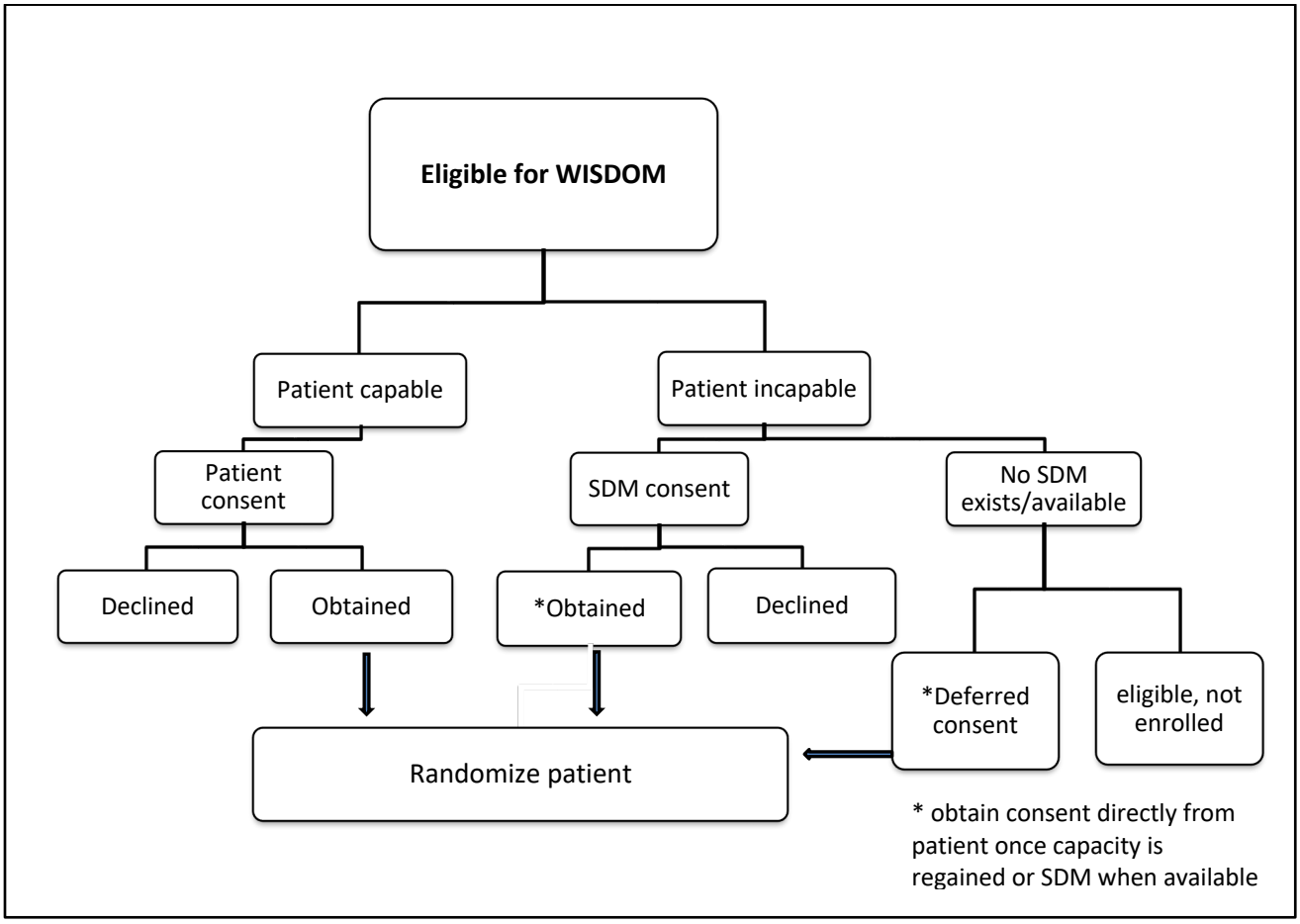
Assessing capacity for consent

Every attempt should be made to explain the rationale and potential risks of the study to the patient, or if he/she is incapacitated, to an SDM. Assessing patient capacity requires considerable clinical judgment.

The modified Aid to Capacity Evaluation (ACE) screening tool (see Appendix A) is recommended as a guideline but centres may use whatever processes are in place at their site for assessment of capacity.

The following flow chart illustrates the possible scenarios for patient consent at most centers:

Figure 2: Pathways for Consent to Randomization



Documentation of Consent Processes

There are several ways in which consent may occur for this study. Each time consent is discussed and/or obtained it must be documented in the study chart. Below are some examples of how consent may arise and the processes that need to be followed.

Patient has capacity to provide consent. Provide the potential participant with a copy of the most current and approved ICF to read and review. Review the details and all pertinent aspects of the study with the potential participant and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any time without changes to the quality of their healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered. After the potential participant has read the ICF, ascertain their willingness to consent to the study. Document whether the potential participant

declines or accepts on the Screening Log. If the potential participant agrees, obtain their written consent. The designated study team member must also sign and date the ICF. Provide a copy of the ICF to the participant and keep the original in a separate file. Document the date and time of consent on the CRFs and as per local site policy.

Patient does not have capacity and a SDM is available. If a patient is deemed not to have capacity to consent, then a SDM should be sought using the patient's pre-determined preferences for care. If the patient's SDM is unavailable, then a standard hierarchical order of people authorized to make medical decisions for an incapacitated patient, based on local practices, should be considered. If an SDM is identified, attempt to obtain consent from this individual using the most recently REB-approved ICF. Review the details and all pertinent aspects of the study with the SDM and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any time without changes to the quality of the patient's healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered. After the SDM has read the ICF, ascertain their willingness to consent to the study on behalf of the patient. Document whether the SDM declines or accepts on the Screening Log. If the SDM agrees, obtain their written consent. The designated study team member must also sign and date the ICF. Provide a copy to the SDM and keep the original in a separate file. Document the date and time of consent on the CRFs and as per local site policy.

In situations where enrollment is based on SDM-provided consent, frequent attempts to verify the patient's capacity must be made to obtain consent from the participant once capacity is regained. Documentation of the attempts to verify capacity must be documented in the study chart. If regained capacity consent is not obtained for any reason, an explanation must be documented in the study chart and REDCap eCRFs.

Regained Capacity following SDM consent. If a participant regains capacity to consent, review the details and all pertinent aspects of the study with the participant and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any time without changes to the quality of their healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered. After the participant has read the ICF, ascertain their willingness to consent to the study. If the participant agrees, obtain their written consent on the currently approved regained capacity consent form. The designated study team member must also sign and date the ICF. Provide a copy to the participant and keep the original in a separate file. Document the date and time of consent as per local site policy.

If the patient chooses to withdraw from the study following regained capacity, he/she should be asked to authorize retention of all data collected to date and/or completion of follow-up for detection of study outcomes at 90 days. Documentation of this authorization or refusal to allow data to be used or follow-up data to be collected must be included in the study chart.

Patient does not have capacity and SDM not located. If the patient is incapacitated and a SDM is not found, the patient may be enrolled and randomized with a deferred consent process, if a deferred consent

process is approved by the local REB. Please provide confirmation of REB approval of the site's deferred consent process in writing to the sponsor prior to study activation.

Deferred consent should be obtained from the MRP but should not be signed by the site PI or Co-Is. In situations where the MRP is affiliated with the study (e.g., PI or Co-Investigator) refer to local REB guidelines on usage of deferred consent models.

It is important to note that deferred consent is not consent. It is a placeholder assent by the treating team as the consent process is being deferred until the participant or SDM is available to take part in the consent process. All efforts must be made by the study team to obtain consent as soon as possible from the SDM once available and/or participant's capacity to consent is regained. Documentation of the attempts to verify capacity must be documented in the study chart.

Figure 3 below show the pathways to participant consent when a deferred consent process is initially employed.

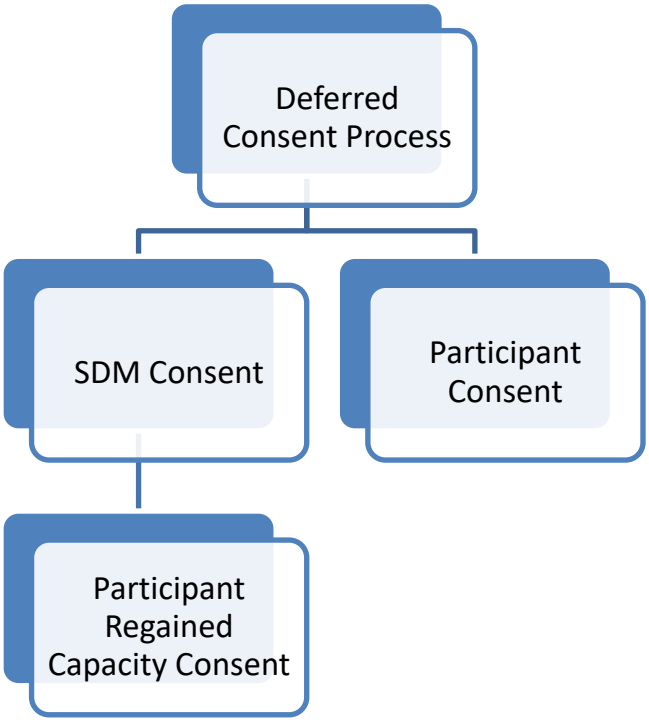
- **Regained Capacity following deferred consent process.** If a participant regains capacity to consent prior to consent being given by an SDM, review the details and all pertinent aspects of the study with the participant and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any time without changes to the quality of their healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered. After the participant has read the ICF, ascertain their willingness to consent to the study. If the participant agrees, obtain their written consent on the currently approved full consent form. The designated study team member must also sign and date the ICF. Provide a copy to the participant and keep the original in a separate file. Document the date and time of consent as per local site policy.

- **SDM Consent following deferred consent process.** If an SDM is identified, attempt to obtain consent from this individual using the most recently REB-approved full ICF. Review the details and all pertinent aspects of the study with the SDM and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any time without changes to the quality of the patient's healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered. After the SDM has read the ICF, ascertain their willingness to consent to the study on behalf of the patient. Document whether the SDM declines or accepts on the Screening Log. If the SDM agrees, obtain their written consent. The designated study team member must also sign and date the ICF. Provide a copy to the SDM and keep the original in a separate file. Document the date and time of consent as per local site policy.

  Regained Capacity following Deferred consent process and then SDM consent. If a participant regains capacity to consent following consent being obtained from an SDM, review the details and all pertinent aspects of the study with the participant and confirm that the study is understood. Answer any questions that may arise. Ensure they are aware that they can withdraw consent at any

time without changes to the quality of their healthcare. Ensure ample time has been given to make a decision regarding participation, and that all questions pertaining to the study have been sufficiently answered. After the participant has read the ICF, ascertain their willingness to consent to the study. If the participant agrees, obtain their written consent on the currently approved regained capacity consent form. The designated study team member must also sign and date the ICF. Provide a copy to the participant and keep the original in a separate file. Document the date and time of consent as per local site policy.

Figure 3: Pathways for Obtaining Full Participant Consent after Deferred Consent



Document the date and time of all consents signed on the Informed Consent and Enrollment log. If consent either from the participant or SDM is not obtained following deferred consent, there must be documentation in the study chart and REDCap eCRFs as to why participant/SDM consent was not obtained. If SDM or participant consent is not obtained following deferred consent, permission/approval from the REB must be obtained to keep the data collected for that participant in the study database.

7.4 Withdrawal of Consent

The participant/SDM can withdraw their consent to participate at any time during the study. Refer to your site's local REB policy regarding the following provisions. Document any discussions regarding consent and withdrawal of consent in the participant's research file.

Provisions of Withdrawal of Consent

a) Participant/SDM does not wish to continue the study treatment but has consented to be contacted for safety assessments (e.g. safety follow-up calls) and the collection of information from their medical records to complete data forms.

b) Participant/SDM does not wish to continue the study treatment and does not want to be contacted for safety assessments. They **do** consent to the collection of information from their medical records.

c) Participant/SDM does not wish to continue the study treatment, does not want to be contacted for safety assessments and **does not** consent to their medical records being accessed. Ensure the participant is informed that all data collected up until the point of withdrawal will be used for study purposes. No further data is to be collected from the participant.

Section 8: Randomization

8.1 Screening and Participant IDs

All patients screened should be included on the screening log per the instructions in Section 5.2. Once eligibility is confirmed, whether the patient is enrolled/randomized or not, a participant ID must be assigned in REDCap. Each new patient entered into REDCap (whether for enrollment/randomization or as eligible but not enrolled), will be assigned a unique Participant ID number.

The patient must be identified by their unique study number and no PHI should be included in all correspondence with the Coordinating Centre. The format of the participant ID number will be 'XXX-###', where the first 3 letters correspond to the site (see Section 2.4) and the last 3 numbers correspond to the patient number. This participant ID is to be written on all participant CRFs and corresponding research documents.

A Patient Screening ID # is listed on the Screening Log spreadsheet in the lefthand column – 0001, 0002, 0003, etc. The Screening ID is assigned based on the numbers in the left-hand column of the screening log at each site and should be entered at the top of the eligibility CRF only. Please note, the Screening ID does not determine the Participant ID. These numbers are separate and independent of each other.

Once it is determined that the patient will be enrolled/randomized or if they are eligible but not enrolled, the site coordinator must create a new record in REDCap (see Section 10.3.2.1 below for details on how to do this) and assign a Participant ID number following a sequential system of assignment. For example, the first patient that is determined to be eligible should be entered as XXX-001. The second patient that is determined to be eligible should be entered as XXX-002. The participant number assignment should be completed regardless of whether the patients are randomized or not if they are entered in REDCap.

Please see Section 10.3.2.2 for additional details on assigning the participant ID number in REDCap.

8.2 Co-enrollment

WISDOM does not restrict co-enrollment into other studies unless the intervention in the other trial is perceived to interact with the WISDOM intervention. This will be determined by the PIs. If a participant is being considered for multiple studies, verify that the competing study(ies) do(es) not prohibit co-enrollment on other studies.

8.3 Randomization in REDCap

Once the patient has been enrolled, the Randomization eCRF in REDCap will be available for completion. See Section 10.3.2 below for details on this process. Once randomization has been completed in REDCap, an email will be sent to the study co-chairs, project manager and the site PI and site coordinator detailing the enrollment, and which arm the participant was allocated to.

Section 9: TREATMENT CONSIDERATIONS

9.1 Timing for Starting Study Allocated CRRT

As outlined in the protocol, participants must begin to receive the study-allocated CRRT dose within 24 hours of starting standard-dose CRRT and after receipt of 12 hours of standard dose CRRT.

This means that from the time of starting CRRT, there is 24 hours to:

- Confirm eligibility,
- Obtain informed consent or document the process for deferred consent,
- Randomize the patient, and
- Begin the study allocated CRRT.

Potential participants can be consented and randomized, if they meet eligibility criteria, prior to initiation of standard dose CRRT. The participant will still need to receive 12 hours of standard dose CRRT and start the study allocated CRRT dose within 24 hours of starting the standard dose CRRT. If participants are randomized prior to initiation of CRRT, there is no time requirement to initiate standard dose CRRT.

Some potential scenarios are outlined below regarding the timing requirements for the study-allocated CRRT.

Example 1: CRRT started and then all study activities were completed: Participant started standard dose CRRT on October 14th at 13:00. Eligibility was confirmed on October 14th at 14:00 and consent was obtained on the same day at 15:00. The study-allocated CRRT must start no earlier than October 15th at 01:00 and no later than October 15th at 13:00.

Example 2: Study activities completed prior to CRRT start: Participant is admitted to the ICU on October 15th at 09:00 and the treating team plans to initiate CRRT. The study team begins assessment of eligibility, obtains consent and randomizes the participant by October 16th at 10:00. Standard-dose CRRT has not yet been started when the participant is randomized. Standard-dose CRRT begins on October 17th at 20:00. The study-allocated CRRT must start no earlier than October 18th at 08:00 and no later than October 18th at 20:00.

Example 3: Study activities completed both prior to and after standard-dose CRRT start: Participant is admitted to the ICU on October 15th at 09:00 and the treating team plans to initiate CRRT. The study team confirms eligibility on October 15th at 15:00. Standard-dose CRRT is initiated on October 16th at 08:00. Consent is obtained on October 16th at 09:00 and the study team randomizes the participant on October 16th at 10:00. The study-allocated CRRT must start no earlier than October 16th at 20:00 and no later than October 17th at 08:00.

9.2 Timing for Study Days

The study intervention information is collected following randomization until CRRT is permanently discontinued. The same information will be collected each day while the participant is receiving CRRT. The first day will be Day 0 and will usually be a partial day.

- For participants already receiving CRRT at time of randomization, Day 0 represents the time from randomization to the end of that 'ICU' day.
- For participants randomized prior to initiation of CRRT, Day 0 is defined as the first day that standard-dose CRRT is started.

The daily data are collected only while patients are receiving CRRT. A daily data form should be completed for each day that the participant receives CRRT even if CRRT is not received for the full day. For example, a 'partial day' may occur if CRRT is stopped temporarily for tests or procedures or if the participant is discharged to the ward, another ICU or another hospital during an 'ICU day'.

Calculation of Day 90 will be based on Day 0 as defined above – either 90 days after the date of randomization if already receiving CRRT or 90 days after the first day standard-dose CRRT is started.

How is a "day" defined in WISDOM?

A 'day' should coincide with the usual 24-hour data collection period in your institution's ICU. Some ICUs will define the 'day' as the calendar day (00:00 – 23:59) while others may consider a 'day' as running from 08:00 – 07:59. To facilitate data collection locally, the 'days' associated with data collection in the WISDOM trial will correspond to the 'days' as defined by your institution's ICU.

For example, if a given ICU collects data from 0800 – 0759, and a patient is randomized, and already receiving CRRT, at 22:00 on August 24, 2024, Day 0 will run from 22:00 on August 24th to 07:59 on August 25th. Day 1 will be from 08:00 on August 25th to 07:59 on August 26th, and so on.

Individual sites must be consistent in the start and stop times defined as the 24-hour time periods for their ICU. Variation in the start and stop times of a 24-hour period between sites will not affect the study data.

9.3 Initiation and Re-initiation of CRRT

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

CRRT will continue until death, transition to intermittent RRT (IRRT) or until kidney recovery with no further requirement for RRT. Transition to intermittent RRT therapies will generally align with hemodynamic stabilization and weaning of vasoactive support (i.e., $SOFA_{CV}$ score <2).

If during their ICU admission a patient has their CRRT temporarily interrupted (e.g., diagnostic imaging, procedures or operations), once restarted, the CRRT should be prescribed according to their study-assigned CRRT dose-intensity. If a patient has prolonged CRRT interruption (>6 hours) (e.g., operative theatre), CRRT should be temporarily restarted at the standard dose-intensity for 6 hours to ensure a period of stabilization, then transitioned to their study-assigned CRRT dose-intensity, as applicable.

9.4 Dose Modifications

Temporary increases in CRRT dose-intensity may be instituted at the discretion of the treating ICU team. Among patients allocated to the lower CRRT dose-intensity, if judged by treating ICU team to require a temporary increase in CRRT dose-intensity, the following actions are proposed:

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, and if applicable, 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 ($NaHCO_3$) either as a continuous infusion or bicarbonate can be added to the replacement/dialysate solutions, and if applicable, 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 and not declining, 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. Any decision to escalate CRRT dose-intensity above the protocol-mandated dose-intensity target will be documented and clinicians will be asked to report the reason(s) for this as: i) inadequate acid-base control; ii) inadequate electrolyte control; iii) inadequate azotemic control; or iv) other (describe).

9.5 Assessment on Clinical Frailty Scale

The Clinical Frailty Scale (CFS) Assessment needs to be completed at the time of enrollment by the MRP or designate. If this is a standard of care assessment, it should have been completed at the time of admission to the ICU. If recorded at ICU admission, this value can be recorded for this study once consent is obtained. If it is not a standard of care assessment when a patient is admitted to ICU, the MRP or designate must complete the CFS assessment at the time of enrollment. The diagram below can be used to complete the assessment based on information gleaned from the patient, family members and clinical notes. The score is meant to reflect the patient's state of health prior to the illness that led to the current hospitalization (e.g., 2-6 weeks preceding hospitalization).

CLINICAL FRAILTY SCALE

1 VERY FIT

People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.

2 FIT

People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.

3 MANAGING WELL

People whose **medical problems are well controlled**, even if occasionally symptomatic, but often **not regularly active** beyond routine walking.

4 LIVING WITH VERY MILD FRAILTY

Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.

5 LIVING WITH MILD FRAILTY

People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.

6 LIVING WITH MODERATE FRAILTY

People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 LIVING WITH SEVERE FRAILTY

Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 LIVING WITH VERY SEVERE FRAILTY

Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.

9 TERMINALLY ILL

Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** Many terminally ill people can still exercise until very close to death.

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/ story and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In severe dementia, they cannot do personal care without help.

In very severe dementia they are often bedfast. Many are virtually mute.

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Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

9.6 Assessment of Glasgow Coma Scale:

If the Glasgow Coma Scale (GCS) score is not readily available in the medical chart, the MRP or designate or the research team can calculate the GCS, using the table below:

GLASGOW COMA SCALE		
Parameter	**Response**	**Points Assigned (please circle)**
Eyes Open	Spontaneously	4
	On spoken command	3
	On pain	2
	No response	1
Best Motor Response	To spoken command	6
	To painful stimulus:	
	Localized pain	5
	Flexion withdrawal	4
	Flexion abnormal	3
	Extension	2
	No response	1
Best Verbal Response	*(Not on ventilator)*	
	Oriented & converses	5
	Disoriented & converses	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
	(On ventilator)	
	Appears oriented	5
	Questionably oriented	3
	Generally unresponsive	1
	TOTAL GCS =	

- Calculate the GCS by assessing each of the three components: eye opening, motor response and verbal response.
- Choose the most accurate, lowest cumulative score available in the 24-hour assessment period.
- If a patient has received sedation or paralytic agents, it is preferable to record the GCS prior to receiving the medications even if outside the 24-hour assessment period.
- If you are unable to obtain reliable pre-sedation GCS, the neurological status should be scored as normal (GCS = 15).
- Patients who receive large amounts of sedation may have their GCS recorded as '3' (ie no response for eye opening, motor, or verbal). Unless there is a documented cause for the decreased level of consciousness (in addition to sedation) this should not be considered an accurate GCS.
- If patient intubated, assign a score "1" for verbal without making an assumption of their verbal capabilities had they not been intubated.

Section 10: Data Collection

The following section will provide guidance on how to complete each element of the CRFs both on paper and in the REDCap database. Daily documentation will continue for the length of time that the participant is receiving CRRT. If a participant has their CRRT temporarily interrupted (e.g., diagnostic imaging or other investigations; procedures or operations) or discontinued with the intent of liberation and requires re-initiation due to ongoing need (after a period of hours or days), once restarted, the daily documentation should note these interruptions and the daily documentation should resume. Participants will remain in the trial for a maximum of 90 days from study enrollment.

10.1 REDCap Databases and Access

REDCap is a secure web-based application for managing research data. There will be two separate databases for this study – one for participant data and one for the regulatory/essential documents. The REDCap platform can be accessed through the following link: https://micyrn.med.ualberta.ca/. Access to the WISDOM databases will be provided while sites are working on the activation procedures for the study, once the REDCap training is completed.

Once individuals have provided the REDCap training documentation, the project manager will request access to the REDCap databases for the WISDOM study on their behalf. Research staff from each site will receive an individual username and password (if they do not already have one), to sign into REDCap, directly from the REDCap Support Team at WCHRI. Research staff may enter data directly into the REDCap database from the source data (i.e., medical chart, etc) or, if they prefer, they may record study information on the paper CRFs and then transcribe into REDCap. The paper CRFs may be used as source data if signed and dated by the PI or designate in real-time. For example, confirmation of eligibility can be documented on the CRFs and used as source data if the PI or Co-I sign it prior to randomization.

After entering your username and password into the REDCap login, you will be able to access the databases, WISDOM (participant database) and Regulatory Binder: WISDOM, under 'My Projects'. Completion of the regulatory database is the responsibility of the site coordinator and replaces the need for a physical paper regulatory binder. No PHI should be uploaded to the regulatory database. All entries in the participant and regulatory databases are subject to monitoring and auditing.

REDCap maintains a clear audit trail for all data entered in the system. Username and passwords should not be shared with anyone else. It is recommended that users log in at least once a month to REDCap. User accounts are suspended when individuals have not logged into their account in more than 180 days. After 180 days, the user will receive an email notifying them of account suspension and to contact the REDCap administrator.

Please email redcap@ualberta.ca to reset your password if locked out. Please note that when the password is reset it is time sensitive. If the user cannot log in and reset their password in the allotted time, the link expires.

10.2 Source Documents

Source documents are the first place that you collect data. Source documents may include intake notes, clinic notes, laboratory reports, phone call logs, etc. and may be paper form and/or electronic medical record. This information is then entered into the CRFs. CRFs are study specific forms which are used to collect the data required from each participant in the study in order to analyze for the primary and secondary outcomes and may be on paper or electronic. If paper CRFs are used to collect the data from the source documents, the data will then need to be entered into the REDCap participant database. The data collected in the eCRFs will be reviewed and queried in order to ensure its accuracy and integrity prior to including it in the analysis.

10.3 Case Report Forms (paper & electronic)

Refer to the participant's hospital medical record to complete case report forms.

Study teams may choose to complete the paper CRFs to document PI oversight and then transcribe the data into the REDCap database or do direct data entry from EMR to the REDCap database. Sites may choose to use a combination of these methods. Please note that in either situation, there must source documents available for review and there must be medical oversight and clear documentation of review/approval by signing of documents (either paper CRFs or electronically in an EMR or in REDCap) by the site PI or Co-Is for eligibility, AEs/SAEs, protocol deviations and other situations where medical-related decisions are made.

If entering data in the paper CRFs and then transcribing into REDCap, please follow the instructions below for paper CRF completion. See Section 10.3.2 for instructions regarding REDCap eCRF completion.

10.3.1 Paper CRF Completion Guidelines

The following sections will provide guidance on the completion of the paper CRFs which were provided with the study activation package. If there are any changes made to these CRFs during the course of the study, the revised CRFs will be provided to you by the study sponsor.

At the bottom of each page of the CRFs package is a space for the PI, Co-I or coordinator to sign and date confirming review of the data that was entered. This should be done in real-time prior to data entry into the REDCap database.

10.3.1.1 Form 1: Eligibility and Enrollment CRF

This CRF should be completed if it has been determined through the screening process that the patient is eligible.

Data Element	Description
Trial Site	Enter the three-letter code for your site, as denoted above in Section 2.4, at the top of each page of Form 1.
Screening ID	Enter the sequential 4-digit number assigned on the Screening Log at the top of each page of Form 1. These numbers are listed in the Excel spreadsheet in the lefthand most column and will follow the pattern: 0001, 0002, 0003, etc. Note: This Screening ID is <u>not entered</u> in REDCap. It is used on Form 1 to connect the

Data Element	Description
	Screening Log entries to the participants that are eventually entered into the REDCap database whether enrolled/randomized participants or entered into the eligible not enrolled dataset.
Inclusion Criteria	Review the patient's chart to confirm each item in the inclusion criteria has been documented. If the patient meets a criterion, select 'YES' on the CRF. All criteria should be answered 'YES' for the patient to be eligible for study inclusion.
Exclusion Criteria	Review the patient's chart to confirm each item in the exclusion criteria has been addressed and documented. If the patient does not meet a criterion, select 'No' on the CRF. All criteria should be answered 'NO' for the patient to be eligible for study inclusion.
Eligibility	If the patient has met all inclusion criteria and none of the exclusion criteria, select 'YES' for both questions: Was 'YES' answered for all inclusion criteria?' and 'Was 'NO' answered to all exclusion criteria?'. If 'YES' is selected for both questions, enter the date and time that eligibility was confirmed by the PI/Co-I. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. This date and time should match the date and time entered in the Screening Log.
Attestation	The PI or Co-I, who reviewed the eligibility, must select 'Yes' or 'No' to agree or disagree with the attestation and then print their name, sign and add date/time of signature to the CRF. See Section 6.3 for alternate documentation requirements for eligibility assessment.
Initial Consent Prior to Randomization	Confirm that consent was obtained from the participant or SDM or that a deferred consent process with assent from the MRP was obtained by selecting 'YES'. If consent/deferred consent was not obtained the participant may still be eligible to be included in the 'Eligible but not Enrolled' dataset.
Type of Consent Obtained	Indicate which type of consent (Deferred consent process with assent from the clinical team, participant consent, or SDM consent) was obtained by checking the appropriate box. Only one box should be checked for the initial consent prior to randomization. Then enter the date and time signatures were obtained on the consent form.
Registration in REDCap	Registration of the participant in REDCap occurs when a new record is created in REDCap and the inclusion exclusion and enrollment eCRF is completed. See details below in Section 10.3.2.1 for how to create a new record and enter the participant data in the REDCap database. If the participant was registered in REDCap, select 'YES' on the paper CRF. Then enter the Participant ID that was created in REDCap for the participant. It should follow the format XXX-###.
Enrollment on the Study	Confirm that the participant was enrolled on the study in REDCap by selecting 'YES' or 'NO'. ➢ If they were enrolled, complete the randomization step in REDCap. ➢ If they were not enrolled, complete the CRF, Form 2: Eligible but not Enrolled in both the paper CRF package and in REDCap.

Data Element	Description
Randomization	If the participant was enrolled and randomized in REDCap, select 'YES' and then enter the date and time that the randomization occurred. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. This date and time should match the date and time the confirmation email from REDCap is received which confirms the randomization and states the arm of the study that the participant has been assigned.
Allocated Study Arm	Select the study arm that the participant was allocated to in REDCap and as noted in the email sent to the site PI and site coordinator following randomization.
Consent Post-Randomization following Deferred Consent	If a deferred consent process was used prior to randomization, this section of the CRF must be completed following randomization. Select 'YES' if consent was obtained (either SDM or participant). Select the Type of Consent obtained – either participant or SDM consent. Then enter the date and time the consent signatures were obtained. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. If consent was not obtained post-randomization, select 'NO' to the initial question. Then provide a reason under 'Please specify why SDM or Participant consent was not obtained post-randomization.' If SDM or participant consent was not obtained post-randomization, please confirm if the REB was notified and permission was given by the REB to keep the data for this participant by selecting 'YES' or 'NO'. If the REB did not give permission to keep the data for a participant for which consent was not obtained, please contact the project manager. Correspondence with the REB which outlines their decision regarding permission to keep the data must be uploaded to the REDCap regulatory database.
Consent Post-Randomization following SDM Consent	If SDM consent was obtained either prior to randomization or post-randomization, this section of the CRF must be completed once it becomes clear if participant regained capacity consent was obtained or not. This may not occur until later in the study timeline. Select 'YES' if regained capacity consent was obtained. Enter the date and time the consent signatures were obtained. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. If regained capacity consent is not obtained, select 'NO' and provide a reason under 'Please specify why Participant regained capacity consent was not obtained post-randomization.'

10.3.1.2 Form 2: Eligible and Not Enrolled

For patients that are eligible for the study but that are not enrolled, a minimum dataset will be collected if allowed per local REB, on the 'Form 2: Eligible and not Enrolled' CRF. If sites are not permitted to provide the minimal data, complete the first question on the form and then do not complete any other part of this CRF.

If a site is permitted to provide the minimal data on this CRF, this form collects information about patient's demographics, blood work, interventions, SOFA score, and clinical outcomes. All fields on this form are mandatory and must be completed. Completion details are outlined below.

Data Element	Description
Participant ID	Enter the Participant ID that was created in REDCap at the top of each page of Form 2. (see Section 10.3.2.2 below for details on participant ID assignment in REDCap). This includes the three-letter code for your site and the number assigned in REDCap when registered.
Did the REB approve collection of the minimal dataset for patients that are eligible but not enrolled?	Select the appropriate response 'YES' or 'NO'. If 'YES' then complete the CRF. If 'NO' then do not complete any other fields on the CRF.
Demographics and Medical Details	Age: Enter the age of the patient on the day of screening in years. Sex: Select the biological sex at birth of the patient. Receiving invasive mechanical ventilation: Select YES or NO to specify if the individual received IMV while in ICU. Receiving any vasoactive therapy: Select Yes or NO to specify if the individual received any vasoactive therapy while in ICU.
SOFA Score	Complete the Sequential Organ Failure Assessment (SOFA) by entering a value for each category according to the criteria provided. The values used for the assessment must be from the 24 hours preceding screening and be the most extreme parameter recorded in that 24-hour period. Once all categories have been assessed, add up all the component scores and enter the value in the Total Score field. See Section 10.3.1.4 for details on assessing each category in the SOFA score.
Death Details	Enter details on whether the individual passed away while in ICU and hospital. If the patient passed away while in the ICU, the response should be 'YES" to both 'Death in ICU' and 'Death in Hospital'. If the patient was discharged from the ICU and passed away following discharge from ICU but while still in hospital, then the response would be 'NO' for Death in

Data Element	Description
	ICU and 'YES' for Death in Hospital.
RRT Receipt	Select 'YES' or 'NO' to specify whether the individual was receiving RRT when discharged from the ICU and hospital.
Reason for Exclusion	Select the reason that the individual was not included in the study. If not included for other reasons not listed on the CRF, please contact the project manager.
If Clinician refusal, provide reason(s) given	Provide the reason given by the clinical team for not allowing the individual to be enrolled on the study.

10.3.1.3 Form 3: Baseline CRF

This CRF should be completed once the participant has been randomized.

Data Element	Description
Participant ID	Enter the Participant ID that was created in REDCap at the top of each page of Form 3. (see Section 10.3.2.2 below for details on participant ID assignment in REDCap). This includes the three-letter code for your site and the number assigned in REDCap when registered.
Demographics	Year of Birth: Enter the year of birth of the participant. Full date of birth is not required for this study. Sex: Select the biological sex at birth of the patient. Weight: Enter the current weight of the participant if it was collected when admitted, or, if not collected at the time of admission, enter a weight collected within the last 365 days, if available in the medical chart, or, provide an estimated weight if not known/not previously documented in the medical chart. The weight should be in kg and rounded to one decimal place.
Hospitalization	Hospital Admission: Enter the date and time that the participant was admitted to the trial site. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. ICU Admission: Enter the date and time that the participant was admitted to the ICU at the trial site. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. Location Prior to ICU Admission: Select the location of the participant prior to ICU admission. If 'Other' is selected, please specify the location. Surgical (within 7 days): Specify if the participant has had surgery within 7 days of the ICU admission by selecting 'YES' or 'NO'. If the response is 'YES', specify if it was an unplanned procedure (i.e., emergency procedure) by selecting 'YES' or 'NO'.
Primary Diagnostic Category	Choose the diagnostic category that is MOST responsible for the hospital admission. If there are multiple concurrent conditions, choose the category most responsible for the participant's ICU admission. If the diagnostic category does not fit within those listed, please choose 'Other' and specify a diagnostic category.
Kidney Function	Baseline serum creatinine: Record the participant's baseline serum creatinine value in μmol/L. Enter the closest outpatient value prior to the present hospitalization that is obtained no more than 365 days before the admission date for the current

Data Element	Description
	hospitalization. If such a value is not available, record the lowest serum creatinine obtained within 24 hours of randomization. Baseline estimated GFR: Using the hyperlink in the CRF and here (**https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi-2021-update**), calculate the baseline estimated GFR and then record the value obtained from this online calculator in the CRF.
Chronic Disease	Hypertension: Choose "YES" if the patient is reported as having a history of hypertension on the ICU admission note. Diabetes Mellitus: Choose "YES" if the patient is reported as having a history of diabetes mellitus on the ICU admission note. Heart Failure (NYHA class III-IV symptoms): Choose "YES" if the patient is reported as having a history of heart failure on the ICU admission note. Coronary Artery Disease (prior MI, angina, ACS): Choose "YES" if the patient is reported as having a history of coronary artery disease on the ICU admission note. Peripheral vascular disease (claudication, bypass, amputation): Choose "YES" if the patient is reported as having a history of peripheral vascular disease on the ICU admission note. Cerebrovascular disease (stroke, TIA): Choose "YES" if the patient is reported as having a history of cerebrovascular disease on the ICU admission note. Liver disease (cirrhosis, hepatic failure, portal hypertension, ascites): Choose "YES" if the patient is reported as having a history of liver disease on the ICU admission note. Chronic lung disease (asthma, COPD, ILD, home oxygen): Choose "YES" if the patient is reported as having a history of chronic lung disease on the ICU admission note. Immunosuppression (chemotherapy, prednisone, other): Choose "YES" if the patient is reported as having a history of immunosuppression on the ICU admission note. Leukemia/Lymphoma: Choose "YES" if the patient is reported as having a history of leukemia/lymphoma on the ICU admission note. Solid organ tumor or metastatic disease: Choose "YES" if the patient is reported as having a history of solid organ tumor or metastatic disease on the ICU admission note.
Clinical Frailty Scale (CFS) Score	Select the most appropriate option based on the assessment made by the MRP or designate (see Section 9 for details on the CFS Assessment). The chosen score is meant to reflect the participant's state of health before the illness that led to the current hospitalization.

10.3.1.4 Form 4: Pre-Randomized Acuity/Organ Dysfunction CRF

Sites **do not** need to calculate the APACHE II and SAPS III scores. If your site has an EMR that automatically calculates these scores, these can be recorded on the CRF (see below). The components for the calculation of the APACHE II and SAPS III will be entered in this CRF. Once entered into REDCap, the calculation will be completed automatically.

The worst value in the 24 hours prior to randomization for each data point should be entered in this CRF unless otherwise indicated. 'Worst values' are defined as those furthest from the normal range, either

higher or lower than the normal reference ranges.

If there is no value or information available in the 24 hours preceding randomization, then select 'not available'. Do not use a value that is available prior to the 24 hours before randomization or after randomization.

Data Element	Description
Participant ID	Enter the Participant ID that was created in REDCap at the top of each page of Form 4. (see Section 10.3.2.2 below for details on participant ID assignment in REDCap). This includes the three-letter code for your site and the number assigned in REDCap when registered.
Acuity and Organ Dysfunction Scores	**APACHE II score at ICU Admission -** If there is an APACHE II score listed in the EMR (calculated automatically by the EMR) at the time of ICU Admission, please enter it in this field. If there is no APACHE II score available in the EMR or if your site does not use an EMR, select 'not available'. **SAPS III score at ICU Admission -** If there is a SAPS III score listed in the EMR (calculated automatically by the EMR) at the time of ICU Admission, please enter it in this field. If there is no SAPS III score available in the EMR or if your site does not use an EMR, select 'not available'.
Parameters Common to Both APACHE II and SAPS III	Age (years): Enter the age of the patient on the day of randomization in years. Temperature (°C): Record the worst temperature (highest or lowest) in the 24 hours preceding randomization in degrees Celsius to one decimal place. Heart Rate (beats/min): Record the worst heart rate (highest or lowest) in the 24 hours preceding randomization. Glasgow Coma Scale (GCS): Record the worst (lowest) value in the 24 hours preceding randomization. WBC count ($x10^9$/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Blood pH: Record the worst value (highest or lowest) in the 24 hours preceding randomization. If no pH data is available, Serum HCO_3 (mmol/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Serum creatinine (µmol/L): Record the worst value (highest) in the 24 hours preceding randomization.
APACHE II Parameters	MAP (mean arterial pressure, mmHg): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Respiratory rate (breaths/min): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Oxygenation: FiO_2, PCO_2 (mmHg), PO_2 (mmHg), PaO_2 (mmHg): Record the worst values (highest or lowest) in the 24 hours preceding randomization for each of these data points. Enter FiO_2 as a decimal (not a percentage). Serum sodium (mmol/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization.

Data Element	Description
	Serum potassium (mmol/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Hematocrit (%): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Acute renal failure: Indicate if the participant has acute renal failure in the 24 hours preceding randomization. If this information is not known, select 'not available'. History of severe organ insufficiency or immunocompromise: Indicate if the participant has a history of severe organ insufficiency or immunocompromise. If this information is not known, select 'not available'. Participant surgical status: If the response to the history of severe organ insufficiency or immunocompromise was 'YES', then indicate what the participant's surgical status is, either 'non-operative or emergency post-operative' or 'elective post-operative'. If the response to the previous question was 'NO', do not response to this question.
SAPS III Parameters	Length of stay before ICU admission: Enter the length of time that the participant has been in hospital prior to their ICU admission. Enter a decimal for a partial day in hospital prior to ICU admission (i.e., if in hospital for half a day prior to ICU admission, the value would be 0.5 days). Intra-hospital location before ICU admission: Select where the participant was within the hospital before being admitted to the ICU. If 'Other' is selected, specify the location. Comorbidities (select all that apply): Confirm if there are any comorbidities by selecting all those that apply. If none apply, select 'no applicable comorbidities'. Use of major therapeutic options before ICU admission: Confirm if there are any vasoactive drugs administered prior to ICU admission by selecting 'YES' or 'NO'. Type of ICU Admission: Select whether the ICU admission was 'planned' or 'unplanned'. Reasons for ICU Admission: Select the reason(s) for the ICU admission (Cardiovascular, Hepatic, Digestive, Neurologic). More than one category may be selected. Based on those selections, further specify the reason(s) for the ICU admission by selecting from the subcategories for each. Select all that apply in each category. For example, if Cardiovascular is selected, review the options in the 'If Cardiovascular' section and select those at apply (rhythm disturbances, hypovolemic hemorrhagic shock, septic shock, anaphylactic shock, or other). If the subcategory does not apply, then leave those fields blank. If none of the categories reflect the reason for ICU admission, then select 'None of the above'. Surgical status at ICU admission: Indicate if there was a surgery procedure at ICU admission and if it was scheduled or emergency. Anatomical site of surgery: If 'surgery' is selected (either scheduled or emergency), select the anatomical site of the surgery. Acute infection at ICU admission: Confirm if there was an acute infection at the time of ICU admission, by selecting 'YES' or 'NO'. If 'YES' is selected, select the type of infection, 'nosocomial' or 'respiratory'.

<table>
<tr><th>Data Element</th><th colspan="2">Description</th></tr>
<tr><td></td><td colspan="2">Total Bilirubin (µmol/L): Record the worst value (highest) in the 24 hours preceding randomization.
Platelet count (x10^9/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization.
Systolic blood pressure (mmHg): Record the worst value (highest or lowest) in the 24 hours preceding randomization.
Oxygenation: Select whether the participant received mechanical ventilation or not in the 24 hours preceding randomization.</td></tr>
<tr><td>SOFA Score</td><td colspan="2">The most extreme values for these parameters in the 24 hours prior to randomization should be used to determine the SOFA score. Based on the information below, select the appropriate score (0 – 4) for each parameter.

Once each parameter has been scored, add up all the values and enter the total score. The value should be in the range of 0 – 24.</td></tr>
<tr><td></td><td>Respiration: PaO_2/FiO_2
> 400 (score 0)
301-400 +/- mechanical ventilation (score 1)
≤ 300 but no mechanical ventilation (score 2)
201-300 + mechanical ventilation (score 2)
≤ 100-200 +mechanical ventilation (score 3)
< 100 + mechanical ventilation (score 4)</td><td>Select all arterial partial pressure of oxygen (PaO_2) values obtained from blood gas samples and the fractional inspired oxygen (FiO_2) that was being administered at the same time. Calculate the PaO_2/FiO_2 quotient for each set of values; the lowest (worst) PaO_2/FiO_2 is used to determine the SOFA-Respiratory score.
Patients who are on veno-venous (V-V) or veno-arterial (V-A) extracorporeal life support should get an automatic score of 4.
In order to assign 3 or 4, the patient must be receiving a form of invasive or non-invasive mechanical ventilation.
For example, if a patient's PaO_2/FiO_2 is 150 but he/she is not receiving mechanical ventilation, the score is 2 and NOT 3.
In some cases, PaO_2 may not have been obtained as part of routine clinical care; in that case, choose the lowest oxygen saturation (SaO_2) for the day and use the chart below to "translate" SaO_2 into PaO_2.
In some cases, FiO_2 may not have been recorded; as an alternative, use the chart below to "translate" O_2 flow rates through face mask or nasal cannula into an FiO_2 value.</td></tr>
</table>

Data Element	Description
	APPENDIX 1: PULMONARY SYSTEM CONVERSIONS **O_2 Saturation Conversion Table[a]** Pulse oximetry O_2 saturation may be used for calculating PaO_2/FiO_2 ratio when ABG is not available **Conversion Table for FiO_2 When Measured on Mask or Nasal Cannula**

SaO_2 (%)	Calculated PaO_2
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Nasal Cannula

100% O_2 Flow Rate (L/min)	FiO_2 (%)
1	24
2	28
3	32
4	36
5	40
6	44

Oxygen Mask

100% O_2 Flow Rate (L/min)	FiO_2 (%)
5-6	40
6-7	50
7-8	60
9	90
10	99+

Mask with Reservoir Bag

100% O_2 Flow Rate (L/min)	FiO_2 (%)
6	60
7	70
8	80

[a] AARC Clinical Practice Guideline, In Vitro pH and Blood Gas Analysis and Hemoximetry. *Respiratory Care*. 38:505-510, 1993.

Coagulation: Platelets (x 10^9/L) • >150 (score 0) • 101 - 150 (score 1) • 50 - 100 (score 2) • 20 - 49 (score 3) • < 20 (score 4)	Select the LOWEST platelet count during the 24 hours prior to randomization.
Liver: Bilirubin • < 20 µmol/L (< 1.2 mg/dL) (score 0) • 20 - 32 µmol/L (1.2 - 1.9 mg/dL) (score 1) • 33 - 101 µmol/L (2.0 - 5.9 mg/dL) (score 2) • 102 - 204 µmol/L (6.0 - 11.9 mg/dL) (score 3) • > 204 µmol/L (> 11.9 mg/dL) (score 4)	Select the HIGHEST bilirubin value during the 24 hours prior to randomization. • If bilirubin during the last 24 hours prior to randomization is unavailable, choose the most recently-collected bilirubin on the current hospitalization and assign SOFA-Liver score based on this value. • If no bilirubin is available prior to randomization, assign a score of 0.

Data Element	Description	
	Cardiovascular: Blood Pressure and Support Requirements • Mean Arterial Pressure ≥ 70 mmHg (score 0) • Mean Arterial Pressure < 70 mmHg (score 1) • Dopamine ≤ 5 µg/kg/min or dobutamine (any dose) or milrinone (any dose) or levosimendan (any dose) (score 2) • Dopamine > 5 µg/kg/min or epinephrine ≤ 0.1 µg/kg/min or norepinephrine ≤ 0.1 µg/kg/min or vasopressin ≤ 1.8 U/hr or phenylephrine (any infusion dose but NOT bolus) (score 3) • Dopamine > 15 µg/kg/min or Epinephrine > 0.1 µg/kg/min or Norepinephrine > 0.1 µg/kg/min or Vasopressin > 1.8 U/hr (score 4)	Patients who are on V-A extracorporeal life support should get an automatic score of 4. Was patient on any norepinephrine, epinephrine or vasopressin during the 24 hours preceding randomization? • If yes, determine the highest dose (even if participant was just on the drug for a brief period) and patient will get a score of 3 or 4. • Score 3: Dopamine 5.1 – 14.9 ug/kg/min or epinephrine/ norepinephrine ≤ 0.1 µg/kg/min or vasopressin ≤ 0.03 U/min or phenylephrine • Score 4: Dopamine > 15 ug/kg/min or epinephrine/ norepinephrine >0.1 µg/kg/min or vasopressin >0.03 U/min or receipt of A-V extracorporeal life support Was patient on phenylephrine ONLY? • Automatic score of 3. Was patient on dobutamine or milrinone ONLY? • Automatic score of 2. If no pressor or inotrope, look for MAP at the time of RRT initiation. • If MAP < 70 mmHg, then assign a score of 1. • If MAP ≥ 70 mmHg, then assign a score of 0.
	CNS – Glasgow Coma Scale (GCS) • 15 (score 0) • 13 - 14 (score 1) • 10 - 12 (score 2) • 6 - 9 (score 3) • < 6 (score 4)	Identify the lowest calculated GCS score during the 24 hours prior to randomization. See GCS table above in Section 9.6 for assessment scoring and details regarding how to score participants if sedated or intubated.
	Renal: Creatinine • ≤ 97 µmol/L (≤1.1 mg/dL) (score 0) • 98 - 168 µmol/L (1.2 - 1.9 mg/dL (score 1) • 169 - 299 µmol/L (2.0 - 3.4 mg/dL) (score 2) • 300 - 433 µmol/L (3.5 - 4.9 mg/dL) or urine output ≤ 500 mL/day (score 3) • ≥ 433 µmol/L (≥ 5.0 mg/dL) or	Use the highest creatinine value during the 24 hours prior to randomization to determine the initial SOFA- Renal score. If urine output is < 200 mL in the 24 hours prior to randomization, then an automatic score of 4 is assigned irrespective of the blood creatinine concentration. If urine output is 200-500 mL/day, crosscheck with highest creatinine value and assign the score based on whether the urine output or

Data Element	Description	
	urine output < 200 mL/d or patient receiving RRT (score 4)	creatinine places the patient in a higher (i.e., sicker) category.
Physiologic Parameters	Hemoglobin (g/L): Record the worst (lowest) value in the 24 hours preceding randomization. INR: Record the worst value (highest or lowest) in the 24 hours preceding randomization. Serum phosphate (mmol/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Serum ionized calcium (mmol/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization. Serum total calcium (mmol/L): Record the worst value (highest or lowest) in the 24 hours preceding randomization.	
Interventions at the Time of Randomization	Invasive mechanical ventilation: Confirm if the participant is receiving IMV by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the following values: • $PEEP_{MAX}$ (cmH_2O) – Maximum value for the positive end-expiratory pressure preceding randomization • MAP_{MAX} (cmH_2O) – Maximum mean airway pressure preceding randomization • $PPlat_{MAX}$ (cmH_2O) – Maximum plateau pressure preceding randomization • FiO_{2MAX} – Maximum fraction of inspired oxygen preceding randomization; enter as a decimal (not a percentage) Non-invasive ventilation (e.g. CPAP, BiPAP): Confirm if the participant is receiving NIV by selecting 'YES' or 'NO'. If 'YES' is selected, provide the maximum FiO_2 value preceding randomization. High Flow Oxygen (HFO_2): Confirm if the participant is receiving HFO_2 by selecting 'Yes' or 'No'. If 'YES' is selected, provide the maximum FiO_2 value preceding randomization. Norepinephrine infusion: Confirm if the participant received norepinephrine prior to randomization by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization. Epinephrine infusion: Confirm if the participant received epinephrine prior to randomization by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization. Vasopressin infusion: Confirm if the participant received vasopressin prior to randomization by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the maximum dose ($Dose_{MAX}$ - units/min) based on values recorded in the 24 hours preceding randomization. Phenylephrine infusion: Confirm if the participant received phenylephrine prior to randomization by selecting 'YES' or 'NO'. If 'YES' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization.	

Data Element	Description
	Angiotensin II infusion: Confirm if the participant received angiotensin II prior to randomization by selecting 'YES' or 'NO'. If 'YES' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization. Dopamine infusion: Confirm if the participant received dopamine prior to randomization by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization. Dobutamine infusion: Confirm if the participant received dobutamine prior to randomization by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization. Milrinone infusion: Confirm if the participant received milrinone prior to randomization by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization. Levosimendan infusion: Confirm if the participant received levosimendan prior to randomization by selecting 'YES' or 'NO'. If 'Yes' is selected, provide the maximum dose ($Dose_{MAX}$ - µg/kg/min) based on values recorded in the 24 hours preceding randomization. Enteral nutrition: Confirm if the participant received any enteral nutrition in the 24 hours preceding randomization by selecting 'YES' or 'NO'. Parenteral nutrition: Confirm if the participant received any parenteral nutrition in the 24 hours preceding randomization by selecting 'YES' or 'NO'.

10.3.1.5 Form 5: Daily Intervention CRF

This CRF should be completed when the participant begins CRRT and then daily throughout the time period when the participant is receiving CRRT. Data should be collected for every day that the participant receives CRRT whether a full or partial day.

Data Element	Description
Participant ID	Enter the Participant ID that was created in REDCap at the top of each page of Form 5. (see Section 10.3.2.2 below for details on participant ID assignment in REDCap). This includes the three-letter code for your site and the number assigned in REDCap when registered.
Continuous Renal Replacement Therapy	
CRRT Initiation	Enter the date and time that standard-dose CRRT was initiated. Note: this date and time may be before or after the patient is randomized but must not be more than 24 hours prior to study-allocated CRRT initiation. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format.
Vascular Access Catheter	Indicate the type of vascular access catheter by selecting one of the following:

Data Element	Description
	• Right internal jugular vein • Left internal jugular vein • Right femoral vein • Left femoral vein • Permanent catheter (tunneled) If there is a different catheter for the CRRT, please select 'Other' and provide the details.
CRRT dose-intensity being received at the time of randomization	The details of the CRRT dose-intensity that the participant is receiving at the time of randomization (prior to any study-specific assignment) should be recorded in this section including: • Dose (total effluent) – enter the value in mL/hr • Dose (hemofiltration) – enter the value in mL/hr • Hemofiltration – pre-filter – enter the value in mL/hr • Hemofiltration – post-filter – enter the value in mL/hr • Dose (dialysate) – enter the value in mL/hr These values should reflect a snapshot of what the participant is receiving at the time of randomization and values should be recorded in mL/hr. If the participant had not started CRRT at the time of randomization, check the box to indicate that it was not yet started and do not complete the other fields regarding CRRT dosing on this CRF.
CRRT Anticoagulation prescribed	Select the anticoagulant that the participant is receiving at the time of randomization. If the patient was started on one anticoagulant and then changed to another enter the first anticoagulant prescribed. If anticoagulant was not prescribed select 'No anticoagulation given'. If the participant had not started CRRT at the time of randomization, do not complete this field.
Study Allocated CRRT Initiation	Enter the date and time that the study-allocated dose CRRT was initiated. Note: this date and time must be a minimum of 12 hours after standard-dose CRRT initiation and must not be more than 24 hours after standard-dose CRRT initiation. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format.
Daily Data Worksheets	
There are two daily data worksheets. The first has the Days 0 – 6 listed at the top of the columns. On the second, the days have been left blank and can be filled in as needed depending on the length of time that CRRT is given. If the second daily worksheet is not needed, it does not need to be filled in or signed at the bottom.	
CRRT Duration	Enter the length of time that CRRT was given on each day in each column. Record the number of full hours and the number of minutes for a partial

Data Element	Description
	hour that CRRT was given.
Time in allocated target range	Enter the length of time that the CRRT was in the dose-intensity range that the participant was allocated at randomization for each day. Record the number of full hours and the number of minutes for a partial hour that CRRT was in the allocated range.
Mode	Select the mode in which the CRRT was given: CVVH, CVVHD, CVVHDF.
Blood Flow rate	Enter the blood flow rate in mL/min for each day.
Dose (total effluent)	Enter the total effluent dose in mL for each day if it is available in the medical chart. If values are listed in the medical chart as mL/hr each hour, add up the hourly values to obtain the total mL for the entire day. Note: REDCap will calculate this value when component data is entered, so if not readily available in the chart, do not need to record on the paper CRFs.
Dose (hemofiltration)	Enter the hemofiltration dose in mL for each day if it is available in the medical chart. If values are listed in the medical chart as mL/hr each hour, add up the hourly values to obtain the total mL for the entire day. Note: REDCap will calculate this value when component data is entered, so if not readily available in the chart, do not need to record on the paper CRFs.
Hemofiltration - prefilter	Enter hemofiltration dose pre-filter in mL for each day. If values are listed in the medical chart as mL/hr each hour, add up the hourly values to obtain the total mLs for the entire day.
Hemofiltration - postfilter	Enter hemofiltration dose post-filter in mL for each day. If values are listed in the medical chart as mL/hr each hour, add up the hourly values to obtain the total mL for the entire day.
Dose (dialysate)	Enter dialysate dose in mL for each day. If values are listed in the medical chart as mL/hr each hour, add up the hourly values to obtain the total mL for the entire day.
Dose (total mean)	Enter the total mean dose in mL/kg/hr for each day if it is available in the medical chart. Note: REDCap will calculate this value when component data is entered, so if not readily available in the chart, do not need to record on the paper CRFs.
Dose (highest hourly)	Enter the highest hourly dose in mL/kg/hr for each day.
Dose (lowest hourly)	Enter the lowest hourly dose in mL/kg/hr for each day.
Number of filter changes	Enter the number of filter changes for each day. If no filter changes were made, enter '0'.
Ultrafiltration (total)	Circle the appropriate symbol to confirm if the value is + or -. Enter the value of the total filtration in mL for each day. If values are listed in the medical chart as mL/hr each hour, add up the hourly values to obtain the total mL for the entire day.

Data Element	Description
Fluid balance (total)	Circle the appropriate symbol to confirm if the value is + or -. Enter the value of the total fluid balance in mL for each day.
Urine Output	Circle the appropriate symbol to confirm if the value is + or -. Enter the value of the total urine output in mL for each day.
Serum base excess	Circle the appropriate symbol to confirm if the value is + or -. Enter the value of the serum base excess for each day.
Serum $pH_{MAX/MIN}$	Enter the highest and lowest values collected for the serum pH for each day. If the pH is only collected once per day, then these values may be the same value.
Serum $[HCO_3]_{MAX/MIN}$	Enter the highest and lowest values collected for the serum [HCO_3] in mmol/L for each day. If the [HCO_3] is only collected once per day, then these values may be the same value.
Serum $[Na+]_{MAX/MIN}$	Enter the highest and lowest values collected for the serum [Na+] in mmol/L for each day. If the [Na+] is only collected once per day, then these values may be the same value.
Serum $[Cl-]_{MAX/MIN}$	Enter the highest and lowest values collected for the serum [Cl-] in mmol/L for each day. If the [Cl-] is only collected once per day, then these values may be the same value.
Serum [K+] MAX/MIN	Enter the highest and lowest values collected for the serum [K+] in mmol/L for each day. If the [K+] is only collected once per day, then these values may be the same value.
Serum [Mg+] MAX/MIN	Enter the highest and lowest values collected for the serum [Mg+] in mmol/L for each day. If the [Mg+] is only collected once per day, then these values may be the same value.
Serum [PO_4-] MAX/MIN	Enter the highest and lowest values collected for the serum [PO_4-] in mmol/L for each day. If the [PO_4-] is only collected once per day, then these values may be the same value.
Serum [urea] MAX/MIN	Enter the highest and lowest values collected for the serum [urea] in mmol/L for each day. If the [urea] is only collected once per day, then these values may be the same value.
CRRT interrupted	Confirm if the CRRT was interrupted by selecting 'YES' or 'NO'.
Duration CRRT interrupted	If 'YES' is selected for the 'CRRT interrupted' question, indicate the duration that the CRRT was stopped on that day. Enter the number of full hours and the number of minutes for a partial hour that the CRRT was stopped.
Reason CRRT interrupted	If 'Yes' is selected for the 'CRRT interrupted' question, provide the reason that the CRRT was interrupted – e.g. surgery, imaging, etc.
CRRT transition to IRRT	Confirm if CRRT was transitioned to IRRT on each day by selecting 'YES' or 'NO'.
Receipt of IMV	Confirm if the participant received IMV on each day by selecting 'YES' or 'NO'.

Data Element	Description
Receipt of NIV	Confirm if the participant received NIV on each day by selecting 'Yes' or 'No'.
Receipt of HFO_2	Confirm if the participant received HFO_2 on each day by selecting 'YES' or 'NO'.
Receipt of any vasoactive	Confirm if the participant received any vasoactive on each day by selecting 'YES' or 'NO'.
Transfused RBC	Confirm if the participant received a red blood cell transfusion on each day by selecting 'YES' or 'NO'.
Transfused FFP	Confirm if the participant received a plasma transfusion on each day by selecting 'YES' or 'NO'.
Transfused PLT	Confirm if the participant received a platelet transfusion on each day by selecting 'YES' or 'NO'.
Supplementation given?	Confirm if the participant received any supplementation on each day by selecting 'YES' or 'NO'. If 'NO" is selected, then the additional supplementation fields below this one do not need to be completed.
Specify which supplementation given	If 'Yes' is selected for the 'supplementation given?' question, indicate which supplements were given each day: Mg+, K+, PO_4-, HCO_3-, protein, multivitamins. If any of the options are not selected, then the corresponding fields below can be left blank.
If Mg+, number of doses	If Mg+ was selected, indicate the number of doses that were given that day.
If Mg+, cumulative dose	If Mg+ was selected, indicate the cumulative dose given that day in grams.
If K+, number of doses	If K+ was selected, indicate the number of doses that were given that day.
If K+, cumulative dose	If K+ was selected, indicate the cumulative dose given that day in mmol.
If PO_4-, number of doses	If PO_4- was selected, indicate the number of doses that were given that day.
If PO_4-, cumulative dose	If PO_4- was selected, indicate the cumulative dose given that day in mmol.
If HCO_3-, number of doses	If HCO_3- was selected, indicate the number of doses that were given that day.
If HCO_3-, cumulative dose	If HCO_3- was selected, indicate the cumulative dose given that day in mmol.
If protein given, number of doses	If protein was selected, indicate the number of doses that were given that day.
If protein given, cumulative dose	If protein was selected, indicate the cumulative dose given that day in grams.
If multivitamins given,	If multivitamins was selected, indicate the number of doses that were

Data Element	Description
number of doses given	given each day.
Data entered by:	Enter the initials of the person that recorded the information on the worksheet and the date that the information was entered for each day.

10.3.1.6 Form 6: Outcomes CRF

This CRF should be completed once the participant has completed the study.

Data Element	Description
Participant ID	Enter the Participant ID that was created in REDCap at the top of each page of Form 6. (see Section 10.3.2.2 below for details on participant ID assignment in REDCap). This includes the three-letter code for your site and the number assigned in REDCap when registered.
CRRT Discontinuation	Enter the date and time that CRRT was permanently discontinued. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. Reason for discontinuation: Provide the reason that the CRRT was discontinued by selecting the appropriate option. If the reason for discontinuation is not listed, please contact the project manager.
Kidney Outcomes	Did the participant receive RRT after CRRT discontinuation?: Confirm if the participant received RRT after CRRT discontinuation by selecting 'Yes' or 'No. If RRT was not received after CRRT discontinuation or CRRT was not discontinued by Day 90, the additional questions about RRT do not need to be responded to. • RRT at ICU discharge: If RRT was received, confirm if RRT was still being received when the individual was discharged from the ICU by selecting 'Yes' or 'No'. • RRT at Hospital discharge: If RRT was received, confirm if RRT was still being received when the individual was discharged from the hospital by selecting 'Yes' or 'No'. • RRT at 30-days (from enrollment): If RRT was received, confirm if RRT was still being received 30 days after enrollment on the study by selecting 'Yes' or 'No'. • RRT at 90-days (from enrollment): If RRT was received, confirm if RRT was still being received 90 days after enrollment on the study by selecting 'Yes' or 'No'. • Last date of receipt of RRT: If RRT was received following discontinuation of CRRT, indicate the last date of receipt of RRT. If the participant is still receiving RRT at Day 90, record the Day 90 date in this field. Date should be in DD/MMM/YYYY format. Serum creatinine at ICU discharge: Record the last serum creatinine collected prior to ICU discharge in µmol/L. If participant is still in ICU at Day 90, record the serum creatinine for Day 90 or the closest value to but preceding Day 90.

Data Element	Description
	Serum creatinine at hospital discharge: Record the last serum creatinine collected prior to hospital discharge in µmol/L. If participant is still in hospital at Day 90, record the serum creatinine for Day 90 or the closest value to but preceding Day 90. Serum creatinine at 90-days (+/- 2 weeks): Record the serum creatinine collected at Day 90 (+/- 2 weeks) in µmol/L. If participant is still in hospital at Day 90, record the serum creatinine for Day 90 or the closest value to but preceding Day 90.
Mortality	Death in ICU: Confirm if the participant died while in the ICU by selecting 'Yes' or 'No'. Death in hospital: Confirm if the participant died while in the hospital by selecting 'Yes' or 'No'. If the participant died in ICU, this should also be a 'Yes' response. Death within 30-days (from enrollment): Confirm if the participant died within 30-days of enrollment by selecting 'Yes' or 'No'. If the participant died within 30 days from enrollment (whether in ICU/hospital or not), this should be a 'Yes' response. Death within 90-days (from enrollment): Confirm if the participant died within 90-days of enrollment by selecting 'Yes' or 'No'. If the participant died within 90 days from enrollment (whether in ICU/hospital or not), this should be a 'Yes' response. Death date/time: If the participant died within 90-days from enrollment, enter the date and time. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format. If the participant was still alive at 90-days, do not enter a death date and time.
Service Outcomes	ICU discharge: Specify the date and time that the participant was discharged from the ICU. If the patient is still in the ICU at Day 90, enter the Day 90 date. Hospital Discharge: Specify the date and time that the participant was discharged from the hospital. If the patient is still in the ICU/hospital at Day 90, enter the Day 90 date. Re-hospitalized within 90-days (from enrollment): Specify if the participant was re-hospitalized within 90-days from enrollment following discharge from hospital by selecting 'YES' or 'NO'. If the participant is still in hospital 90 days after enrollment (i.e., they have not been discharged from the original admission), the response should be 'NO'.
End of Study	Did the participant complete the study and vital status assessment at 90 days?: Specify if this participant completed the study by selecting 'Yes' or 'No'. Completion of the study includes transitioning off CRRT because no longer needed or death and being able to confirm vital status at 90 days. If YES, Day 90 date: If the participant completed the study intervention and a Day 90 vital status was obtained, enter the Day 90 date. If NO, Study End Date: Enter the date that the participant last received study-related treatment or the date that the study team last collected data for the participant (i.e., the date the participant was removed from CRRT due to

Data Element	Description
	withdrawal of consent or date when participant was lost to follow-up). <u>If the participant did not complete the study intervention, please specify why:</u> Select the reason the participant did not complete the study. If the reason is 'Other', provide additional details.

10.3.1.7 Form 7: Protocol Deviations CRF

This CRF should be completed when a protocol deviation occurs. This form can be copied as many times as necessary to record all protocol deviations for each participant.

Data Element	Description
Participant ID	Enter the Participant ID that was created in REDCap at the top of each page of Form 7. (see Section 10.3.2.2 below for details on participant ID assignment in REDCap). This includes the three-letter code for your site and the number assigned in REDCap when registered.
What was the nature of the protocol deviation?	Select the appropriate deviation from the predefined options. If the deviation does not fit any of the provided categories, select, 'Other' and provide details of the protocol deviation.
If selected, 'Study Procedures – CRRT dose escalated above the protocol mandated dose-intensity target', specify the reason for dose escalation	If 'Study Procedures – CRRT dose escalated above the protocol mandated dose-intensity target' is selected, specify the reason for the dose escalation. If the reason does not fit any of the provided categories, select, 'Other' and provide details of the reason for the dose escalation.
Deviation Description	Provide additional details of the deviation including the specifics of what occurred, the impact to patient safety and data integrity.
Date of Deviation	Enter the date that the protocol deviation occurred. Date should be in DD/MMM/YYYY format.
Was there any Impact to patient safety or data integrity due to the protocol deviation?	Indicate if there was an impact to patient safety or data integrity by selecting 'YES' or 'NO'. If there was an impact to patient safety or data integrity, provide additional details on the impact to patient safety.
Did the participant continue in the study?	Confirm if the participant continued with the study by selecting 'Yes' or 'No'.
Was the deviation reported to the REB?	Confirm if the protocol deviation was reported to the local REB by selecting 'Yes' or 'No'. Note: it may not be required that all deviations be reported to the REB. Please report them per your local REB reporting policies. If the protocol deviation was reported, specify the date that it was reported to the REB on the CRF.

10.3.1.8 Form 8: Adverse Events and Serious Adverse Events CRF

This CRF should be completed when adverse or serious adverse events occur. Review Section 12 below for details of AE/SAE reporting requirements. This form may be copied as many times as necessary to record all AEs and SAEs. There should be one AE log for each participant. The AE log may need to be updated over time as AEs/SAEs resolve.

Data Element	Description
Participant ID	Enter the Participant ID that was created in REDCap at the top of each page of Form 8. (see Section 10.3.2.2 below for details on participant ID assignment in REDCap). This includes the three-letter code for your site and the number assigned in REDCap when registered.
AE Log	
AE#	Assign each AE recorded a sequential number.
AE Event	Describe the AE as per CTCAE terminology.
Severity	Select the severity of the AE. Only a PI/Co-I can complete this assessment.
Related to Study Treatment	Select the degree that the AE is related to the study treatment. Only a PI/Co-I can complete this assessment.
Serious	Indicate if the AE is serious per the definitions of a SAE in Section 12.1. If the AE is an SAE, the second page of Form 8 must be completed. Only a PI/Co-I can complete this assessment.
Expected	Indicate if the AE was expected. Only a PI/Co-I can complete this assessment.
Study Treatment Administration Status	Select whether the treatment was changed as a result of the AE.
Outcome	Indicate what the outcome of the AE was. If the AE/SAE is not resolved at the time of investigator sign-off, select 'On-going'. If resolves at a later date, the outcome can be updated, and the entry initialed and dated.
Date of Site Awareness	Record the date that the site became aware of the AE.
AE Onset Date	Record the start date of the AE.
AE Stop Date	Record the stop date of the AE, when known. This may be after the investigator has reviewed and signed off on the initiation of the event. If added at a later date, the addition should be initialed and dated.
Reporter Signature/Date	The person who recorded the details of the AE must sign and date the AE log.
Investigator Signature/Date	The PI/Co-I must review and complete the assessments for relatedness, expectedness and seriousness. Once these assessments are complete, the PI/Co-I must sign and date each AE entered.
Serious Adverse Event Form	
Did the participant experience an SAE?	Confirm if the participant experienced an SAE by selecting 'Yes' or 'No'.
Date/Time of SAE	Enter the date and time that the SAE occurred. Date should be in DD/MMM/YYYY format. Time should be in 24-hour clock format.
Grade	Select the correct grade of the SAE as per CTCAE.

Data Element	Description
Description of the SAE	Provide a description of the SAE.
Treatments implemented for the SAE	Describe the actions taken to treat the participant and/or resolve the SAE.
Outcome	Select the outcome of the SAE from the list provided.
Was the SAE reported to the REB?	Confirm if the SAE was reported to the local REB by selecting 'Yes' or 'No'. Note, it may not be required that all SAEs be reported to the REB. Please report them per your local REB reporting policies. If the SAE was reported, specify the date that it was reported to the REB on the CRF.

10.3.2 REDCap eCRF Completion Guidelines

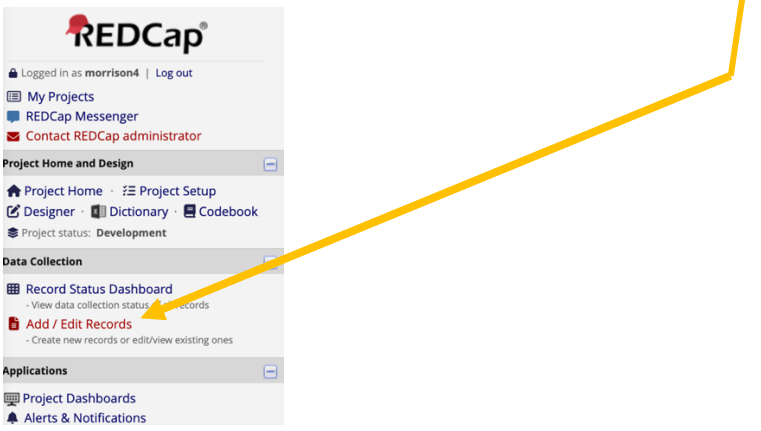
Each center will be responsible for completing the eCRFs in REDCap for their participants. Sites must complete all study eCRFs in REDCap no later than two weeks from the completion date of the patient's participation in the study except for the eCRFs required for confirmation of eligibility which must be completed and submitted **in order to randomize the participant.**

In addition, AE and SAE information must be entered into REDCap within the timelines specified below in Sections 12.3 & 12.4.

Partial data can be entered and saved in the REDCap eCRFs. Before completing the eCRF, data should be verified. It is recommended that data verification is performed by a second delegated team member. Once the data is reviewed, the form can be completed by selecting "Complete" for the Form Status and then "Save & Exit". Complete medical records are not required to be uploaded to the database, the purpose is to capture source information for applicable datapoints as outlined above.

10.3.2.1 Entering a New Participant:

To enter a new participant into the database, click on the **Add / Edit Records** under Data Collection (left hand side of the screen).



The Add / Edit Records screen will be displayed. In the 'Enter a new or existing Record ID' field, enter a new Participant Study Number (see 10.3.2.2 below for details on how to assign a number) and press then enter.

10.3.2.2 Participant Study ID Assignment

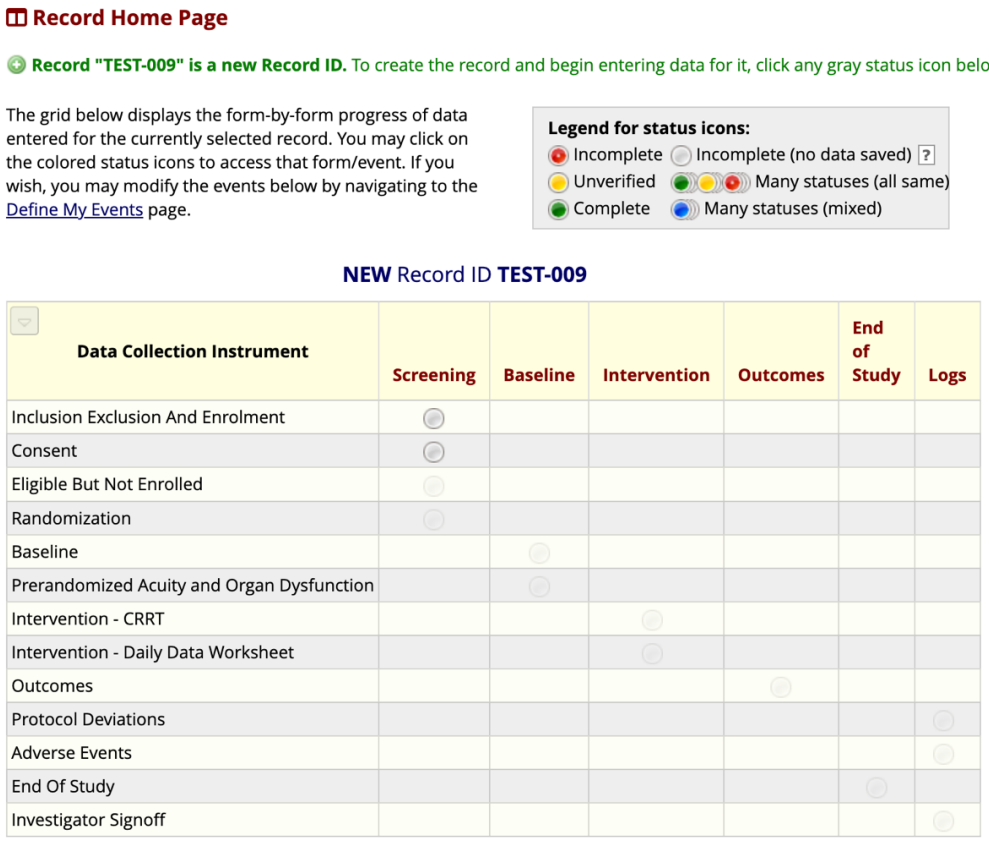
The Participant Study ID is assigned at the site in sequential order using the following format (3-letter site code - patient number [XXX]):

1. Each site has been assigned a three-letter site code as noted in Section 2.4 above. This is the code that makes up the first half of the participant ID Number.
2. Patient number: (n+1) from most recently eligible patient at either site. Record as three digits.
    a. Example: 1st participant from the University of Alberta Hospital = UAH-001,
    2nd participant from University of Alberta Hospital = UAH-002

The last three digits correspond to the participant number, starting at 001 and increasing by '1' with each participant entered in REDCap (e.g., UAH-001, UAH-002, UAH-003, etc) at each site.

- **Note** that both the leading **3-letter code and the 3-digit study number** are to be entered on the paper CRFs (if using them), separated by a '– '.
- If you unsure of how to assign the participant's study number, please contact the Project Manager for assistance before beginning.

In the 'Enter a new or existing Record ID' field in REDCap, enter a new Participant Study ID and press 'Enter' to create a new study record and view the Record Home Page.



10.3.2.3 General Considerations for REDCap Data Entry

10.3.2.3.1 Date and Time Fields

Date fields follow the format: DD-MMM-YYYY.

Time fields follow the format: HH:MM. Times should be entered in 24-hour clock format.

If the day is unknown, please report the day as the 15th of the month. If the 15th does not make logical sense in relation to other date fields on the form, use either the 1st or 30th.

If the day and month are unknown, report the month as June and the day as the 15th. If the 15th does not make logical sense in relation to other date fields on the form, use either the 1st or 30th.

Full date of birth is not required to be entered. Only the year of birth is requested for this study.

10.3.2.3.2 Icons and Meanings:

The status of the eCRF pages is denoted with a colour:

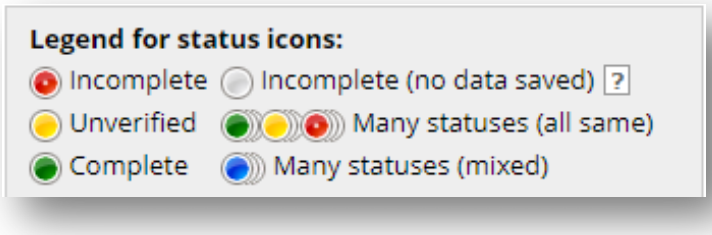
Red – Incomplete

Yellow – Unverified

Green – Complete

Colourless – Incomplete (no data entered/saved)

Blue – many statuses (mixed), for repeating forms



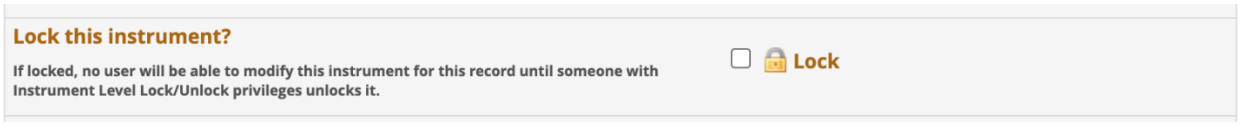
After you enter data on each form/CRF page, you will be asked to indicate the Form Status, by selecting "incomplete", "unverified or "complete".

- If all fields have been entered and the page is complete, please select "**complete (green)**".
- If there are fields that still require your attention or you are planning to enter data at a later date, please select "**incomplete (red)**".
- In general, "**unverified**" does not need to be selected for this trial.

10.3.2.3.3 Locking Instruments

REDCap has a feature that allows instruments to be locked. This should not be used for this study

except when investigators are applying their e-signature to a form.

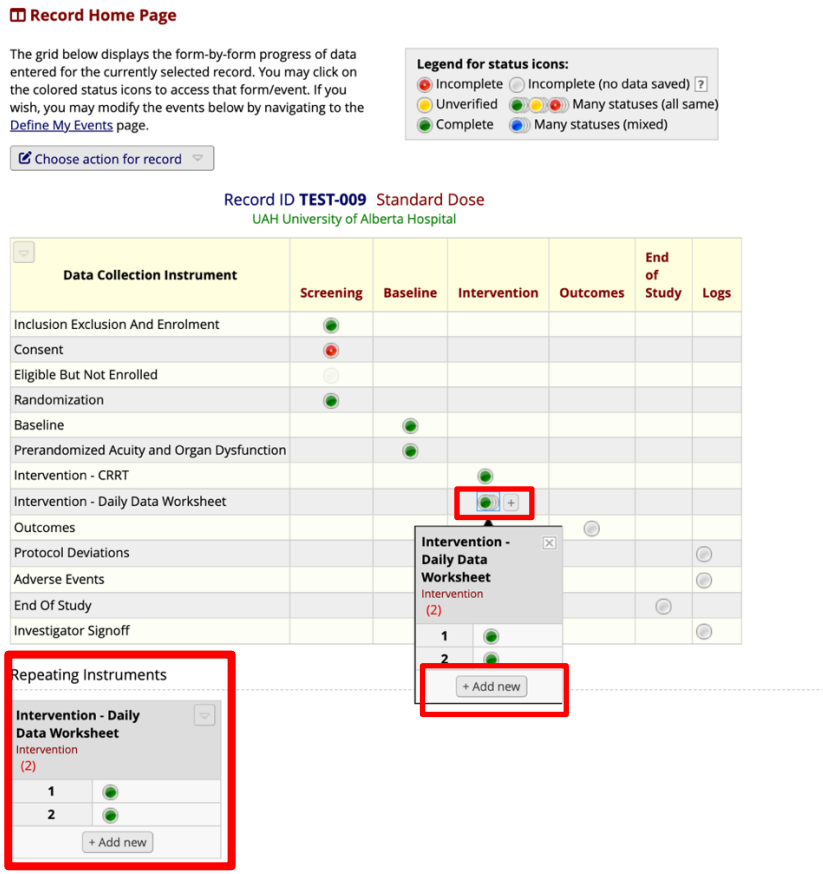


10.3.2.3.4 Repeating Instruments

Many forms in the participant database and regulatory database are set up as repeating instruments to allow the same data from multiple days of intervention to be entered or similar documents (such as different versions of the protocol) to be uploaded, as needed.

To add a new form for recording a second and subsequent CRF of the same type, select the '+' button next to the status icon or select '+Add new' under 'Repeating Instruments' located at the bottom of the Record Home Page.

Each repeating instrument that is created is accessible via the 'Repeating Instruments' menu at the bottom of the **Record Home P**age or by clicking on the status icon for the particular instrument. To revisit the eCRF page for a specific day or document that has already been entered/uploaded, select the status icon next to the desired item in the list of eCRFs to open the corresponding instance of the instrument.



10.3.2.3.5 Missing Data

If data is not available or missing for a specific field, please select 'not available' if that option is available.

A value must be entered in all fields (or 'not available' selected) in the database. If there are any that cannot be completed, please contact the project manager to discuss. Once all available data has been entered, save the form/eCRF page as "**complete (green)**".

NOTE: An error message may appear when trying to save a form if all the required data fields are not complete. If this occurs, review the error message, and fill in any missing data. If the data is still missing or does not exist, select "Ignore and leave record" to exit the page. For some eCRFs, data may need to be entered at a later date so ignoring the error message is OK.

The missing data may be queried during central monitoring. Sites will be asked to provide an explanation as to why the data is missing in their response to the query in REDCap.

10.3.2.3.6 Protocol Deviations

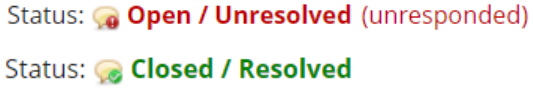
If protocol-required assessments or visits are missed, complete the data collection eCRF page(s) and confirm that the assessment/visit was not done/not available. Once all available data has been entered or all fields responded to with 'not available', save the form/CRF page as "**complete (green)**". Record missed protocol required assessments as protocol deviations in the Protocol Deviation Log in REDCap.

10.3.2.3.7 Data Entry Timelines

Complete all data entry for participants as soon as possible, but in REDCap no later than two weeks from the completion date of the patient's participation in the study except for the eCRFs required for confirmation of eligibility which must be completed and submitted **in order to randomize the participant** and the AE/SAE eCRFs which must be completed per the reporting timelines specified below.

10.3.2.3.8 Data correction procedures

The Coordinating Centre will review the data periodically and may issue data queries. The study team will be notified when a review has been completed and when a query has been issued. All new queries or queries that have not been responded to can be viewed by clicking on **Resolve Issues** in the lefthand column and filtering by "Open/ unresolved issues". After the Project Manager verifies the updated information that is provided/corrected, the query will be closed and the status will change to "closed/resolved".



10.3.2.3.9 Data query resolution process and timelines

Unless otherwise specified, the site team should respond to any open queries **within 2 weeks** of the

date of the notification from the coordinating center.

When responding to queries, the site should correct the data, if appropriate, and respond to the query with a comment regarding the query (i.e. whether it was corrected or whether it was correct as entered, etc.).

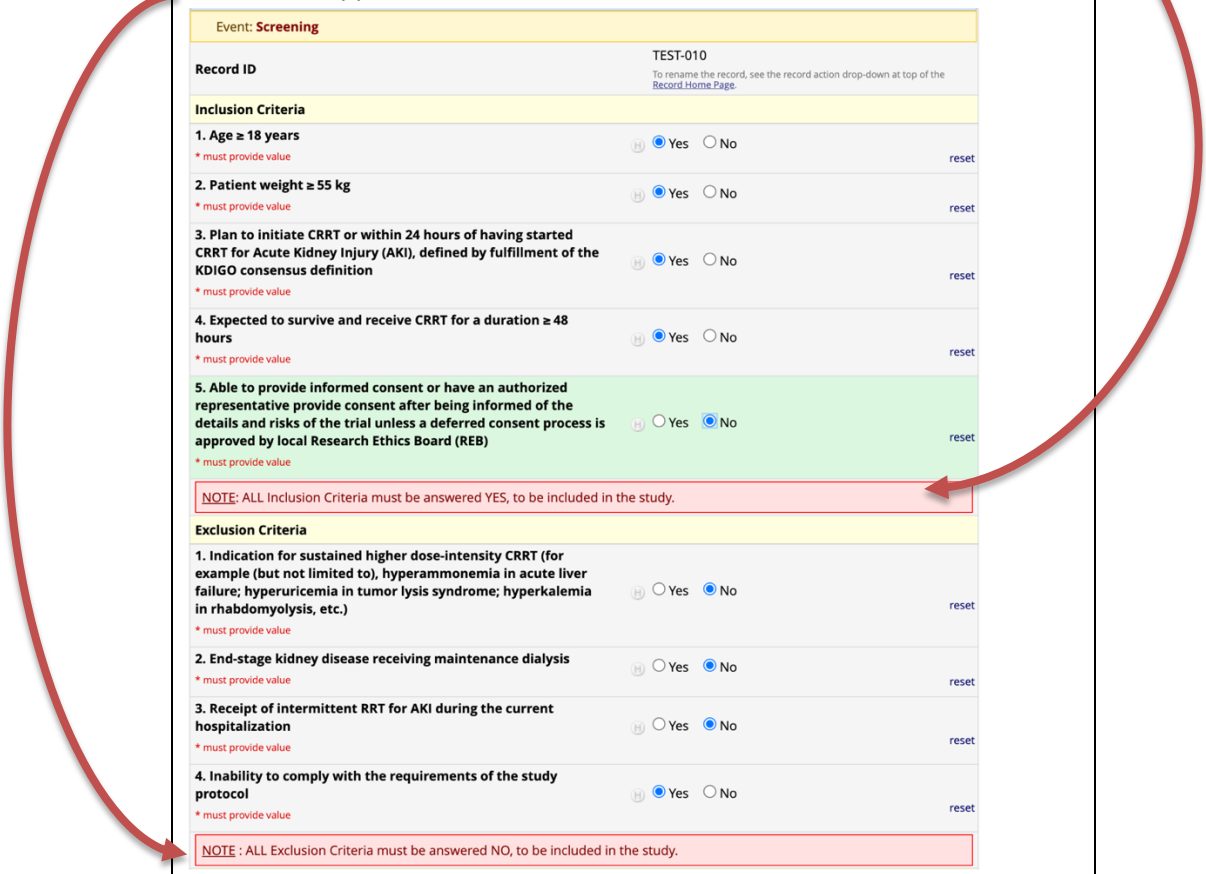
10.3.2.3.10 Data Range Alerts

In the REDCap database, some lab values have been assigned reference ranges. If a value that is outside the range is entered, a text box will appear to alert the data entry person that this value may be out of range. For patients who are critically ill in the ICU, it is expected that the lab results may be out of normal ranges. The REDCap alert is intended to ensure that the data is double-checked prior to saving and will not prevent the data from being saved in the database.

10.3.2.4 Participant Database eCRF Specific Instructions for Completion

The following tables provide instructions for completing each eCRF in the WISDOM REDCap participant database. The CRFs in REDCap have been created based on the paper CRFs. Please refer to Section 10.3.1 for details about the elements that are to be recorded. Only information specifically related to the entry in REDCap will be outlined below. The 'Intervention – Daily Data Worksheet', 'Protocol Deviations' and 'Adverse Events' are repeating eCRFs so that multiple days of intervention or multiple AEs/SAEs and PDs can be entered.

Screening

Form	Completion Information
Eligibility and Enrolment	The details of eligibility must be entered for all participants that are believed to be eligible in the pre-screening phase as outlined above in Sections 5 & 8. If the participant is eligible, all the Inclusion criteria will be responded to as 'Yes'. If any are not answered or the response is 'No', a RED banner will appear. Similarly, if the participant is eligible, all the Exclusion Criteria will be responded to as 'No'. If any are not answered or the response is 'Yes', a RED banner will appear.  If the participant is eligible and all eligibility criteria have been responded to correctly, the RED banners disappear. If all inclusion and exclusion criteria are responded to and the participant appears to be eligible, then the questions under 'Eligibility' can be answered with 'Yes'.

Form	Completion Information
	The 'date and time of full eligibility' field will appear when both eligibility questions are responded to with 'YES'. The date and time can be entered by clicking on the 'Now' button if the REDCap eCRF is being completed by the PI/Co-I in real-time or by entering the date and time that the PI/Co-I signed the paper CRF if the data is being entered by the site coordinator at a later time. The 'Form Status' can then be changed to 'Complete'. Click on 'Save and Exit Form' so the data will be saved.
Consent	If Consent was not obtained, select 'NO' for 'Was consent obtained?', and change the 'Form Status' to 'Complete'. Click on 'Save & Exit Form'. This will make available the 'Eligible But Not Enrolled' eCRF for completion. If Consent was obtained, select 'YES' for 'Was consent obtained?'. This will allow additional questions to appear. Select the 'type of consent obtained:' o Deferred consent with assent of the clinical team o Surrogate Decision-Maker (SDM) or Legally Authorized Representative (LAR) o Participant Consent Once an option is selected, additional fields will appear to enter the date and time of consent. If consent is deferred or SDM consent was initially obtained, additional fields for when SDM &/or participant consent is obtained post-randomization will appear. <u>These fields do not need to be completed when initially enrolling the participant prior to randomization.</u> <u>It is expected that the study team will return to this eCRF and complete these fields post-randomization to outline if additional consent(s) was obtained and provide an explanation if consent was not obtained post-randomization.</u> This may require returning to this eCRF multiple times. Once all the <u>initial</u> consent information has been entered, complete the question, 'Was the participant enrolled in this study?'. If the participant was ultimately not enrolled, answer 'No'. This will allow the 'Eligible But Not Enrolled' eCRF to be made available for completion. If the participant was enrolled, answer 'Yes'. This will allow the 'Randomization' eCRF to be made available for completion.

Form	Completion Information
	Until the eCRF is fully completed (i.e., when the consent post-randomization is obtained), the 'Form Status' should be listed as 'Incomplete'. Click on 'Save and Exit Form' each time new entries are made so that all data entered is saved. Note: An error message will appear when clicking on 'Save & Exit Form' if the question 'Was consent obtained to continue participation post-randomization?' was not answered. Click on 'Ignore and leave record'. All other data will be saved. Return to the eCRF once the data is available to respond to this question. Once all the post-randomization consent information has been added, change the 'Form Status' to 'Complete'. Click on 'Save & Exit Form'.
Eligible But Not Enrolled	If the patient was not consented (either deferred or SDM/participant consent) or was ultimately not enrolled even if consent was obtained (either deferred or SDM/participant consent), this eCRF will become available when the response is 'No' in the Consent eCRF to the questions about whether they consented or were enrolled. Some sites may not be permitted by their REB to enter data for participants for whom consent (SDM/Participant) was not obtained or that their treating team did not provide assent through the deferred consent process. Please ensure that you are aware of what your REB has approved for your site when responding to the first question: 'Do you have permission from your REB to complete the 'Eligible but not Enrolled' eCRF? If your REB does not allow data entry without signed consent from the participant or SDM or deferred consent, respond 'No', change the 'Form Status' to 'Complete' and click on 'Save & Exit Form'. If your REB has approved the entry of the minimal dataset without signed consent from the participant or SDM or deferred consent, or consent was obtained but the participant was not enrolled/randomized in the trial, respond 'YES' to the question, 'Do you have permission from your REB to complete the 'Eligible but not Enrolled' eCRF? Additional fields will appear for completion. Complete all fields in the eCRF. This may require returning to this eCRF multiple times to record the details at discharge from ICU and hospital. Until the eCRF is fully completed, the 'Form Status' should be listed as 'Incomplete'. Click on 'Save and Exit Form' each time new entries are made so that all data entered is saved.

Form	Completion Information
	Once all fields are complete, change the 'Form Status' to 'Complete'. Click on 'Save & Exit Form'.
Randomization	If the participant was consented and enrolled per the previous eCRFs, this eCRF will be available to complete. To randomize the participant, click on the 'Randomize' button in the 'Randomize the participant' field. Another text box will appear listing the treatment group that the participant has been assigned to: 'Standard Dose' or 'Low Dose'. Click 'Close' to clear this text box. An email will immediately be sent by the REDCap database to the study project manager, study co-chairs, site study coordinator and the site PI with the participant ID #, site and the group the participant was randomized to. Enter the date and time that the email was received in the 'Randomization date' and 'Randomization time' fields in the eCRF. Once all fields are complete, change the 'Form Status' to 'Complete'. Click on 'Save & Exit Form'.

Baseline

Form	Completion Information
Baseline	The Baseline eCRF is separated into several categories. Please complete all fields in each section as was outlined above in Section 10.3.1.3. Note: if the weight entered is <55 kg, an alert email will be sent to the site PI and coordinator as a weight less than 55 kg will make them ineligible. Once all fields are complete, change the 'Form Status' to 'Complete'. Click on 'Save & Exit Form'.
Prerandomized Acuity and Organ Dysfunction	The Prerandomized Acuity and Organ Dysfunction eCRF is separated into several categories. Please complete all fields in each section as was outlined above in Section 10.3.1.4. **Note:** Sites **do not** need to calculate the APACHE II and SAPS III scores. If your site has an EMR that automatically calculates these scores, these can be recorded in the eCRF. The components for the calculation of the APACHE II and SAPS III will be entered in this eCRF and REDCap will complete the calculation of these scores.

	Oxygenation: Based on the value entered for FiO_2, some of the other oxygenation values may disappear in REDCap as they will not be needed for the APACHE II calculation. Enter values for all the fields that appear in REDCap. Once all fields are complete, change the 'Form Status' to 'Complete'. Click on 'Save & Exit Form'.

Intervention

Form	Completion Information
Intervention – CRRT	A description of the data to be entered in the Intervention - CRRT eCRF is outlined above in 10.3.1.5. Once all data has been entered, change the Form Status to 'Complete' and click on 'Save and Exit'.
CRRT Treatment Start, Day 0	This eCRF should record the data from either that day of randomization or the day that the participant begins CRRT prior to the study-allocated dose (See Section 9.2 for further details). A description of the data to enter is provided above in Section 10.3.1.5 under the Daily Data Worksheets section. Note: The Dose (total effluent), Dose (hemofiltration) and Dose (total mean) will autopopulate in REDCap when the components of the value are entered in REDCap. Once all data has been entered, change the Form Status to 'Complete' and click on 'Save and Exit'.
Intervention – Daily Data Worksheet	This form is set up as a repeating instrument to allow capture of data from more than one day of intervention. The form will auto-populate the Day field in each form consecutively when a new form is created and cannot be changed by the person entering data. There should be one eCRF for each day that the participant receives CRRT. If there is a full 24 hours that the patient did not receive CRRT and then CRRT is re-initiated, please contact the project manager for details on how to document. A description of the data to enter is provided above in Section 10.3.1.5 under the Daily Data Worksheets section. Note: The Dose (total effluent), Dose (hemofiltration) and Dose (total mean) will autopopulate in REDCap when the components of the value are entered in REDCap. Once all data has been entered, change the Form Status to 'Complete' and click on 'Save and Exit'.

Outcomes

Form	Completion Information
Outcomes	A description of the data to enter is provided above in Section 10.3.1.6. Once all data has been entered, change the Form Status to 'Complete' and click on 'Save and Exit'.

End of Study

Form	Completion Information
End of Study	A description of the data to enter is provided above in Section 10.3.1.6. Once all data has been entered, change the Form Status to 'Complete' and click on 'Save and Exit'.

Logs

Form	Completion Information
Protocol Deviations	A description of the data to enter is provided above in Section 10.3.1.7. For entry of multiple deviations, follow the instructions for repeating instruments above. Once all data has been entered, change the Form Status to 'Complete' and click on 'Save and Exit'. If there are no protocol deviations for a participant by the end of the study, select 'No' to the question, 'Were there any protocol violations AND/OR deviations?', change the Form Status to 'Complete' and click on 'Save and Exit'.
Adverse Events/Serious Adverse Events	A description of the data to enter is provided above in Section 10.3.1.8. Reporting requirements are listed in Section 12 below. Once all data has been entered, change the Form Status to 'Complete' and click on 'Save and Exit'. For entry of multiple AEs/SAEs, follow the instructions for repeating instruments above. If a participant does not have any AEs during their study participation this form should not be completed. Leave the Form Status as incomplete.
Investigator Signoff	This eCRF must be completed for every participant. Only the site PI can complete this eCRF. The site PI must log in with their own username and review the data for the participant. Once they have reviewed the participant data in all eCRFs, they can change the Form Status for the Investigator Signoff eCRF to 'Complete', click on 'Lock' and then click on e-signature. A text box will

	appear and the PI will need to enter their username and password and press enter. Once this has been completed, click 'Save and Exit'.

10.4 REDCap Regulatory Database Completion Guidelines

Each center will be responsible for completing the instruments (sections) in the regulatory database. Sites must complete all sections, as applicable, prior to site activation and provide updates to the regulatory database on an on-going basis within two weeks of new documentation becoming available.

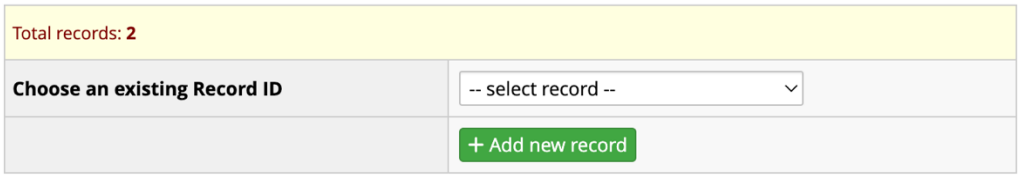
Please note partial data can be entered and saved in the REDCap regulatory database. Once the data is complete for an instrument or instance in an instrument, the form can be completed by selecting "Complete" for the form status and then selecting "Save & Exit".

Resolution of all queries that are generated upon review by the study sponsor is expected to be completed within 2 weeks of a query being generated.

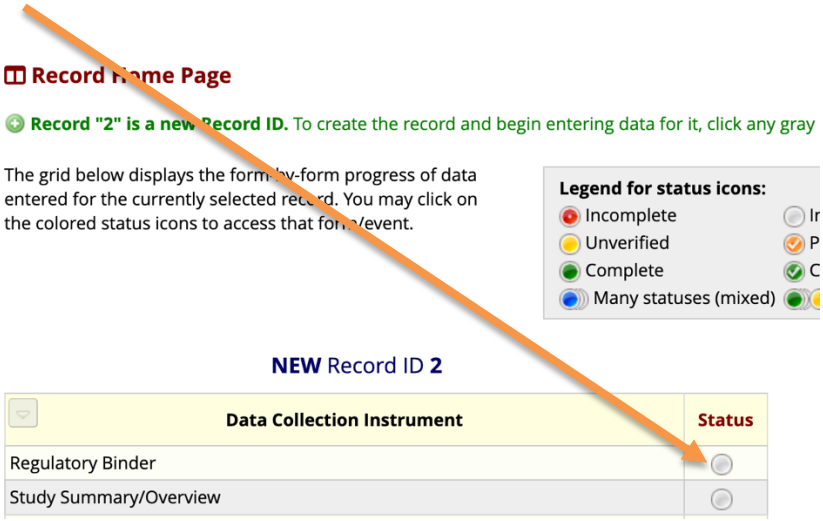
10.4.1 Creating the Regulatory Database:

In the Regulatory Binder: WISDOM database, to create the regulatory database for your site, click on the **Add / Edit Records** under Data Collection (left hand side of the screen) similar to how a new participant was created in Section 10.3.2.1.

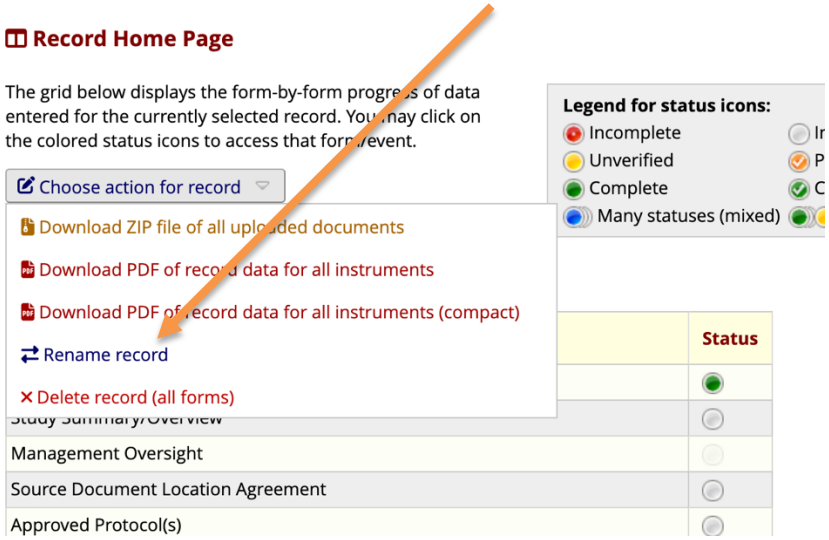
Then click on the green '+ Add new record'.



A Record Home Page will appear. To begin populating the individual instruments, click on the grey circle next to 'Regulatory Binder'.



Once at least one instrument has been completed and saved, it will be possible to change the name of the Record ID, click on 'choose action for record' and select 'Rename record'.



A new window will appear. Type the name of the site, as listed in Section 2.4, in this text box and click 'rename record'.

The sections below provide details on how to complete all the fields in each section (also known as instruments) contained in the regulatory database.

10.4.1.2 Regulatory Binder

Field	Completion Information
Site Name	Enter the full site name (no abbreviations) as listed in Section 2.4.
Is your site the lead site for the study?	Select 'NO' unless you are the University of Alberta Hospital (UAH) site.
Full Study Name	Enter the full title of the study as listed on the front page of the protocol
Site Principal Investigator	Enter the PI's name. If the PI changes during the course of the study, this field should be updated.
Site Research Coordinator	Enter the site research coordinator's name. If the site coordinator changes during the course of the study, this field should be updated.
Form Status	Once all details are entered, change the Form status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.3 Study Summary/Overview

Field	Completion Information
REB Number	Enter the number assigned to your local ethics application.
ClinicalTrials.gov ID	Enter the NCT number (NCT06446739) for this trial which is listed on the front page of the protocol.
Enrollment started?	Click 'YES' once enrollment has started.
Enrollment Start Date	Enter the date that enrollment started. This will be the date on your activation letter provided by the sponsor.

Notes	Add any notes that might be applicable to the enrollment, such as if enrollment is temporarily stopped during the course of the study.
Enrollment completed?	When the enrollment is completed or stopped, select 'Yes'.
Enrollment End Date	Enter the date that enrollment stopped.
Notes	Add any notes regarding why enrollment was stopped. For example, study reached accrual goals, or study accrual stopped for safety.
Form Status	Fill in the information that can be completed when enrollment starts and leave the other fields blank. Leave the Form Status as 'Incomplete' and click 'Save & Exit Form'. Once enrollment is completed, the remaining fields can be completed in this form. Once all data has been entered in this eCRF at the end of the trial, change the Form Status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.4 Source Document Location Agreement

The source data location agreement form provided with the study activation package will (once completed) outline where the source data will be located for the trial. Once the project manager and the site team have confirmed where the source data will be located, it can be signed and uploaded to the instrument, under 'Upload Source Document Location Agreement'. If revisions to the source document location agreement are needed, please contact the project manager. This instrument is a repeating instrument to allow for revised agreements to be uploaded.

Field	Completion Information
Upload Source Document Location Agreement	Upload the final signed document.
Description of Source Document Location Agreement	The date the form is signed should be entered here in DD/MMM/YYYY format.
Form Status	Once all details are entered, change the Form status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.5 Approved Protocol(s)

This instrument is for filing all versions of the protocol that are approved by your REB. To upload multiple protocol versions, follow the instructions for repeating instruments above.

Field	Completion Information
Protocol Version Date	Enter the version date of the protocol that has been provided by the sponsor.
Upload Protocol	Upload the protocol document
Description of Protocol	Enter a brief description including amendment #, version # (if applicable), and changes that were made with this version. If it is the original/initial protocol for your site, enter 'initial approved protocol' along with the version #.
Protocol Signature Page Completed	The Site Statement of Compliance is located on Page 4 of the protocol. The site PI is required to sign and date this form for each version of the protocol implemented at the site. Once the page is signed, select 'Yes'. A field to upload the signed page will appear.

Upload Protocol Signature Page	Once signed, the statement of compliance form can be uploaded to this field.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.6 Approved Informed Consent(s)

This instrument is for filing the approved blank consent forms (not consents signed by participants). To upload multiple sets of consents, follow the instructions regarding repeating instruments above.

Field	Completion Information
How many consent forms will be reported?	Indicate the total number of consent forms that will be uploaded in this instance. The number of consents will be determined by the processes that are permitted by your local REB. The study sponsor has provided templates for a Deferred Consent Process, Main Consent for Participant or SDM, and Regained Capacity Consent following SDM consent. Once the number of consents that are to be uploaded is entered, the appropriate number of fields for the number of consents specified will appear. If all consents are not updated at the same time, upload only those that have been revised in a single instance. For example, if the Deferred Consent Process form and Main Consent are revised after the initial approval but not the Regained Capacity Consent, the number of consents to upload to the second instance would be two.
Upload Approved Informed Consent #1	Upload the first informed consent form.
Description of Informed Consent #1	Enter a brief description including title of ICF (ie SDM/participant consent, regained capacity consent, or deferred consent) and version # (if applicable).
Version Date	Enter the version date of the ICF.
Upload Approved Informed Consent # 'X'	Repeat these steps above for the other ICFs.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.7 HREB Approvals and Correspondence

This instrument will be used to store the REB approval and acknowledgement letters and all submission documents and correspondence with the REB. To upload multiple REB approval letters, follow the instructions for repeating instruments above.

Field	Completion Information
Select an REB submission Type	Choose the type of submission from the list – initial, amendment/modification, renewal, reportable events. Once a selection has been made, other fields will appear.

	If another type of submission is needed, please contact the project manager.
Upload HREB Approval Letter	Upload the approval/acknowledgment letter received from the REB.
Description of HREB Letter	Add a description so it is easy to find the document later, such as 'Initial Protocol v1.0 Approval' or 'Protocol v2.0 Approval', or '2024 Annual Renewal', or 'Reportable Event #1 - SAE'.
HREB Approval Date	Enter the date noted on the Approval Letter.
Protocol Version Date	If the submission to the REB included an original protocol or protocol revision, enter the date of the protocol that was approved. If no protocol was submitted with the submission to the REB, then click not applicable.
Upload HREB Correspondence	The submission documents and back and forth correspondence, prior to approval, for each approval/acknowledgement letter should be uploaded in this field. For sites using ARISE, if all REB communications occur on ARISE, then you do not need to upload any of the communications here. For sites that are not using ARISE, all REB Communications (submission documents, correspondence received during review of submissions) must be uploaded here. To upload multiple documents for a submission, zip them together in a folder. Click on 'upload file', then drag and drop of the zipped folder onto the 'choose file' button in the Upload File window that appears. Note: do not click 'choose file' and then select the zipped folder as it will not upload properly.
Description of HREB Correspondence	A short description of what the submission documents are for should be entered in this field, including the reason for the submission and date of submission.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.8 HREB Documentation

This instrument should be used to file the REB membership list document and the letter of attestation that certifies that the REB complies with REB membership requirements per TCPS2 and ICH GCP and any updates to these documents that occur during the study. To upload multiple REB documents (membership lists or attestations), follow the instructions for repeating instruments above.

Field	Completion Information
Upload List of REB Panel Members	Upload the membership list available from your REB.
Description of Panel Members List	Provide a brief description including the date of the list.
Upload Letter of Attestation	Upload the Letter of Attestation provided by the REB, if applicable. For sites using ARISE, this letter is available through the link provided in

	the REDCap instrument. For non-ARISE sites, REBs may not have a letter of attestation if they include the attestation on the REB approval letters directly.
Description of Letter of Attestation	Provide a brief description including the date of the letter. For non-ARISE sites, if there is not a separate attestation letter, please indicate 'N/A – attestation contained in REB Approval letters'
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.9 HREB Recruitment and other Participant Materials

This instrument is to file any other documents besides protocol and ICFs that are approved by the REB, including written information for recruitment, posters, advertisements, patient diaries, questionnaires, etc. To upload multiple participant materials, follow the instructions for repeating instruments above. Upload each document in its own instance.

Field	Completion Information
Upload Document	Upload the REB-approved document.
Description of Document	Provide a brief description identifying the type of document (ie wallet card, poster, drug diary, questionnaires, etc).
Version	Enter the version # and/or date of the document.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.10 Study Agreements & Institutional Approvals

This instrument is to file all the study agreements and institutional approvals needed to set the study up at your site. To upload multiple agreements, follow the instructions for repeating instruments above.

Field	Completion Information
Type of Study Agreement	Select the type of agreement. At a minimum, the agreement between the site and the sponsor should be included in this section. Once the type of agreement is selected additional fields ('Upload Agreement' and 'Description of Agreement') will appear. If 'Other' is selected, an additional field will appear to provide additional details on the type of agreement.
Upload Agreement	Upload the final signed agreement.
Description of Agreement	Include the final date of signatures in the description and whether it is an initial agreement or addendum to a preexisting agreement.
Type of Institutional Approval	Select the type of institutional approval. Additional fields will appear to upload and provide details of the approval.
Upload Approval	Upload the institutional approval letter. Upload any documents that are received from your institution related to approval of conducting the research.
Date of Approval	Enter the date of approval listed on the letter.
Description of Approval	Provide a brief description of what the approval letter is for. This may be an overall approval from your health authority/hospital, departmental approvals, such as critical care/ICU, lab, imaging, etc.

Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.11 Study Team Member Information (CVs, licenses)

This instrument captures the CVs and medical licenses for those study team members who are required to maintain their certification in order to participate in the conduct of the study. To upload documents for multiple individuals, follow the instructions for repeating instruments above. Each individual should have their own instance of this form.

Field	Completion Information
Study Team Member Name	Enter the name of the individual.
Upload Signed and Dated CV	The CV (resume) must be signed and dated by the individual. Electronic signature & date or wet ink signature & date are both acceptable. The file can be uploaded to this field as a pdf or Word document. The CV only needs to be uploaded once at the beginning of the study. If additional CVs for an individual need to be uploaded, they can be uploaded in the same field.
Description of CV	Enter a description of the CV, including the date it was signed.
Indicate the # of Practice Permits	Select the number of practice permits to be added. This field can be revised every year as a new practice permit is received. Once a number is selected, additional fields will appear.
Upload Practice Permit # 1	Upload the practice permit document.
Expiration Date for Practice Permit #1	Enter the expiration of the practice permit.
Upload Practice Permit # 'X'	Repeat these steps above for adding new practice permits
Form Status	This form may not be complete until the end of the study as updated CVs and licenses may be required over the duration of the study. The form status should be left as 'incomplete' until the end of the study as a reminder that additional documents may need to be uploaded. Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.12 Study Team Member Information (certificates)

This instrument captures the TCPS2 and GCP training certificates for all study team members. To upload documents for multiple individuals, follow the instructions for repeating instruments above. Each individual should have their own instance of this form.

Field	Completion Information
Study Team Member Name	Enter the name of the individual.
Upload TCPS2 certificate	Upload the TCPS2 certificate for each individual. TCPS2 certification does not have an expiry date so only needs to be uploaded once at the beginning of the study. If additional certificates need to be uploaded, they can be

	uploaded in the same field.
TCPS2 Completion Date	Enter the date that the TCPS2 course was completed as listed on the certificate.
Indicate the # of GCP certificates	GCP certificates have expiration dates of two or three years depending on institutional policies. Select the number of GCP certificates to be added for an individual. This can be revised every time a new certificate is received. Once a number is selected, additional fields will appear.
Upload GCP ICH E6 training certificate	Upload the GCP certificate.
GCH ICH E6 Completion Date	Enter the completion date of the training as listed on the certificate.
GCH ICH E6 Expiration Date	Enter the expiration date of the training as listed on the certificate. If there is no expiration date, three years from date of completion will be accepted.
Form Status	This form may not be complete until the end of the study as updated TCPS2 and GCP certificates may be required over the duration of the study. The form status should be left as 'incomplete' until the end of the study as a reminder that additional documents may need to be uploaded. Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.13 N2 SOP Attestation

All study team members must have documentation of SOP training. Your team may use local internal SOPs and policies to complete this training or you may use the N2 SOPs available through the regulatory database.

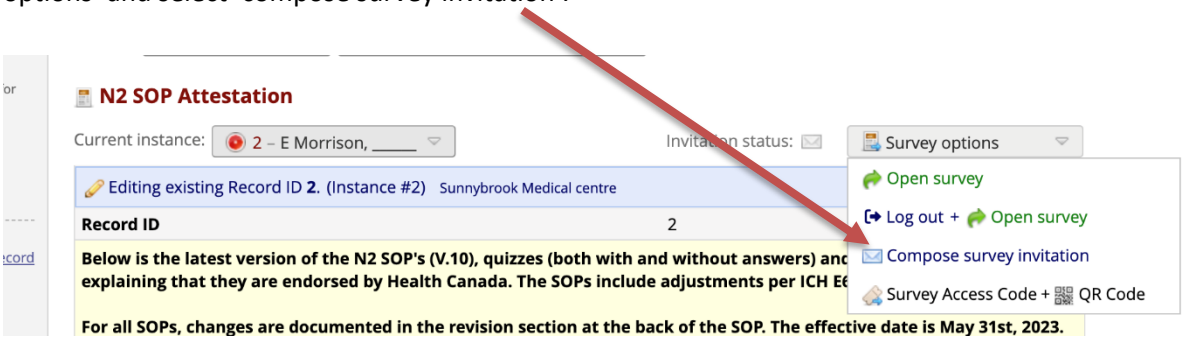
If your site has its own SOP training policy and process for documentation of the SOP training. Please upload the documentation of SOP training for each individual on the delegation log to the SOP Acknowledgement Log Instrument (see Section 10.4.1.14 below).

If your site would like individuals to complete the N2 SOP training through the REDCap database, this instrument is set up to be able to send as a survey, so that an invitation can be sent to each individual who needs SOP training.

To setup the training for multiple individuals, follow the instructions for repeating instruments above. Each individual should have their own instance of this form to complete the survey.

For a new individual, when you click on the status icon, the list of N2 SOPs will appear, with an attachment below. Enter the name of the study team member in the appropriate field and then click 'Save & Exit Form' at the bottom of the page. An error message will appear indicating that all fields have not been completed. Click on 'Ignore and leave record'.

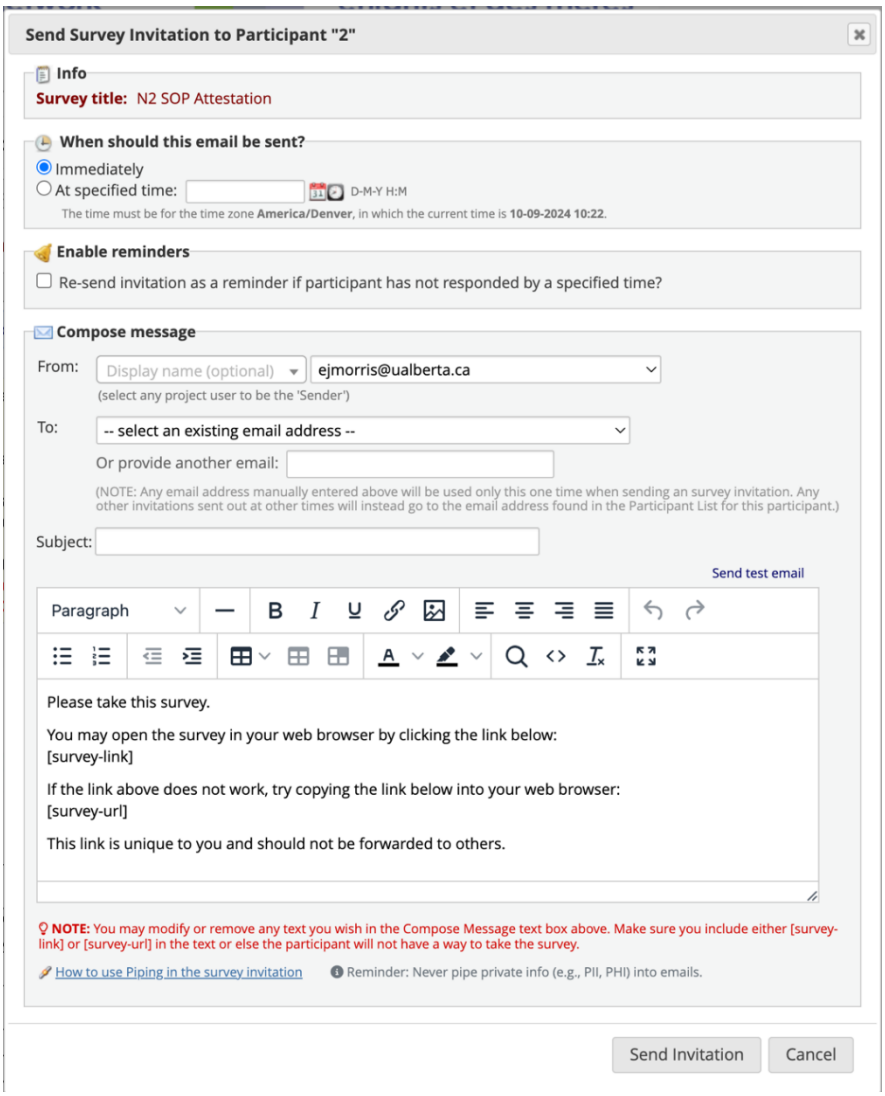
Click on the status icon beside the form that was just created. At the top of the form click on ‘survey options’ and select ‘compose survey invitation’.



A new form will appear which will allow you to send the invitation to complete the training to the individual. Under ‘compose message’, enter the email address of the sender and the email address of the person you are sending the email to. Enter the subject of the email (suggested: N2 SOP Training Requirement for WISDOM Trial). The text in the body of the email can be changed as long as ‘[survey-link]’ and/or ‘[survey-url]’ are included.

In the ‘Enable Reminders’ section, you can set a timeframe when the REDCap system will send out reminders if the individual has not responded to the survey request. By clicking on the ‘resend invitation’ additional features will appear so that reminders can be sent via email daily or weekly and for a certain number of times.

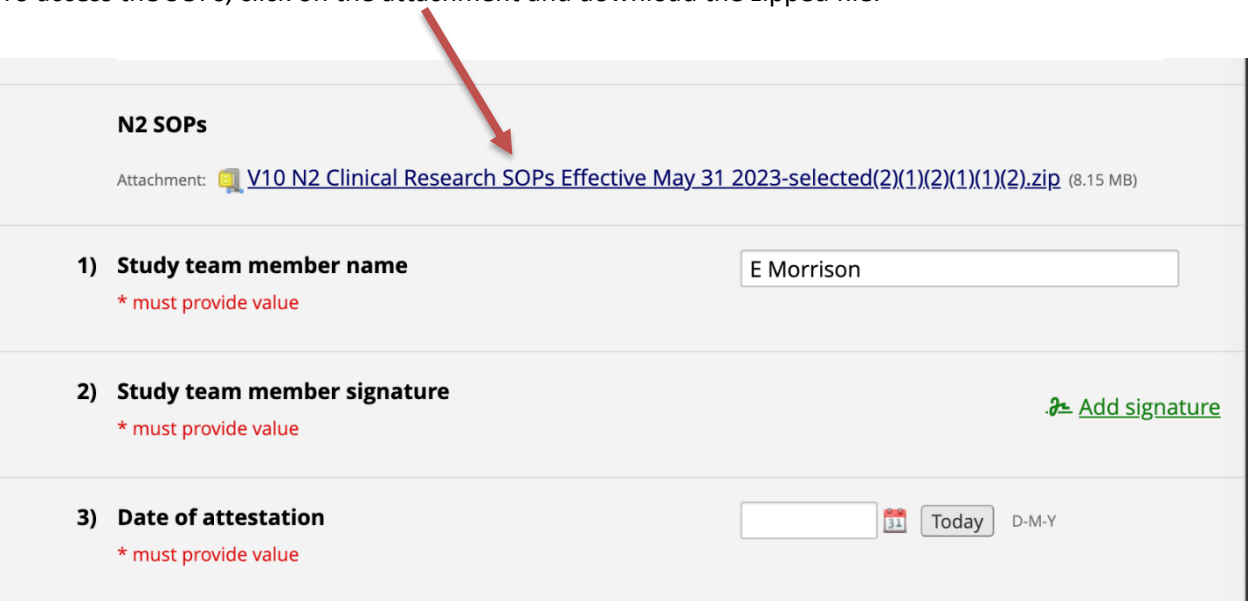
Once the invitation and message are ready to send, click on ‘Send Invitation’ at the bottom of the form. A text box will appear asking if you want to leave the page or stay on the page. Select ‘Leave page’.



The individual will receive an email with the link to the survey. When the individual clicks on the link, a new tab on their browser will open the survey.

> Please take this survey.
>
> You may open the survey in your web browser by clicking the link below:
> N2 SOP Attestation
>
> If the link above does not work, try copying the link below into your web browser:
> https://micyrn.med.ualberta.ca/surveys/?s=CG3K78UWc2z9ddNA
>
> This link is unique to you and should not be forwarded to others.

To access the SOPs, click on the attachment and download the zipped file.



Each individual should review all SOPs contained in the downloaded folder which are applicable to their delegated tasks/assigned role.

Once the SOPs have been reviewed, the individual should click on 'add signature' and using finger, mouse, or stylus provide their signature. Click 'Save signature' when done.

Enter the date of completion of the review in the Date of Attestation field. Then click 'Next Page'.

On the next page, a read-only copy of the response is provided, which can be downloaded by clicking on 'view pdf'. Click on the attestation confirming that all information is correct and that by signing electronically it is the equivalent of a wet ink signature. Then click 'Submit'.

Once the individual has responded to the survey the status icon will be green with a check mark in the middle.

The Form Status will automatically be changed to 'Complete' when the survey response is completed.

10.4.1.14 SOP Acknowledgement Log

If your site has their own SOP training policy and process for documentation of the SOP training. Please upload the documentation of SOP training for each individual on the delegation log to this instrument. To

upload the training for multiple individuals, follow the instructions for repeating instruments above. SOP training can also be done in a group training session and one training log can be uploaded for all attendees.

Field	Completion Information
Upload SOP Acknowledgement Log	Upload the documentation of SOP training for either an individual or a group.
Description of SOP Acknowledgement Log	Provide a description of the training log that was uploaded. Include the date of training and whether it was for an individual (include their name) or a group.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.15 Study Personnel Training Log

This instrument is for filing the documentation of protocol training for the initial protocol training and all subsequent amendment training. Training for other study documents (such as the MOP) can also be included in this instrument. This form can be used to file both documentation of group training and individual training. To upload multiple training logs, follow the instructions for repeating instruments above.

Field	Completion Information
Upload Study Training Log	Upload the documentation of training for either an individual or a group.
Description of Study Training Log	Provide a description of the training log that was uploaded. Include the date of training, whether it was for an individual (include their name) or a group and the document version date or # that the training is for.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.16 Training Materials

This instrument is for filing the training slides/documents that are used to provide training throughout the study. To upload multiple training materials, follow the instructions for repeating instruments above.

Field	Completion Information
Upload Training Materials	Upload the training slides/documents.
Description of Study Training Log	Provide a clear description of the training document that was uploaded. i.e SIV slides, dated DDMMMYYYY; Protocol v2.0 slides dated DDMMMYYYY, etc.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.17 Delegation of Responsibility Log

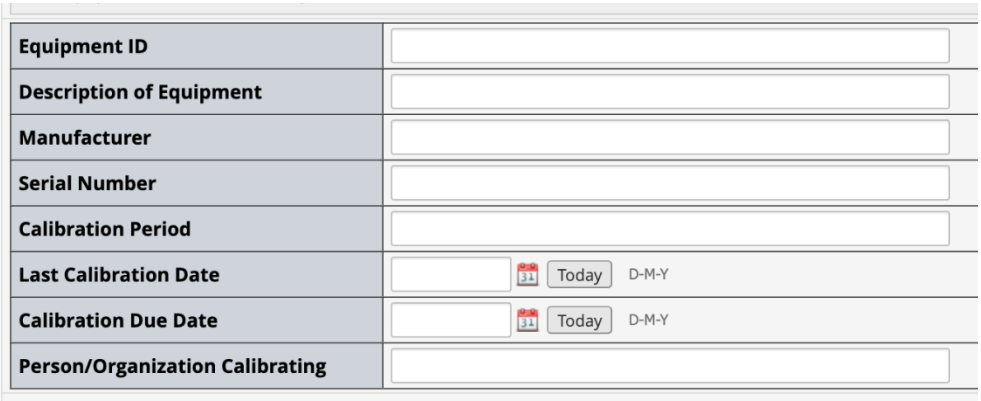
This instrument is for filing the initial delegation log and any updates to the delegation log during the study. To upload multiple delegation logs, follow the instructions for repeating instruments above.

Field	Completion Information
Upload Study Delegation Log	Upload the delegation log and any revisions. The initial delegation log must be uploaded prior to site activation. Any revisions to the delegation log

	should be uploaded in real-time as the revisions are made during the study. The final delegation log after study close out should also be uploaded to this instrument.
Description of Study Delegation Log	Provide a clear description of the delegation log that was uploaded. i.e include the date of the most recent change to the delegation log or the date of upload.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.18 Facilities and Equipment

If there is any study-specific equipment used for this trial, the equipment calibration log, maintenance log and certificate from the manufacturer should be included in this instrument. Details about the equipment should be entered in the text fields and the logs and certificates uploaded to the appropriate fields. If there is more than one piece of equipment, data for each can be entered in separate instances. To enter data for more than one piece of equipment, follow the instructions for repeating instruments above.



It is not anticipated that there will be any study-specific equipment for the WISDOM study. If there is no study-specific equipment (ie it is used as part of the standard of care intervention, provided by the institution and was not provided by the sponsor), then this instrument does not need to be completed. Leave all fields blank and do not change the Form Status.

10.4.1.19 Laboratory Certification and Normal Values

Information regarding the laboratory and normal values should be added to this instrument. Any revisions to these documents should be uploaded in real-time as the revisions are provided during the study. For example, if the certification is updated, the lab normal reference ranges are changed or if a new Lab Director is hired, the updated documents should be added to this instrument. To upload multiple lab documents, follow the instructions for repeating instruments above.

Field	Completion Information
Laboratory Name	Enter the name of the laboratory used to process and analyze samples. If Alberta sites are using APL, then they can click on the checkbox. For Alberta sites using Alberta Precision Laboratories, the laboratory certificates and NTF re normal values can be found here:

	https://nactrc.ca/researchers/ahs-laboratory-services/. The documents for APL should be downloaded from the website and uploaded to the appropriate field in this instrument.
Upload Laboratory Certification	Upload the current Lab Certification document.
Description of Laboratory Certification	Provide a description of the certificate, including when it was issued and/or when it expires.
Laboratory Director's Name	Enter the name of the lab director.
Upload Laboratory Director's CV	Upload the current signed and dated CV for the laboratory director.
Description of the Laboratory Director's CV	Provide a description of the lab director's CV, including the date it was signed and dated.
Upload Laboratory Normals	Upload the current laboratory normal reference ranges document for the lab.
Description of Laboratory Normals	Provide a description of the lab normal document, including the date it was issued.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.20 Screening & Enrollment Log

The Screening Logs and the Informed Consent and Enrollment Logs as outlined in Sections 5.2 and 5.3 should be uploaded to this instrument each month. To upload multiple screening logs, follow the instructions for repeating instruments above.

Field	Completion Information
How will screening and enrollment be captured?	Select 'Independent Screening and Enrollment Log'. This will allow additional fields to appear for upload of the Screening Logs and the Informed Consent and Enrollment Logs.
Upload Screening and Enrollment Log	Upload the screening or enrollment log document into this field.
Description of Screening and Enrollment Log	For Screening Logs, enter in the 'Description of Screening and Enrollment Log' field: **Screening Log – MMMYYYY**. The date in the description field should match the date in the filename of the screening log. For the Informed Consent and Enrollment Log, enter in the 'Description of Screening and Enrollment Log' field: **ICF & Enrollment Log – DDMMMYYYY.** The date in the description field should be the date of upload.
Form Status	Once all fields in the form are complete, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.21 Master ID Log

As this is a multicentre study, the sponsor should not see the PHI for the patients so the Master ID log should not be uploaded to this instrument.

Field	Completion Information
Will a Master Identification Log be Uploaded?	Select 'No'.
Form Status	Change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.22 Subject Visit Tracking Log

If your site will utilize a participant visit tracking log for this study to ensure all follow-up is completed, the document can be uploaded to this instrument. Updates to the participant visit tracking log can be uploaded throughout the duration of the study. To upload multiple visit tracking logs, follow the instructions for repeating instruments above.

Field	Completion Information
Will the study utilize the subject tracking log?	If your site will use a participant visit tracking log, select 'YES'. Additional fields will appear to allow the document to be uploaded and a description to be added. If your site will not use a participant visit tracking log, select 'NO'.
Upload Subject Visit Tracking Log	Upload the documentation for tracking participant visits.
Description of Subject Visit Tracking Log	Provide a description of the tracking log that is uploaded. The description should include the version date of the document, or the last date it was modified.
Form Status	If using a subject visit tracking log, once the documents are uploaded and a description provided, select 'Complete' and 'Save and Exit Form'. If not using a subject visit tracking log, change the status to 'Complete' and click on 'Save and Exit Form'.

10.4.1.23 Case Report Form

This instrument is for uploading the blank CRFs provided by the sponsor. To upload revised CRFs, follow the instructions for repeating instruments above.

Field	Completion Information
Will the study team upload CRFs/worksheets?	The response to this question should be 'Yes' since paper CRFs are provided by the sponsor for this study. Additional fields will appear for uploading the CRFs and providing a description.
Upload CRF or Worksheet	Upload the CRF Package provided by the sponsor. If the CRFs are revised, they should be uploaded in a new instance.
Description of CRF or Worksheet	Provide a description of the CRFs that were uploaded. The description should include the version date of the CRFs.
Form Status	Once the documents are uploaded and a description provided, select 'Complete' and 'Save and Exit Form'.

10.4.1.24 Reporting SAEs to HREB

As this is a non-regulated trial per Health Canada, reporting of SAEs to Health Canada is not required. However, SAEs may need to be reported to the local REB per their reporting policies. To upload multiple

instances of the documentation of SAE reporting to the REB, follow the instructions for repeating instruments above.

Field	Completion Information
Upload SAE Reporting Form	Upload the completed SAE reporting form that was submitted to the REB.
Description of SAE Reporting Form	Provide a brief description of the SAE, including the participant ID & date of SAE.
Form Status	Once the documents are uploaded and a description provided, select 'Complete' and 'Save and Exit Form'.

10.4.1.25 Disclosures of CoI

All site principal investigators and steering committee members must declare any financial or other real or perceived conflicts of interest in relation to this trial. All individuals must complete the financial disclosure and conflict of interest form provided by the sponsor. To upload multiple COI forms, follow the instructions for repeating instruments above.

Field	Completion Information
Upload Disclosures of Conflicts of Interest Form	Upload the complete disclosures of COI form for each individual.
Description of Disclosures of Conflicts of Interest Form	Provide a brief description of the form, including the name of the individual and the date signed.
Form Status	Once the documents are uploaded and a description provided, select 'Complete' and 'Save and Exit Form'.

10.4.1.26 NTF

A note-to-file is a record commonly used to document an unusual occurrence during a clinical trial. When written appropriately, these notes provide clarity, establish accountability, and enable an event to be reconstructed during future review.

NTFs can be used to document:

- operational decisions made
- instructions from the sponsor
- unusual events that are important to remember

Each NTF should identify the issue or deviation from the protocol/SOPs/Sponsor requirement(s), provide a reason/explanation for the occurrence, include a corrective action/preventative action (CAPA) plan and be signed and dated by the responsible party within a timely manner. NTFs addressing an occurrence that affects participant safety and/or eligibility should be reviewed and signed and dated by the PI prior to the implementation or continuation of study interventions or procedures.

This instrument can be used to store any NTFs that are written by the site or provided to sites by the sponsor throughout the duration of the study. NTFs can be entered in two different ways in this instrument.

- A completed and signed pdf of a NTF can be uploaded

- The NTF can be written within the instrument and signed electronically within REDCap.

To upload or create multiple NTFs, follow the instructions regarding repeating instruments above.

Field	Completion Information
Select method of reporting the NTF	If a NTF has been written and saved as a pdf after signing or if a memo/NTF has been sent to the site by the sponsor, select 'Upload a completed and signed NTF'. Additional fields will appear to upload the file and provide a description of the NTF. If the NTF will be written within the instrument, select 'Complete and sign a NTF'. Additional fields will appear to fill in.
If NTF was written outside of REDCap,	
Upload NTF	Upload the NTF or memo.
Description of NTF	Provide a description of the NTF/memo. The description should, at minimum, include the date of the NTF and a brief description of what the NTF is about.
If NTF is to be written in REDCap,	
Date of NTF	Enter the date that the NTF is being written
Study ID of NTF	If this NTF is about a specific participant(s), enter the participant ID #(s). If it is not related to a particular study participant(s), enter 'N/A'
Subject Line of NTF	Enter a brief description about the NTF – what is it for, why it is being written
NTF	Write the body of the memo. This should include what has occurred to necessitate a NTF any corrective actions that have been taken and preventative measures so similar occurrences do not occur in the future. The NTF should provide enough detail to make it clear without having to look for further information elsewhere as to what occurred and what is being done.
Signatures	If the PI is required to sign the NTF, please click on the box 'select this box if the QI/PI needs to sign the NTF'. Additional fields will appear for the QI's name and date of signature. The QI will then need to log in to REDCap and add their signature by clicking on 'add signature' and signing with mouse, finger or stylus. The NTF can also be sent as a survey to the PI for signature. See details above in 10.4.1.13 for sending the NTF as a survey for signature. If the coordinator is permitted to sign the NTF, then do not click on the 'select this box if the QI/PI needs to sign the NTF'. The coordinator can then add their name and date of signature and click on 'add signature' and sign with mouse, finger or stylus.
Form Status	Once the documents are uploaded and a description provided or the NTF has been written and signed, select 'Complete' and 'Save and Exit Form'.

10.4.1.27 Other Documents

This instrument can be used to file any documents for which there is not a place for them elsewhere in the regulatory database. These might include emails, meeting notes and other trial-related materials. To upload multiple documents, follow the instructions for repeating instruments above.

Field	Completion Information
Upload Other Document	Upload the document.
Description of Other Document	Provide a brief description of the document. At minimum, the description should include the date of the document and a brief description of the content of the document.
Form Status	Once the documents are uploaded and a description provided, select 'Complete' and 'Save and Exit Form'.

10.4.1.28 Monitoring

This instrument should be used to file all communications regarding monitoring, either documents received or documents sent to the monitor. All follow up letters/reports from monitoring visits should be retained in this section. It is recommended that the investigator sign off on a copy of the follow up letter and have that copy filed (proof of receipt and knowledge of issues noted and activities that occurred during a periodic monitoring visit) in this section. Any significant communication between study team members and the monitoring team is also recommended to be filed here. To upload documentation for each monitoring visit or other correspondence, follow the instructions for repeating instruments above.

Field	Completion Information
Communication 'To' or 'From' Study Team	Select whether the communication is to the study team or from the study team. Additional fields will appear.
Type of Communication	Select from the options regarding what the type of communication – Monitoring Plan, SIV, PMV, Close Out Report, Other. Based on the type selected additional fields will appear.
If Monitoring Plan selected:	
Date of Monitoring Plan	Enter the date of the document
Upload Monitoring Plan	Upload the document provided by the sponsor.
Description of Monitoring Plan	Provide a description of the monitoring plan.
If SIV selected:	
Upload SIV Agenda	Upload the agenda for the SIV Meeting
Description of SIV Agenda	Provide a description of the SIV agenda.
Date of SIV	Add the date that the SIV occurred.
Upload SIV Report	Upload the final SIV report received from the monitor/sponsor
Description of SIV Report	Provide a description of the SIV report including the date of the report.
If PMV selected:	
Upload PMV Agenda	Upload the agenda, if one was provided. This could also be the email provided describing what will be done during the PMV.
Description of PMV Agenda	Provide a description of the PMV agenda.
Date of PMV	Add the date that the PMV occurred.
Upload PMV Report	Upload the final PMV report received from the monitor/sponsor

Description of PMV Report	Provide a description of the PMV report including the PMV # and the date of the report.
If Close Out Visit selected:	
Upload Close Out Visit Agenda	Upload the agenda, if one was provided. This could also be the email provided describing what will be done during the close out visit.
Description of Close Out Visit Agenda	Provide a description of the Close Out Visit agenda.
Date of Close Out Visit	Add the date that the close out visit occurred.
Upload Close Out Visit Report	Upload the final close out visit report received from the monitor/sponsor
Description of Close Out Visit Report	Provide a description of the close out visit report including the date of the report.
If Other selected:	
Date of Other Communications	Add the date of the document or the date that the documents are being uploaded.
Upload Other Communications Document	Upload the document. This option should be used to file any important communications (source documents, emails, notes, etc) with the monitor or sponsor regarding monitoring.
Description of Other Communications Document	Provide a description of the communication document, including a brief description of the contents and the date of the document. For source documents, the description should follow the format: 'De-identified source documents for participant <XXX-###> <dd/mmm/yyyy>'.
Form Status	Once all fields are completed, select 'Complete' and 'Save and Exit Form'.

10.4.1.29 Study Closeout

This instrument is to provide the documentation from the REB acknowledging the closure of the study.

Field	Completion Information
Upload REB Study Close Out Notification Letter	Upload the document.
Description of REB Study Close Out letter	Provide a brief description of the document. At minimum, the description should include the date of the document.
Form Status	Once the document is uploaded and a description provided, select 'Complete' and 'Save and Exit Form'.

Section 11: Study Completion and Closeout Procedures

11.1 End of Study for Participants

A participant will be considered to have completed the study if they remain on study through to the end of CRRT (i.e., transition to IRRT or death) and a vital status assessment is completed at 90 days after enrollment. The duration of participation on active treatment for each individual participant will vary but the total length of participation will be a maximum of 90 days (or less) for all participants.

11.2 Withdrawal from Study

Participants and/or their SDM may withdraw from the study at any time upon request without prejudice to further treatment. It is not required that the participant/family give the reason for withdrawal. When participants no longer want to participate in the study and no longer authorize the principal, sub-investigators or study team members to continue collecting their outcome data, it should be documented in the participant's chart and in the eCRF that they have withdrawn consent.

Refer to your site's local REB policy regarding the following provisions. Document any discussions regarding consent in the participant's research file.

Provisions of Withdrawal of Consent

a) Participant/SDM does not wish to continue in the study but has consented to be contacted for safety assessments (e.g. safety follow-up calls) and the collection of information from their medical records to complete data forms.

b) Participant/SDM does not wish to continue the study and does not want to be contacted for safety assessments. They **do** consent to the collection of information from their medical records.

c) Participant/SDM does not wish to continue in the study, does not want to be contacted for safety assessments and **does not** consent to their medical records being accessed. Ensure the participant is informed that all data collected up until the point of withdrawal will be used for study purposes. No further data is to be collected from the participant.

The Site Principal Investigator may withdraw a participant from the study for the following reasons:

- Withdrawal of informed consent (participant or SDM withdraw for any reason);
- If any clinical Adverse Event (AE), laboratory abnormality, or other medical condition or situation occurs that prevents participant from continuing on the study treatment;
- Lost-to follow-up;
- Death;
- Protocol Violation

11.3 Lost to Follow-Up

Participants are followed daily while in ICU. Once discharged from ICU and hospital, there will be a 30-day and 90-day follow-up for outcomes. The follow-up may be completed by review of data in the EMR or may require a phone call to the participant to gather the outcome data being collected.

If the participant is unable to be contacted by the study site members, the participant will then be deemed

lost to follow-up. The Site PI or study team member should use all reasonable efforts to establish contact with the participant before the patient is declared lost to follow-up. The site team member should try to contact the participant no more than three times to confirm the 30-day and 90-day outcome data. These contact attempts must be documented in the participant's medical record or study file.

A participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up if the participant continues to be unreachable.

11.4 End of Study for Sites

The end of the study for participating sites will be once accrual goals have been met globally, all data has been entered, queries have been addressed/resolved in the REDCap databases and the sponsor has indicated that the study can be closed with the local REB.

If a site wishes to close the study prior to the end of accrual globally, please contact the project manager.

11.5 Site Procedures for Study Close Out

Each study site will be required to complete the following procedures prior to study close out:

- Confirmation that all data for all participants has been collected and case report forms (eCRFs in REDCap) are complete;
- Resolution of all queries in the REDCap database;
- Review of all the completed case report forms and sign-off by PI in REDCap;
- Resolution of all follow-up action items from monitoring visits and CAPA plans implemented;
- Close-out monitoring visit conducted by study sponsor
- Archiving of study documents per instructions from study sponsor;
- Inform the local research ethics board that the study has ended and provide the close-out letter from the REB to the sponsor.

11.6 Retention of Study Documentation

The Site Principal Investigator is responsible for retaining records, including the identity of all participating patients (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, source documents, research documents and detailed records of treatment disposition in a secure location for a minimum of 15 years following the completion of the clinical trial. Sites must consult with the study sponsor to confirm that destruction of the study documents is permitted prior to their destruction.

Section 12: Adverse Events

Participants should be closely monitored for any change to their health (including any troublesome medical occurrences) from randomization through to end of CRRT.

In this study, as there is no investigational agent, events can be specified as Adverse Events (AEs) and Serious Adverse Events (SAEs) according to the criteria detailed in their definitions below. It is the responsibility of the site PI, or delegated Co-I listed on the TDL, to review, assess and report all events to the WISDOM Coordinating Centre according to the procedures outlined in this section.

AEs/SAEs must be collected from the time of randomization to end of CRRT. Follow-up of AEs/SAEs should occur to resolution of the AE/SAE or discharge from hospital whichever occurs first. Only AEs/SAEs that are related to the intervention need to be reported in the REDCap database.

12.1 Definitions

12.1.1. Adverse Events (AE)

An adverse event is any untoward medical occurrence in a patient enrolled in the trial which does not necessarily have a causal relationship with the intervention.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational intervention, whether or not considered related to the investigational intervention.

For the purposes of this study, since patients are in ICU, AEs, SAEs and death are expected to occur frequently. As such AE and SAE reporting will follow recommendations set out for trials in this population by Cook et al. which requires that AEs/SAEs be pre-defined.

The following will be considered AEs/SAEs for this trial and should be reported in REDCap:

AE	Definition
Serum K+	<3.0 or >6.0 mmol/L
Serum Mg+	<0.5 or >1.5 mmol/L
Serum PO_4+	<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 HCO_3	<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
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 red blood cells (RBC); ➢ Bleeding at other critical sites (e.g., epidural, intraocular or intraarticular); ➢ Bleeding requiring an invasive intervention (e.g., re-operation) – see below for possible examples of bleeding that may require invasive intervention and require reporting

Examples of Bleeding requiring an invasive intervention:

- ➢ Hemorrhage at site of CVC insertion: defined as bleeding described by clinician inserting catheter requiring transfusion of ≥ 1 unit(s) of packed red blood cells and/or surgical intervention/repair within 12 hours following insertion.

- ➢ CVC-associated bloodstream infection: defined as bacteremia in 2 blood culture sets (one drawn from dialysis catheter and the other from another site) with no proven alternative source for bacteremia as per ICU attending OR culture-positive recovery of the same organism from the dialysis catheter upon removal.

- ➢ Ultrasonographically confirmed thrombus attributed to dialysis CVC: defined as any confirmed occlusive or non-occlusive thrombus in the vein in which a dialysis CVC was placed (or remains in place) or in the venous system drained by the vein in which the dialysis CVC was placed; further qualified by pulmonary embolism as a result of thrombus. Please note that one should only consider CVCs inserted for the purpose of RRT.

- ➢ Pneumothorax following dialysis CVC insertion (for catheters placed in the internal jugular or subclavian positions): defined as air in the pleural space on routine chest x-ray that is performed following dialysis CVC insertion; further qualified by requirement for chest tube placement. Please note that one should only consider CVCs inserted for the purpose of RRT.

- ➢ Hemothorax following dialysis CVC insertion (for catheters placed in the internal jugular or subclavian positions): defined as blood in the pleural space following CVC insertion; further qualified by requirement for chest tube placement. Please note that one should only consider CVCs inserted for the purpose of RRT.

- ➢ Inadvertent arterial puncture at time of dialysis CVC insertion. Please note that one should only consider CVCs inserted for the purpose of RRT.

If there are other bleeding events that require an invasive intervention, please contact the project manager and study PI for confirmation as to whether the event needs to be reported.

12.1.2. Serious Adverse Event (SAE)

Any untoward occurrence that at any dose:

- Results in death,

- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital abnormality or birth defect
- Other medically important event (is not immediately life threatening or results in death or hospitalization but may jeopardize the participant or require intervention to prevent one of the above outcomes)

NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

12.2. Assessment

12.2.1. Causality Assessment

The causality assessment is the determination of a relationship between a study intervention and an AE. The site PI or Co-I should use his/her clinical judgement to determine the existence of a reasonable possibility that the intervention caused or contributed to an AE.

The AE source documents should allow the PI or Co-I to confirm whether the study intervention is definitely, probably, possibly, unlikely or unrelated to the study intervention.

If the site PI, or delegate, is unsure about whether or not the intervention caused or is related to the event, then the event will be handled as “related” to the intervention for reporting purposes of the trial.

12.2.2. Expectedness Assessment

Events are classified as expected or unexpected based on whether the nature, severity and/or frequency is consistent with the risk information known about the intervention. The assessment of expectedness serves as a guide for defining the regulatory reporting obligations.

12.2.3. Seriousness Assessment

An event is classified as serious if it is associated with effects threatening the life or physiological functions of a participant as outlined above in Section 12.1.2. The assessment of seriousness serves as a guide for defining regulatory reporting obligations.

12.2.4. Severity Assessment

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). It should be noted that severity is not the same as seriousness and does not factor in the decision-making for regulatory reporting obligations.

12.3. Adverse Event (AE) Reporting

For this study, all AEs/SAEs should be recorded on the Adverse Event Worksheet. AEs that are

determined by the PI, or delegate, to be definitely, probably, or possibly related to the intervention will be reported in the REDCap database. Adverse events that are assessed and documented on the AE Worksheet as unrelated or unlikely related to the intervention do not need to be reported in REDCap.

Investigations into potential AEs should be done during each contact with a participant. Investigations may be done through specific questioning and as appropriate, by examination.

Information on all AEs should be recorded promptly in the source document (e.g., medical chart, progress notes), and assessed by the site PI or delegate in a timely manner. The AE CRFs in REDCap should be completed using source documents by a delegated research team member within 5 days of site awareness. All signs, symptoms, and abnormal diagnostic procedures should be recorded in the source, though should be grouped under one diagnosis on the AE Worksheet. Each AE should then be categorized in accordance with Common Terminology Criteria for Adverse Events (CTCAE) classifications.

The site PI or a Co-I is responsible for reviewing and assessing all AEs to determine relatedness. If the PI/Co-I is unable to sign off on paper AE logs or in the REDCap database, chart notes demonstrating review and oversight can be added to the participant's medical chart. Alternatively, sites can document their specific procedure for identifying, assessing and documenting review of AEs in a Note to File.

If the site investigator or delegated Co-I is unsure about whether the intervention caused or is related to the event, then the event will be handled as "related" to the intervention for recording purposes of the trial. If the causality assessment is "unknown but not related" to the intervention, this should be clearly documented in the source documents.

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency.
- At the discretion of the PI or co-I, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of treatment exposure
- Medical or surgical procedures unrelated to the CRRT intervention.

AEs/SAEs should be documented on the Adverse Event Worksheet (Form 8 in the CRF package) described above in 10.3.1.8 and entered into the REDCap database as described in 10.3.2.4 above. The AE information for related AEs/SAEs must be entered into the eCRF in REDCap no later than 5 calendar days from the time the site becomes aware of the event. The Adverse Event Worksheet and eCRF in REDCap should be updated during subsequent visits or points of contact, as required (ie to enter stop dates, etc). At the end of the study, the paper AE logs can be uploaded to the REDCap regulatory database under Other Documents.

12.4. Serious Adverse Event (SAE) Reporting

As for AEs, only trial-related SAEs should be reported through the AE/SAE instrument in the REDCap participant database. Trial-related SAEs must be reported in the eCRF within 24 hours of the study team becoming aware of the SAE.

Sites must also report SAEs to their local REB per their reporting policies. See details above in 10.3.2.4 for reporting SAEs in the REDCap participant database and 10.3.1.8 for completion of the paper SAE reporting CRF.

Section 13: Protocol Deviations

A protocol deviation is a divergence from the study protocol, procedures and/or regulatory requirements at the site. Deviations will be recorded using the Protocol Deviation CRF and in the REDCap participant database.

Some examples of protocol deviations which may occur 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
- Confidentiality Breach
- SAE Reporting: Did not notify coordinating centre of SAE within 24 hours of becoming aware

The above are possible examples of deviations. There may be other deviations that occur, and they should be recorded on the protocol deviation log as well. It is the site PI's responsibility to determine if the protocol deviation requires reporting to the local REB per their reporting policies.

13.1. Potential Planned Protocol Deviations

If a potential deviation from the study protocol, procedures or regulatory requirements is recognized prior to the deviation occurring, it is best to contact the project manager and study co-chairs in advance for guidance. Email the project manager with the details of the request for the protocol deviation. In consultation with the study co-chairs, the potential deviation will be reviewed. A response will be communicated to the site regarding the request for a planned deviation and next steps. The correspondence regarding the deviation must be filed in the site's REDCap regulatory database. When the deviation occurs, the site must complete the protocol deviation CRF and report it in the REDCap database. The site will be responsible for confirming if the protocol deviation needs to be submitted to the REB and to record the date of REB acknowledgement.

NOTE: The approval of deviation requests are intended to facilitate required modifications to the study protocol for single events, and are not to be used repeatedly for reoccurring events. There are no waivers or deviations acceptable for eligibility.

13.2. Protocol Deviations (identified after occurring)

If a deviation from the study protocol, study procedures outlined in the MOP or regulatory requirements occurs, the study team should complete the *Protocol Deviation CRF* and enter the information in the REDCap database within 5 days of becoming aware of the deviation.

Follow the steps below when completing a *Protocol Deviation Form*:

1. Complete the protocol deviation paper CRF as outlined in Section 10.3.1.7 above.
2. Have the PI review the form and complete the Signature/Date section demonstrating their review and oversight.

3. Enter the deviation data in the REDCap protocol deviation instrument in the database as outlined in Section 10.3.2.4 above.
5. As applicable, per local REB reporting requirement policies, submit the protocol deviation information to the REB and upload any information received from the REB to the REDCap regulatory database.

13.3. Deliberate Action

Deliberate actions implemented to avert an immediate hazard to a participant are protocol deviations that are of the most extreme circumstances, and should be communicated to the sponsor immediately, specifically if the participant's safety is at risk. This may or may not be combined with requesting a deviation from the sponsor and may also require guidance from the PI or other medical staff.

Completion of the *Protocol Deviation Form* may be associated with the requirement to complete additional forms, such as Adverse Event Worksheets or Serious Adverse Event forms, which should be completed and sent to the sponsor for review promptly.

13.4. Noncompliance

Noncompliance with the study protocol, SOPs, GCP, other applicable regulatory requirements, and applicable institutional policies and procedures by the site will be addressed by the Sponsor. Significant noncompliance that could impact the safety of the study participants or the validity of the data will be determined by the Sponsor. Sites may be requested to implement a corrective and preventative action plan (CAPA) that is appropriate to the situation.

Section 14: Monitoring/Data Quality Management

While the WISDOM trial is a not regulated under Health Canada Division 5 regulations, to ensure participant safety and data integrity, monitoring is needed per ICH GCP E6. The regulatory requirements for monitoring will be fulfilled by the DMCC for the duration of this study. The current recommendations described in the ICH GCP E6: Guideline for Good Clinical Practice and the FDA Guidance for Industry: Oversight of Clinical Investigations – A Risk Based Approach to Monitoring (released Aug 2013) where both centralized monitoring and on-site/remote monitoring approaches can be developed to ensure clinical trial quality and participant safety.

14.1. Study Monitoring

Study monitoring is conducted to verify the safety of human study participants and to ensure the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation.

Monitoring will be done remotely for the duration of the study unless on-site monitoring visits are warranted. The extent and nature of monitoring conducted by the sponsor will ensure that the study is being conducted and documented in a manner that is compliant with the approved protocol / amendment(s), GCP and any other applicable regulatory requirement(s).

14.2 Regulatory Database Review

Regulatory documents – including consents, signed delegation log, REB approval letters and other essential documents – must be added to the regulatory database by study sites in a timely manner for review by the coordinating center. Periodic review of the documents will be completed by the coordinating center. If any documents are missing or deficient, the coordinating center will notify the site PI and coordinator of the need to provide updated documents in the REDCap database.

14.3. Remote Monitoring Plan

14.3.1 Objective of Remote Monitoring Plan

The purpose of this section is to outline the study-specific procedures related to remote monitoring and source data verification (SDV) for STARRT-AKI trial. This section on remote monitoring outlines:

a) Critical variables
b) Methods utilized to identify potential data quality issues
c) The action taken by central coordination team to reconcile any discrepancies in the data

14.3.2 Remote Monitoring for WISDOM

This is a multi-centre clinical trial with up to 12 participating sites in Canada. Remote monitoring is performed to ensure that the data collected is comprehensive, accurate and collected according to the protocol and supporting operational documents (Manual of Procedures). The purpose of the SDV is to ensure the following:

a) Patient meets the eligibility criteria for the study;

b) Standard operating procedures are followed for obtaining consent and the process is appropriately documented;
c) Complete and accurate data is entered onto the electronic Case Report Forms (eCRFs)

14.3.3 Remote Monitoring Activities

Remote monitoring will be performed at all participating sites. This includes targeted SDV of eCRF data on 2 of the first 5 patients randomized at each site, followed by a random 10% of participants enrolled after the initial 5. The critical data variables entered in REDCap will be source verified. A list of these variable can be found in Section 4.3.1. Targeted SDV focuses on the data in the following eCRFs:

a) Eligibility and Enrolment
b) Consent
c) Randomization
d) Baseline
e) Intervention – CRRT
f) Intervention – Daily Data Worksheet
g) Outcomes
h) Adverse Events and Serious Adverse Events
i) Protocol Deviations

The project manager will provide sites with the SDV Tool, which is a document listing key variables for targeted SDV. Sites are asked to complete the SDV Tool and send it to the project manager, along with de-identified source documents for selected variables listed on the SDV Tool. Appropriate instructions will be provided to sites on how to complete the SDV tool, de-identify source documents, and send these documents to the central coordination team using secure file transfer. If possible, source documents can also be reviewed by the central coordination team through remote access to a site's EMR.

Upon receipt of the completed SDV Tool and the appropriate source documents, the central coordination team reviews these documents to ensure that the data is consistent with the data entered on the eCRF. The review includes checking the eCRF entries in REDCap for accuracy and completeness against source documents. The central coordination team maintains a monitoring log of all patients for whom source documents are requested, received, and verified. Variables are marked as 'verified' in the monitoring log, once the review is complete. Urgent issues are communicated on an ongoing basis as needed with the PIs/Sponsor.

A follow up email is sent to the site's Principal Investigator and Primary Study Coordinator once the review is completed. The follow up email includes a summary of the data reviewed, issues identified, and any corrective actions needed. The monitoring follow-up email will include a timeline within which the issues identified must be resolved. If the site is unable to meet this requirement, sites will be asked to contact the project manager immediately. The project manager will work with the sites to resolve issues in a timely manner.

14.3.3.1 SDV Variables

All the variables below are included in the SDV tool. Sites monitored are required to complete the SDV tool for all variables that are listed in this appendix. In addition, de-identified source documents will be

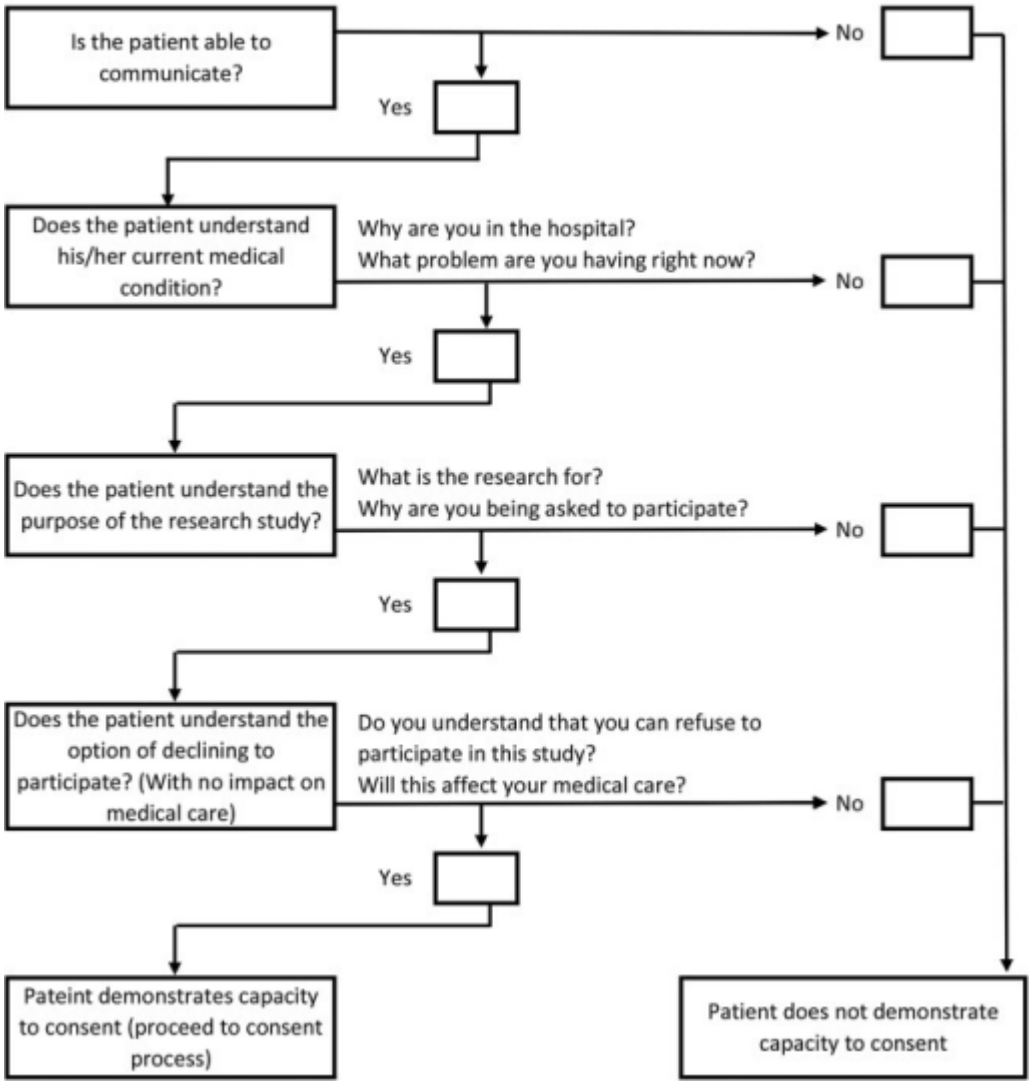
collected from sites for selected variables as specified in the table below.

Form	Field/Variable	Source Document Required?
Inclusion Exclusion and Enrolment	• All criteria as outlined in the protocol and eCRF • Date and time of eligibility	Yes
Consent	• Date and time of initial consent • Type of consent model • Date and time of Post-randomization consent	No
Randomization	• Date and time of randomization • Allocated Arm	No
Baseline	• Year of birth • Weight • Hospital admission date & time • ICU admission date & time • Baseline serum creatinine	Yes
Intervention - CRRT	• CRRT Initiation Date & time • Study Allocated CRRT Initiation Date & Time	Yes
Intervention – Daily Data Worksheet	• CRRT Duration • Time in Allocated Target Range • Blood flow rate • Dose (total effluent) • Dose (hemofiltration) • Hemofiltration – prefilter • Hemofiltration – postfilter • Dose (dialysate) • Dose (total mean) • Dose (highest hourly) • Dose (lowest hourly) • Ultrafiltration (total) • Fluid balance (total)	Yes
Outcomes	• CRRT Discontinuation Date & Time • RRT at 90-days • Date of last receipt of RRT • Serum creatinine at 90-days • Death within 90-days • Date and time of death	Yes
Adverse Events and Serious Adverse Events	• Adverse event type • Date of onset	Yes (for SAEs only)

	• Relationship to study treatment • Expectedness • Stop Date	
Protocol Deviations	• Type of deviation • Description of deviation • Date of deviation	No

APPENDIX A:

Patient Modified Aid to Capacity Evaluation (ACE)* Screening Tool



A:

Buchner DL, Bagshaw SM, Dodek P, Forster AJ, Fowler RA, Lamontagne F, Turgeon AF, Potestio M, Stelfox HT. Prospective cohort study protocol to describe the transfer of patients from intensive care units to hospital wards. BMJ Open. 2015 Jul 8;5(7):e007913. doi: 10.1136/bmjopen-2015-007913. PMID: 26155820; PMCID: PMC4499701.