Appendix 1. STARRT- AKI Steering Committee members

Neill KJ Adhikari	Sunnybrook Health Sciences Centre, Toronto, Canada
Sean Bagshaw	University of Alberta, Edmonton, Canada
Ruminder Bajwa*	Baxter, Mississauga, Ontario
Rinaldo Bellomo	Austin Hospital, Melbourne, Australia
Didier Dreyfuss	Hôpital Louis Mourier, Paris, France
Bin Du	Peking Union Medical College Hospital, Beijing, China
Martin Gallagher	The George Institute, Sydney, Australia
Stéphane Gaudry	Hôpital Louis Mourier, Paris, France
Eric Hoste	University of Ghent, Ghent Belgium
Michael Joannidis	Medical University Innsbruck, Innsbruck, Austria
François Lamontagne	Université de Sherbrooke, Sherbrooke, Canada
Kathleen Liu	University of California San Francisco, San Francisco, USA
Danny McAuley	Queen's University Belfast, Belfast, United Kingdom
Shay McGuiness	Auckland City Hospital, Auckland, New Zealand
Alistair Nichol	St. Vincent's University Hospital, Dublin, Ireland
Marlies Ostermann	Guy's and St. Thomas Hospital NHS Foundation, London, UK
Paul Palevsky	University of Pittsburgh, Pittsburgh, USA
Ville Pettila	Helsinki University Hospital, Helsinki, Finland
Antoine Schnieder	Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
Orla Smith	St. Michael's Hospital, Toronto, Canada
Suvi Vaara	Helsinki University Hospital, Helsinki, Finland
Ron Wald	St. Michael's Hospital, Toronto, Canada
Matthew Weir	London Health Sciences Centre, London, Ontario

- **Non voting**

STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI)

Operations Manual

Version 4.0

Date: April 2, 2018

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Glossary of Terms

°C	Degrees Celsius
ACE	Aid to Capacity Evaluation
AKI	Acute Kidney Injury
CRRT	Continuous renal replacement therapy
CHF	Congestive Heart Failure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CT	Computerized Tomography
DM	Diabetes Mellitus
DMCC	Data Management Coordinating Centre
eCRF	Electronic Case Report Form
FiO_2	Fraction of Inspired Oxygen
GFR	Glomerular filtration rate
Hr	Hour
ICU	Intensive Care Unit
IHD	Intermittent hemodialysis
IV	Intravenous
kg	Kilogram
mL/min	Milliliter per minute
mm^3	Cubic milliliter
mmol/L	Millimoles per litre
µmol/L	Micromoles per litre
MRI	Magnetic Resonance Imaging
PaO_2	Partial pressure arterial oxygen
RRT	Renal Replacement Therapy
SaO_2	Arterial oxygen saturation
sCr	Serum Creatinine
SDM	Substitute Decision Maker
SLED	Sustained low efficiency dialysis
SOFA	Sequential Organ Failure Assessment
µg	Microgram

Part 1: General Information

Study Chairs

Name and Institution	Address, Phone, Email
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STARRT-AKI Steering Committee

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

Members of the Steering Committee:

Neill KJ Adhikari, MDCM	Eric Hoste, MD PhD	Paul Palevsky, MD
Sean Bagshaw, MD MSc	Michael Joannidis, MD	Ville Pettila, MD
Rinaldo Bellomo, MD	François Lamontagne, MD	Orla Smith, RN PhD
Didier Dreyfuss, MD	Kathleen Liu, MD	Suvi Vaara, MD
Bin Du, MD	Shay McGuinness, MD	Ron Wald, MDCM
Martin Gallagher, MD PhD	Alistair Nichol, MD	Matthew Weir, MD
Stephane Gaudry, MD	Marlies Ostermann, MD	

Data and Safety Monitoring Board

The STARRT-AKI trial has a Data and Safety Monitoring Board (DSMB) to monitor participant safety, data quality, and the general progress of the study. The DSMB membership includes experts in nephrology, critical care, clinical trial methodology, and biostatistics.

Members of the Data and Safety Monitoring Board:

Kathy Rowan, PhD (Chair)	Dean Fergusson, PhD
Stuart Goldstein, MD	David Harrison, PhD
Timothy Walsh, MD	

Data Management and Coordination Centre (DMCC)

The Applied Health Research Centre (AHRC) will serve as the global Data Management and Coordination Centre for the STARRT-AKI trial. The study database will be housed on secure servers at the AHRC in Toronto, Canada.

For questions about study operations please contact:

Nikita Chavda, Clinical Research Specialist I
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Part 2: Screening and Eligibility

Philosophy of screening

The over-arching goal is to identify patients with severe AKI (KDIGO Stage 2 or 3) who have a reasonable chance of needing RRT at some point during their ICU stay but who have no urgent indications for RRT at the time of screening.

When should screening occur?

Screening sweeps should occur in the morning and ideally again in the afternoon. Nighttime, weekend or holiday screening are encouraged *where feasible*. Theoretically, there is no limit on the frequency or number of times a patient may be re-screened. You may re-screen individuals who are not initially eligible for the trial as several conditions for eligibility are inherently dynamic. This applies to the inclusion criteria in which patients need to meet criteria for AKI; for example, a patient with an elevated sCr may not meet the AKI criterion for doubling in sCr at a given time (e.g., 180 µmol/L at time of screening from baseline of 100 µmol/L) but at a later time, he/she may become eligible when his/her creatinine is found to be 210 µmol/L. In addition, exclusions 1, 2, 9 and 10 are potentially transient and a patient is not terminally excluded if one of these is met. For example, if the potassium is 5.7 mmol/L (exclusion 1) at the time of a given screen, the patient is ineligible but potentially eligible at a later time point if the serum potassium drops to ≤ 5.5 mmol/L, assuming the other eligibility criteria are still met. If

exclusion 9 is invoked (i.e. clinician(s) feels that immediate RRT is mandated), the patient may be re-screened if RRT did not actually commence. By the same token, when a clinician excludes a patient due to the perception that deferral of RRT is mandated (exclusion 10), this is frequently because the patient is not perceived to be sick enough or that the AKI is about to recover. However, such patients should be rescreened. For example, if the patient's kidney function continues to deteriorate (or not recover), or if the patient's health deteriorates in other domains, the clinician may change his/her mind and become agreeable to randomization.

Exclusion criteria 3 to 8 are generally immutable and if a patient meets any one or more of these, he/she is excluded from further consideration in the trial. However, in theory these too may be dynamic. For example, if the philosophy of care for the patient changes (e.g., RRT not initially an option for patient and then patient/family changes their mind), exclusion 4 may be revoked, thereby making the patient potentially eligible.

Screening Logs

The main purpose of the screening log is to capture the reasons why patients are excluded from the trial. Screened patients who meet all the inclusion criteria should be entered in the screening log. If a patient does not meet ALL the inclusion criteria, he/she should not be entered in the screening log.

For example, if a female patient's serum creatinine is 110 μmol/L (meets inclusion criterion 3) but does not meet one of the criteria for severe AKI (as per inclusion criterion 4), she should not be entered on the screening log. Individual patients should only be assigned one screening number. A patient's record should only be finalized into the log once a terminal decision has been made regarding their study entry (i.e., those in the process of re-screening due to a potentially dynamic exclusion criterion should not be finalized until a final decision has been made regarding their eligibility for the trial). For example, if a given patient who is screened for the trial is provisionally eligible but the attending clinician feels that RRT must be deferred (i.e., exclusion 10 is invoked), that patient should be entered into the screening log but the final outcome of the screen should only be logged once it becomes clear what the final disposition is for that patient with respect to the trial.

Sites will use Screening log V3.0 2017-02-28 to log the above-mentioned information.

- **Subject Screen ID (Column A of screening log)**: Each patient that is entered on the screening log should be assigned a Subject Screen ID (Column A of Screening log). Please ensure that the Screening IDs entered on the screening log follow the format "XXXX." For example, the first patient that is entered on the screening log would be assigned Screening ID "0001," the second patient would be "0002" and so on. The log for each site should be continuous. Thus, please continue adding patients to the log on an ongoing basis and forward the updated log on a monthly basis.

- **Medical Record Numbers (Column B)**: This information should only be kept locally within your site, and should not leave your institution. As such, please ensure that the MRNs are deleted prior to sending the logs to the Coordinating Centre.

- **Screen Date (Column C):** Enter the LAST DATE when the patient was screened.

- **Columns D-K:** Document the exclusion criteria for each patient. For example, if a patient has met exclusion criteria # 1 and 2, then document this by entering "Yes" for E1 and E2.

- **Date and Time of Provisional Eligibility (Columns L-M):** Provisional eligibility is denoted when a patient meets ALL inclusion criteria, and exclusions 1-8 are all found to be NOT present (i.e. patient does not meet any of exclusions 1-8). As such, enter the date and time when patient FIRST met ALL the inclusion criteria but none of exclusions 1-8.

- **Column N:** If a patient meets exclusions 9 or 10, then indicate this by using the correct option from drop down menu button under column N. For example, if a patient's immediate RRT is mandated due to life threatening electrolyte abnormality, then please select the option "Yes, Immediate RRT – life threatening electrolyte abnormality" from the drop-down menu button. If the reason for Immediate RRT or Deferral of RRT is unknown or is not listed in the drop down menu options, then please select "Yes, Immediate RRT – Other" or "Yes, Deferral of RRT – Other" respectively. Please only use the options provided in the drop-down menu to enter information for E9 or E10. *Please do not enter free text in this column as we will not be able to analyze any free text that is entered*.

  Note: For any patients who meet exclusions 9 or 10 (i.e. if "Yes" is indicated on Column N for a patient), please also complete the Provisionally Eligible but not Randomized Form (Form 3). Please refer to Page 8 for guidelines on how to complete the Provisionally Eligible but not Randomized Form (Form 3).

- **Columns O-P:** If a patient is excluded from the trial due to co-enrollment in another clinical trial, then please indicate this by entering "Yes" under Column O and indicate the study name under Column P. PLEASE NOTE THAT STARRT-AKI ENCOURAGES THE RECRUTIMENT OF ALL FULLY ELIGIBLE PATIENTS, EVEN IF ENROLLED IN OTHER TRIALS. IF YOU HAVE ANY QUESTIONS ABOUT OTHER TRIALS AND THEIR POTENTIAL IMPACT ON STARRT-AKI, PLEASE CONTACT RON WALD OR SEAN BAGSHAW.

- **Columns Q-T:** If a patient is fully eligible for the trial, then update the information entered for the patient on the screening log and indicate the date and time of fully eligibility, whether informed consent was obtained for the patient, and the 7-digit RAVE ID assigned by the database.

Please email each month's screening log to the attention of the STARRT-AKI Project Manager on the FIRST business day of the subsequent month. The following method should be used to ensure that confidential patient information is not transmitted out of each institution:

- Save the document as a new file using "Save As" and name the document "STARRT-AKI - <insert site number> - <insert yyyy-mm>
- Delete the Medical Records Number and other personal identifiers from the new file, and "Save". This is the file that should be sent to the AHRC on a monthly basis. If you have a local coordinating centre for your region, please also copy your lead contact at this centre on the email.

Form 3: Provisionally Eligible but not Randomized and Fully Eligible but not Randomized

Please refer to the Form 3 Excel Spreadsheet to complete this form. This spreadsheet should be provided to you upon site activation by the Coordinating Centre. This form should only be completed on Form 3 Excel Spreadsheet (NOT on Medidata RAVE). As such, please submit the completed Excel Spreadsheet to the Coordinating Centre upon completion on a quarterly basis.

This form is only completed for non-enrolled patients whose FINAL reason for non-participation was one of the following:

- Exclusion 9 (clinician believes that immediate RRT is mandated); or
- Exclusion 10 (clinician believes that deferral of RRT is mandated); or
- Patient is fully eligible but consent could not be secured.

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. Each of these different sections are indicated in the top row of the excel spread sheet. Data entry guidelines for each of these sections are described below:

Demographics:
Please begin data entry in Form 3 Excel spread sheet by entering the patient's Screening ID. The Screening ID should correspond with the patient's Screening ID as entered on the screening log. For example, if you are completing Form 3 for a patient with screening ID "0003" on the screening log, then their Screening ID on Form 3 should also be entered as "0003." Some of the columns throughout this form have drop down menu options. Please select the appropriate response to each question, where applicable, using the drop-down menu button.

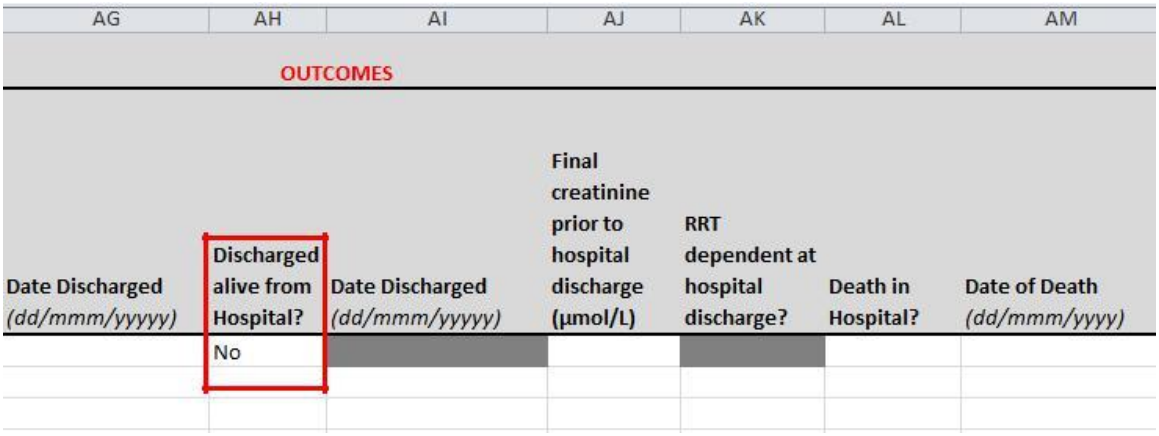
Note: Patient Initials are restricted to 3 characters; Excel will auto generate an error message if 4 or more characters are entered for Patient Initials. Similarly, Patient Age must be greater than or equal to 18 years; Excel will auto generate an error message when a number less than 18 is entered for patient's age.

Blood work:
Please enter the value for each variable within this section as recorded in patient's medical chart. The bloodwork values collected in Form 3 should reflect the last available value at the time when the patient's eligibility was being assessed. Serum Potassium and Serum Bicarbonate must be collected in mmol/L. Urea can be collected in either mmol/L for sites that evaluate serum urea or mg/dL for sites that evaluate blood urea nitrogen (BUN), and Serum Creatinine can be collected in µmol/L or mg/dL. Please select the appropriate units for urea and creatinine using the drop-down option provided in the "units" column for each of these respective variables.

Interventions:
Please indicate whether or not the patient is receiving mechanical ventilation and/or vasopressors using the "Yes" or "No" drop down options. The receipt of mechanical ventilation, inotropes and vasopressors should reflect what was happening at the time of screening.

SOFA:
A SOFA score incorporating multiple clinical domains from the preceding 24 hours should be completed. The most extreme score for each organ system in the preceding 24 hours should be selected. Please select the appropriate responses using drop down options for each variable collected to calculate the total SOFA score.
Note: The Total SOFA Score will be auto calculated upon entering individual scores for each variable. See *Data Completion Manual* for further guidance on completion of the SOFA score.

Outcomes:
This section collects information related to patient's hospitalization and discharge from the hospital. Key clinical events over the patient's course of hospitalization will be recorded. These data may only be submitted from sites where permitted by the local ethics board. Certain fields in this section of the form may not be applicable to patients depending on their outcomes. Fields which are not applicable to the patient will be automatically greyed out as you enter data, as shown below.



AG	AH	AI	AJ	AK	AL	AM
	OUTCOMES					
Date Discharged *(dd/mmm/yyyyy)*	Discharged alive from Hospital?	Date Discharged *(dd/mmm/yyyyy)*	Final creatinine prior to hospital discharge (µmol/L)	RRT dependent at hospital discharge?	Death in Hospital?	Date of Death *(dd/mmm/yyyy)*
	No					

As shown in the image above, Date Discharged and RRT dependence at hospital discharge are not applicable if "No" is selected for "Discharge alive from hospital?" Please do not enter any data in fields which are greyed out, as they are not applicable.

Completing data entry:

Once data entry is completed for all the sections for a particular patient, please select "Yes" for the "Form Completed?" question at the end of the form. If "Yes" is selected, the patient's information, as collected in this form, will be locked for editing. If you would like to make any corrections to the form, please change your response to "No" for "Form Completed?". By doing so, the patient's information will be unlocked for editing.

Overview of Eligibility Criteria

Please refer to the study protocol for rationale regarding each of the inclusion or exclusion criteria. The inclusion criteria will assist research staff in first establishing the presence of severe AKI through objective means. Once all the inclusion criteria are met, a series of 8 circumstances for exclusion is

verified. If none of these exclusions is relevant to the patient, the patient is then considered **provisionally eligible**. Provisionally eligible patients are then reviewed with the attending physician(s) caring for the patient (i.e., the ICU physician and where applicable, the nephrologist). Conversion of a *provisionally* eligible patient to a *fully* eligible patient rests on the non-objection of the attending physician(s) to the patient's participation in the trial. The attending physician(s) must declare that neither immediate RRT is absolutely mandated nor deferral of RRT is absolutely mandated. This expression of equipoise is the final step to FULL ELIGIBILITY which will in turn lead to subsequent efforts to enroll the patient into the trial. The exact time of FULL ELIGIBILITY being met signifies the beginning of the 12 hour window during which the patient must be consented, randomized, and commenced on RRT if randomized to accelerated RRT strategy.

Inclusion Criteria

The inclusion criteria are designed to identify a population of critically ill adults with severe AKI.

1. **Age ≥ 18 years.**
   Operational definition: Patient's age on the day of eligibility screening.

2. **Admission to a critical care unit (ICU).**
   Operational definition: Any unit where there is capability to administer invasive mechanical ventilation.

   There is no limit or restriction related to the amount of time the patient is "expected" to be in the ICU. The only important factor is that the patient is screened and randomized while still admitted to the ICU. If he/she is then transferred to a non-ICU ward shortly after randomization, this is a clinical (non-research) decision and does not in any way affect the participant's status in the trial.

3. **Evidence of kidney dysfunction.**
   Operational definition: Creatinine (Cr)** ≥100 µmol/L (women) and ≥ 130 µmol/L (men) based on most recent bloodwork available prior to screening and *that has not declined by > 27 µmol/L compared to the highest value recorded in the preceding 48 hours*. Creatinine will often fluctuate during a hospitalization and slight increases or decreases in Cr may be of little clinical relevance. However, for this trial we want to avoid enrolling patients who might have evidence of kidney recovery. A Cr drop of 27 µmol/L or more from a previous value in the preceding 48 hrs might signify such recovery and such patients should not be enrolled. However, this patient should be closely monitored as kidney function can deteriorate once again as expressed by a further rise in the serum creatinine.

   ** Though this document, the protocol and the eCRF may refer to *serum* creatinine (sCr), all blood creatinine values (eg, whole blood, plasma), including those obtained from point of care meters, are acceptable

4. **Evidence of severe AKI based on at least one of the following three criteria:**

i. **≥ 2-fold increase in creatinine (Cr) from baseline;**

Operational definition: The baseline Cr is an *outpatient* reading within 365 days of the current admission date; if multiple pre-hospitalization values are available, the one closest to the date of hospital admission will be used. If an outpatient pre-hospitalization value is not available during the 365 days prior to admission date, the lowest Cr value obtained during the current hospitalization should be taken as the baseline. In circumstances where a patient arrives in the ER as an outpatient, and undergoes routine blood work which indicates high creatinine, and the patient is later admitted to the hospital, the bloodwork which is done in the ER is to be viewed as part of the current hospitalization. This criterion is met if the current Cr is ≥ 100% higher than the baseline value.

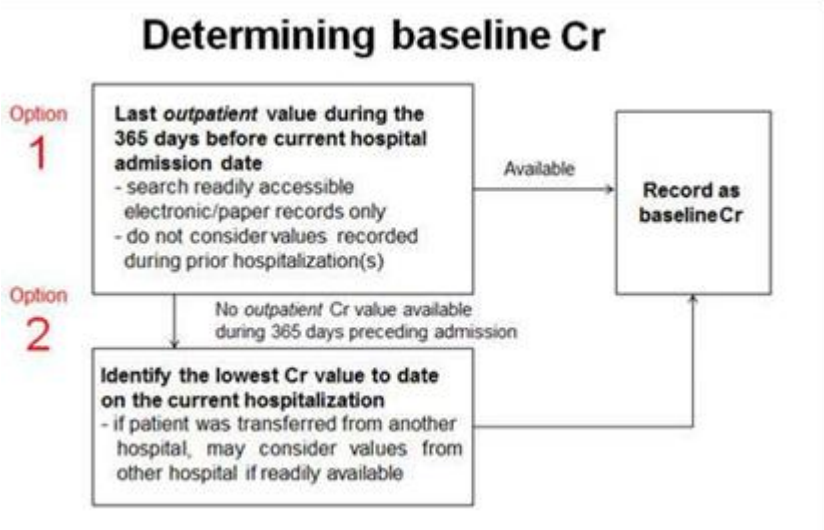
There should always be a baseline Cr. Please refer to the **Determining Baseline Serum Creatinine** flow chart below.

ii. If current Cr is ≥ 354 µmol/L (4.0 mg/dL) with evidence of a minimum increase of at least 27 µmol/L (0.3 mg/dL) from the baseline Cr;

Operational definition: If current Cr is ≥ 354 µmol/L and the patient has experienced an increase of 27 µmol/L or more from the documented baseline, based on the definition delineated above for baseline Cr. There should always be a baseline sCr. Please refer to the **Determining Baseline Serum Creatinine** flow chart below.

iii. Urine output < 6.0 mL/kg over the preceding 12 hours;

Operational definition: Calculate the sum of hourly urine output values for the preceding 12 hours from the current time of screening; if it is below 6.0 mL/kg, then patient meets this criterion. The study coordinator will note the participant's weight in kilograms based on the FIRST recorded weight in hospital. This information will be sought from the flow sheet from the patient's first day in hospital at the study site. If not documented at that time, the flow sheet from subsequent days may be reviewed for the patient weight. Ideally, the earliest available weight will be used. If no weight has been documented on any of the flow sheets, then the study coordinator will ask the attending physician and bedside nurse to provide an estimated weight and the average of these estimates will be the baseline weight. In order to fulfill this criterion, the patient must be in the ICU for a minimum of 12 hours for the requisite urine output data to be available. A patient in the ICU for < 12 hours would not be able to meet the severe AKI requirement based on the urine output.



**creatinine concentrations obtained from point of care meters are acceptable

Exclusion Criteria

1. **Potassium concentration > 5.5 mmol/L.**

   Operational definition: Based on last available bloodwork. If a patient previously had a value > 5.5 and received therapy to lower the value to ≤ 5.5 (eg, the patient had a potassium value of 5.9 mmol/L and it is now 5.4 mmol/L), this would not render the patient ineligible. **Only the value at the time of screening matters.** This criterion is dynamic and subject to review on subsequent screening rounds; if a value of > 5.5 mmol/L rendered a patient excluded, a subsequent value that is ≤ 5.5 mmol/L would invalidate this exclusion and the patient may be eligible assuming all other criteria are met. (Some hospitals will obtain potassium data from arterial blood samples and/or use point of care meters to perform the analysis; these are both acceptable. The source of the sample and the method of analysis are not relevant. The only thing that matters is that the most recent available blood potassium concentration- from any source- is used for screening purposes.)

2. **Bicarbonate concentration < 15 mmol/L.**

   Operational definition: Based on last available bloodwork which may be derived from any source i.e. routine biochemistry, arterial blood gas, or venous blood gas. Please note that some labs may refer to the bicarbonate as the "Total CO_2". Although the normal reference range for bicarbonate may differ depending on which source it is derived from, <15 mmol/L is an exclusion regardless of the source that the value is obtained from. If a patient previously had a value < 15 mmol/L and received therapy to raise the value to ≥ 15 mmol/L, this would not render patient ineligible. **Only the value at the time of screening matters.** This criterion is dynamic and subject to review on subsequent screening rounds; if an initial value of < 15 mmol/L rendered a patient "excluded", a subsequent value that is ≥ 15 mmol/L would invalidate this exclusion and the patient may be eligible assuming all other criteria are met.

3. **Presence of a drug overdose that necessitates initiation of RRT**

   Operational definition: If noted in the chart or directly from the treating team that RRT was required for treatment of a toxic ingestion of any kind.

4. **Lack of commitment to escalate life support with the addition of RRT**

   Operational definition: Critical care team has deemed the patient not eligible for escalation in life support in the form of initiation of RRT, or substitute decision makers have declined offer of same. There may be a patient who is "Do Not Resuscitate (DNR)" or for whom CPR in the event of cardiac arrest has been declined but if patient/SDM still considers RRT to be a viable treatment option, then such a patient should NOT be excluded from STARRT-AKI.

5. **Any RRT within the previous 2 months (either acute or chronic RRT)**

   Operational definition: If recorded in the medical record by any clinician following the patient. The receipt of dialysis and/or hemofiltration exclusively during cardiopulmonary bypass (i.e., with filter added to bypass circuit) should not be considered when reviewing this exclusion criterion.

6. **Kidney transplant within the past 365 days**

   Operational definition: As reflected in the medical record.

   Note regarding exclusions 5 and 6: For patients who have no known medical history, are found to be unresponsive, or for whom no medical data is available in the system, criterion 5 and/or 6 are deemed void.

7. **Known pre-hospitalization advanced chronic kidney disease, defined by an estimated glomerular filtration rate < 20 mL/min/1.73 m^2**

   Operational definition: The coordinator will review all readily available OUTPATIENT creatinine values within 365 days prior to the date of admission for the current hospitalization (which may have started at a hospital from which the patient was directly transferred). The value closest to the admission date will be considered and will be used to calculate the corresponding estimated glomerular filtration rate using an online calculator. A value of < 20 mL/min/1.73 m^2 derived from the CKD-EPI equation will be grounds for exclusion.

   The creatinine, age, sex, and race (Black/non-Black) is entered into a calculator found at: http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr

   It is expected that a large number of patients will not have readily available outpatient pre-hospitalization creatinine data. Only outpatient creatinine values can be used to calculate the eGFR for the purpose of assessing this criterion. I**n the case of a missing or unavailable outpatient creatinine values, this exclusion criterion is not applicable.**

8. **Presence or strong clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, scleroderma renal crisis) or acute interstitial nephritis.**

   Operational definition: If explicitly described in the medical record as confirmed or strongly suspected as the cause of AKI by the clinicians following the patient. On occasion, one of these conditions may be discovered as being the cause of AKI *after* the patient is enrolled in the trial. This occurrence is within the spectrum of usual clinical care and would not be considered a protocol violation. In addition, the usual trial interventions would continue even if one of these conditions was retrospectively identified as the cause of AKI.

IF THE PATIENT MEETS ALL OF THE ABOVE INCLUSION CRITERIA AND NONE OF EXCLUSIONS 1-8, THEN THE PATIENT IS DEEMED *PROVISIONALLY* ELIGIBLE AND THE ATTENDING CLINICIANS WILL THEN BE APPROACHED BY THE RESEARCH TEAM TO CONFIRM THEIR COMFORT WITH THE TRIAL ENROLLMENT USING THE TWO EXCLUSION CRITERIA DESCRIBED BELOW:

9. **Clinician(s) caring for patient believe(s) that immediate renal replacement therapy is absolutely mandated.**

   Operational definition: The study team will speak to the Critical Care attending physician, and at relevant sites, to the Nephrology attending physician caring for the patient, and ask if he/she agree

with the statement: “Renal replacement therapy must be initiated immediately in this patient.” If at least one of the clinicians answers “Yes”, the clinician will be asked to identify the primary reason for mandating the immediate start of RRT. If the clinical team strongly feels that there is a pressing clinical reason to start AKI, this indicates a lack of clinical equipoise and the patient cannot be enrolled in the trial.

10. Clinician(s) caring for patient believe(s) that deferral of renal replacement therapy initiation is mandated.

Operational definition: The study team will speak to the Critical Care and, at relevant sites, the Nephrology attending physician caring for the patient and ask if he/she agrees with the statement:

“Renal replacement therapy must be deferred in this patient.” If at least one of the clinicians answers “Yes”, the clinician will be asked to identify the primary reason for mandating the deferral of RRT. Usually, this exclusion is invoked when the clinician(s) caring for the patient believe that the patient has an extremely high chance of imminent kidney recovery. In this situation, there is a lack of clinical equipoise and the patient cannot be enrolled in the trial.

Important notes regarding exclusions 9 and 10: The objective of these exclusion criteria is to ensure that there is a collective sense of equipoise with respect to application of either of the trial interventions to a given patient. If a clinician believes that a patient is so sick that RRT MUST be delivered immediately (i.e., allocation to the standard arm would potentially harm the patient), then he/she should invoke exclusion 9. On the other hand, if a clinician believes that a patient’s severe AKI has a high likelihood of imminent recovery (i.e., allocation to accelerated RRT would potentially harm the patient), then he/she should invoke exclusion 10.

It is important to remind clinicians that exclusions 9 and 10 are not meant to provide them with an opportunity to express how they generally treat patients. For example, if a certain clinician would generally prefer to defer dialysis for patients who are in a similar situation to the ones being considered for the trial, this alone is not sufficient justification for invoking exclusion 10. Rather, to invoke exclusion 10, he/she must be convinced that deferring dialysis is the unequivocally right thing to do and that the patient will not derive benefit or might be harmed by entering the trial. Usually, this is because of a perception of IMMINENT kidney recovery. In summary, invoking these exclusions should only occur if a physician believes that there is a compelling clinical rationale for one RRT strategy or the other such that randomization would be unethical.

Finally, both exclusions 9 and 10 are dynamic criteria. If a clinician initially invoked exclusion 9 (RRT initiation is mandated) but for some reason, RRT was not commenced, the patient may be reconsidered for the trial assuming the other eligibility criteria are still met. More commonly, a clinician may have the impression that a given patient might recover imminently and invoke exclusion 10 (RRT deferral is mandated). On a subsequent screening round, assuming that RRT has not commenced and all eligibility criteria still exist, coordinators are encouraged to ask clinicians if their initial view regarding the imperative of deferring RRT still exists. If the reservation is no longer present (often because the patient’s kidney function has not recovered +/- a clinical deterioration in other

domains), the patient may become eligible assuming all other inclusion criteria are still met and exclusions 1-8 are ruled out.

Which clinicians do I confer with regarding exclusions 9 and 10?

In all situations, since he/she is the most responsible physician (MRP) for any potential trial participant, the ICU physician (or his/her delegate) should always be approached regarding a patient's eligibility for the trial. The key question is whether the trial needs to be discussed with the Nephrology service as well. This ultimately depends on the usual practice at that centre regarding the initiation of RRT. In principle, STARRT-AKI study procedures should not lead to an alteration of usual practice at a given study site.

Scenario 1: Centres where Nephrology is not involved in the initiation of RRT

If the usual practice at your site is to not mandate nephrologist involvement in the initiation of RRT (i.e., ICU service can make decision unilaterally and write RRT orders), there is no need to confer with the Nephrology service regarding exclusions 9 and 10.

Scenario 2: Centres where Nephrology is involved in the initiation of RRT

At sites where the Nephrology service makes the decisions regarding RRT initiation (and writes the orders for RRT), it is crucial to involve the Nephrology service for provisionally eligible patients and ask the attending physician (or his/her delegate) to comment on exclusions 9 and 10. The Nephrology service may not have received a formal consult on a patient who meets STARRT-AKI eligibility criteria. If this is the case, please confirm that the ICU physician answers "No" to criteria 9 and 10 and then ask the attending ICU Physician, or the local Study Investigator, to involve the Nephrology service as soon as possible to confirm their willingness to enroll the patient.

Exclusions 9 and 10 and the Furosemide Stress Test

Discussions with the attending physicians following the achievement of provisional eligibility are a crucial part of the enrollment process in this trial. Though patients may meet the study inclusion criteria and have none of exclusions 1-8, we are relying on clinician judgment to tell us whether a patient's condition mandates immediate RRT initiation, or alternatively, if a patient's clinical condition is such that he/she is likely to have imminent kidney function recovery. Both such patients should be excluded from this trial.

This approach understandably entails some degree of subjectivity on the part of the attending physicians. The trial will allow clinicians to utilize a variety of clinical tools to make their determination given that no single biomarker has emerged as an adequately robust predictor of AKI progression and the subsequent need for RRT.

In patients with oliguric AKI, a patient's response to a furosemide bolus is a frequently-employed prognostic tool of AKI progression in clinical practice; specifically, a limited response in terms of urine output (with varied definitions of what constitutes a "poor" response) might suggest that the patient is

likely to require RRT or have AKI that will not recover in the near future. This diagnostic strategy, aptly named the "Furosemide Stress Test" has been standardized and evaluated by Chawla and Koyner et al. In preliminary studies, they have found that a urine output of < 200 mL in the 2 hours that follow an intravenous furosemide bolus (1-1.5 mg/kg) has strong sensitivity and specificity for AKI progression. These results are currently being validated in larger studies.

Though not mandated by the trial, clinicians wishing to risk stratify prospective trial participants using the "furosemide stress test" will be asked to follow the method outlined in these studies (provided in Appendix A). For example, for a provisionally eligible patient who clinicians are reluctant to enroll in STARRT-AKI due to the possibility of imminent renal recovery, a low urine output in response to a furosemide bolus (i.e., a "positive furosemide stress test") might change the physician's impression regarding trial eligibility.

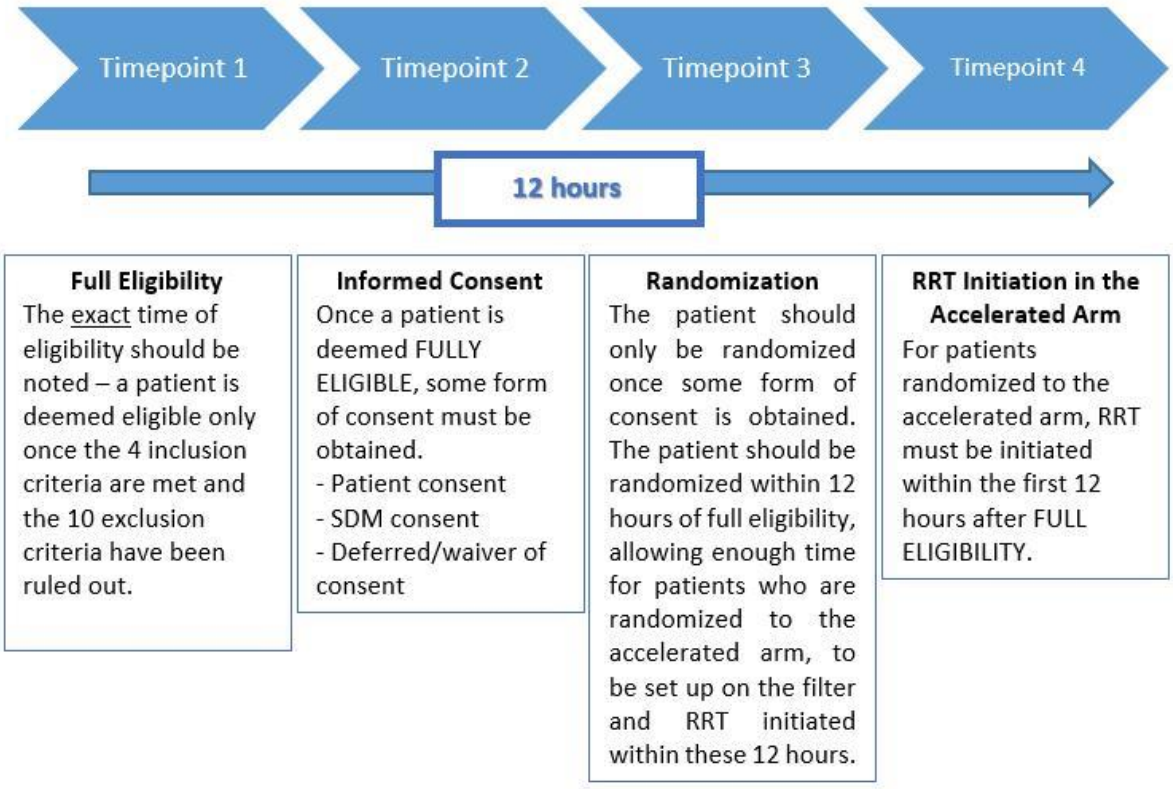
What should be done once all the eligibility criteria are met?

Once full eligibility is determined, the exact time of full eligibility should be noted.

Within 12 hours of full eligibility:

1) consent should be obtained (from patient or substitute decision maker) or documentation of decision to use delayed/waiver of consent;
2) patient should be randomized, and
3) if the patient is randomized to the accelerated arm, the patient should start RRT.

The start of the 12-hour window has no relation to the creatinine doubling or any other biochemical index of AKI. **The 12-hour window begins when all eligibility criteria are met.** Usually, the clinician(s) assent to patient enrolment (answering "No" to both questions 9 and 10) are the final 2 eligibility criteria that are met prior to full eligibility being established. If the patient cannot be randomized within 12 hours of full eligibility, the patient can be considered ''fully eligible but not enrolled.''



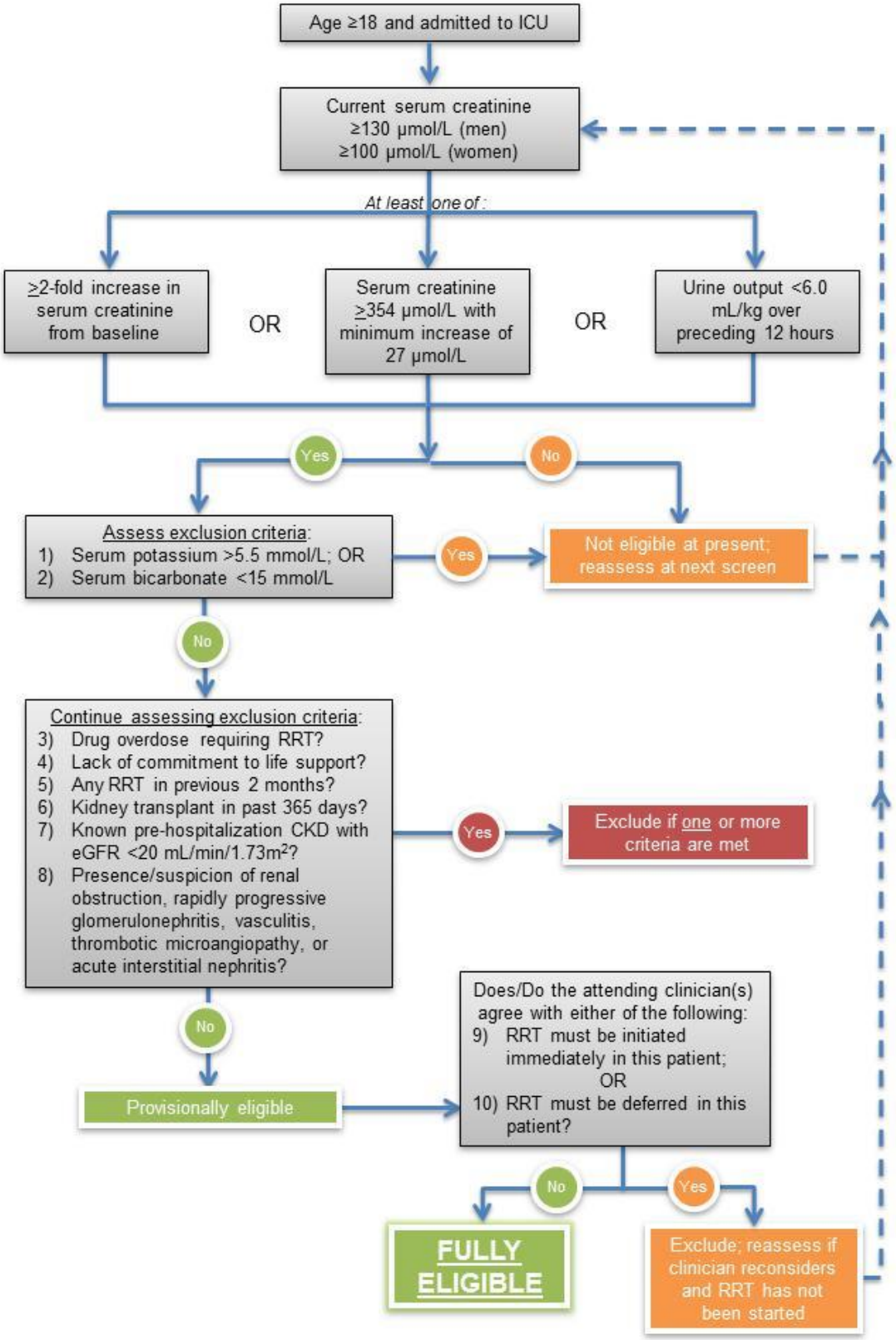
Which patients are entered in the study database/eCRF?

While all patients recorded on the screening log will be assigned a screening number, **only patients who are fully eligible and whom you are ready to randomize, will be entered in the study database** and assigned an auto-generated 7-digit subject ID by Medidata RAVE.

Each time that a patient is added to the study database, a subject ID number is generated by which the patient will be identified in all correspondence with the DMCC. The format of the subject ID number is 'XXX-XXXX', where the first 3 digits correspond to the site number and the last 4 digits correspond to the patient number. For example, the 1st patient enrolled at site 011 will have subject ID: 011-0001. The eCRF will assign patient numbers in sequence based on the order in which they are added to the database (i.e., 011-0001 will be followed by 011-0002, 011-0003, 011-0004, etc.).

Note that if you start to enter a patient into the RAVE database but realize that the patient is not fully eligible or you decide not to randomize the patient, you can re-use that patient number for the next patient that you want to randomize (as long as the patient number is not already used for a randomized patient).

The following algorithm has been created to assist with determination of eligibility:



Part 3: Consent

POLICIES REGARDING CONSENT MECHANISMS MAY DIFFER BETWEEN CENTRES AND ACROSS JURISDICTIONS. PLEASE FOLLOW LOCAL POLICY.

Initiating the consent process

Note to users: The policies and procedures around consent should always follow local guidelines as prescribed by your research ethics board. The information below reflects policies followed at many Canadian centres and may not be completely applicable at your centre.

Patients and/or their SDMs will be approached by the Site Investigator or Research Nurse/Coordinator.

Ideally, a member of the "circle of care" 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, the Investigator(s) in question will excuse him/herself from involvement in the consent process in order to avoid an impression of a conflict of interest or undue influence. Initial contact will be made either in person or via telephone. Prior to this discussion, the Research Nurse/Coordinator will discuss patient suitability for trial enrollment with one of the site Investigators. The study team also will ensure that the patient/family has been informed regarding the patient's clinical condition and diagnoses and potential eligibility for a research study by the attending team (MD/RN).

If a SDM cannot be identified, some centres may permit enrollment through a deferred consent or waiver of consent mechanism. In the case of deferred consent, the patient will be enrolled in the trial with repeated attempts made after enrollment to secure consent from the SDM. In all cases of consent by SDM or deferred consent, the patient will be asked to consent to the trial once he/she regains capacity. In some jurisdictions, a waiver of informed consent may be granted for the trial and this may be accompanied with a possibility for the patient/SDM to opt out of the trial.

The following general statements may be used in the initial telephone/in-person conversation with patients and SDMs. Please note that it is difficult to script the conversation given that it is not possible to anticipate the responses of the patient or SDM with any degree of certainty. Script may be modified depending on whether discussion is with patient or SDM.

"Hello. My name is (insert name of research personnel) and I am the research nurse/coordinator in the ICU at (insert name of hospital). As a large teaching and research facility, (insert name of hospital) participates in a number of research studies. In critical care, research is the best method we have to advance our understanding of disease and improve detection, prevention, and treatment of critical illness. As such, we feel it is important to offer opportunities for research participation to our patients and families for their consideration. When patients are in the ICU, we are usually not able to converse with them due to the severity of their illness or the treatments that we administer to support them (mechanical ventilation, sedation). Because of this, we ask family members to act as substitute decision makers and to make decisions for the patient based on their best knowledge of what the patient would want for themselves if they could speak. Participation in any type of research is entirely voluntary and you have the right to refuse research or withdraw from research at any time. As (insert name of physician) has explained to you, (insert patient name) has a condition called acute kidney injury which

means that his/her kidneys have been damaged over the course of this illness. (Insert patient name) has acute kidney injury of such severity that dialysis needs to be considered for him/her. Dialysis is a treatment in which a machine will be purifying (insert patient name)'s blood in order to replace some of the functions normally performed by the kidney, including the removal of toxins. One of the challenges we face in this field is that we do not know when the right time to start dialysis is. Some people believe that starting dialysis early is a good idea. Others would prefer to wait until there is a pressing need to do so. We are currently conducting a study that is comparing these two approaches: starting dialysis right now or standard care where the physicians will simply follow (insert name of patient) and decide to start dialysis based on their judgment. Would you be willing to discuss the possibility of (insert name of patient) participating in a research study with me?"

If the patient/SDM is willing to discuss the possibility of participation in the trial, move forward to review the contents of the consent form. For SDMs that are not on site, send a copy of the consent form via fax or email to assist the SDM in the decision making process. If phone consent is obtained, the SDM's name will be recorded on the consent form and the person obtaining consent as well as a witness to consent will sign the consent form. The witness will listen to the Research Nurse/Coordinator's discussion with the SDM and will be placed on the phone to confirm the SDM's consent to participate.

Endeavors will take place to have the SDM sign the original consent document at their earliest convenience, if possible (i.e., first visit to the hospital). Document the consent discussion both in the study file and in the patient's standing medical record.

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 a substitute decision maker (SDM).

Assessing patient capacity requires considerable clinical judgment. The modified Aid to Capacity Evaluation (ACE) screening tool is recommended as a guideline but centres may use whatever standardized operating processes are in place at their site (see Appendix B).

Consent scenarios

The following consent situations may arise:

1. **Patient has capacity to provide consent**. He/she may consider inclusion in the study and should be consented using the most current consent form as approved by the local Ethics Board. A consent checklist will be provided to sites and can be used to document the consent discussion.

2. **Patient does not have capacity and SDM available**. If patient is deemed not to have capacity then a SDM should be sought using the patient's pre-determined wishes. If the patient's SDM is unavailable, then a standard hierarchical order of persons authorized to make medical decisions for an incapacitated patient, based on local practices, should be considered. If a SDM is identified, attempt to obtain consent from this individual using the consent form approved by the local Ethics Board. If the SDM cannot be present to sign in person, the consent discussion may be carried out over the phone ideally (but not necessarily) after faxing or emailing a copy of the consent form to the SDM. A consent checklist will be provided to sites, which may be used to help confirm that the SDM clearly understands what is being asked of them and *must* be completed in the event that consent obtained by phone/fax/email.

In situations where enrollment is based on SDM-provided consent, frequent attempts to verify the patient's capacity should be made (e.g., every 72 hours or as deemed appropriate by the local Ethics Board). A sample capacity form is available in the appendix.

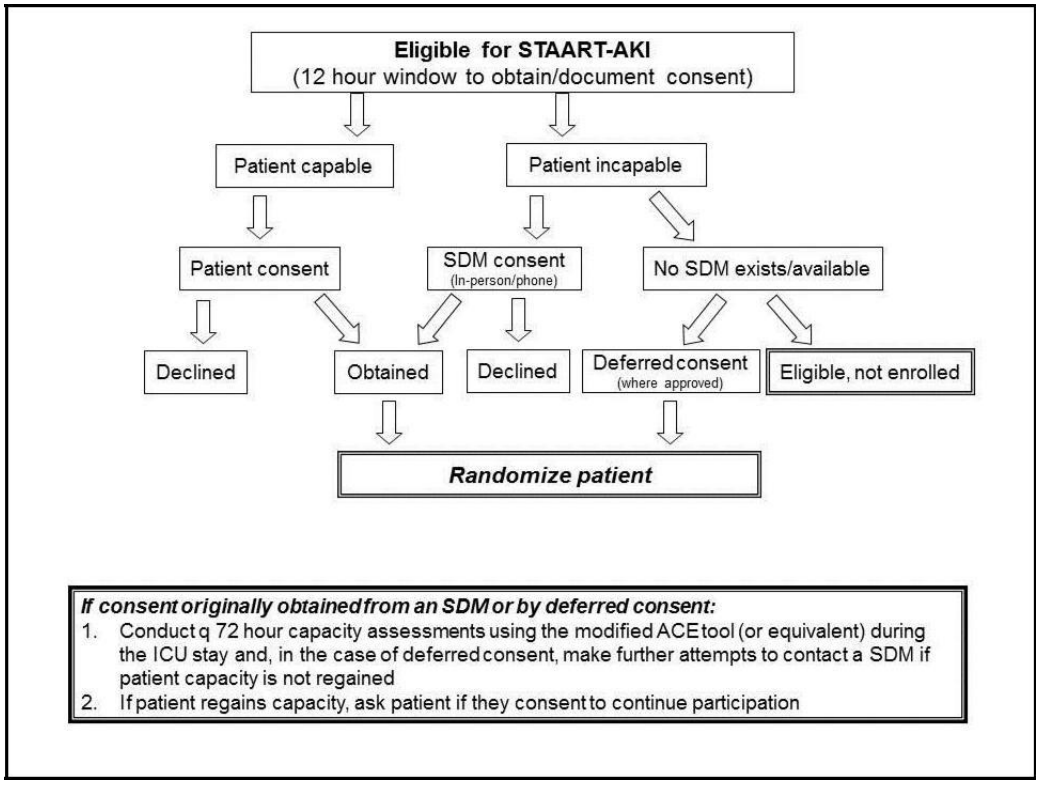
If a patient has been enrolled in the study with consent obtained from a SDM, he/she should be consented once capacity is regained. If the patient chooses to withdraw from the study, he/she will be asked to authorize retention of all data collected to date and/or completion of follow-up for detection of study outcomes at 90 days.

3. **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 deferred or waived consent, <u>if approved by the local Research Ethics Board</u>.

If an SDM is located, he/she will be asked to offer consent for the trial using the consent form approved by the local Ethics Board.

Even if an SDM authorizes continuation of the trial after initial enrollment using a deferred consent model, once the patient regains capacity, he/she should be consented using the consent form approved by both the local Ethics Board and the sponsor. If the patient refuses to continue participation in the trial, he/she will be given the option of authorizing the research team to follow him/her for the 90-day follow-up period and collect outcome data.

The following flow chart illustrates the possible scenarios for patient consent at most centres (please note: this may not apply at centres with a *waived consent* policy in which the participant is enrolled with an option to opt out):



Part 4: Randomization

Fully eligible and consented (regular, SDM, or deferred/waiver of consent) patients will be randomized 1:1 to accelerated versus standard initiation of RRT, stratified by site and with variable block sizes.

Randomization will occur through the electronic study database (see Data Entry Guidelines) and will be contingent upon prior completion of the eligibility page, confirming full eligibility of the participant, and confirmation of consent (regular, SDM, or deferred/waiver of consent) on the consent page.

Once a patient is randomized, the Study Coordinator at each study site will record the patient's name, medical record number, date of birth, unique personal health care number (if applicable) and subject ID number in a secure study file.

Part 5: Initiation of Renal Replacement Therapy (RRT)

After consent has been obtained and the arm to which the participant has been randomized is known, the plan for RRT initiation will depend on the arm of the study, as described below.

Procedures to follow for patients randomized to accelerated RRT initiation

RRT needs to be initiated AS SOON AS POSSIBLE but no longer than 12 hours after the full eligibility criteria have been met. Please note that the final stage of full eligibility is generally reached once the attending physicians affirm their non-objection to the patient's enrollment (i.e., exclusions 9 and 10 are rejected). By the same token, a patient may remain provisionally eligible for an unlimited period of time prior to full eligibility being achieved. However, the "12-hour clock" only commences once FULL ELIGIBILITY is met. For this reason, it is crucial that all of the following take place in order to ensure that this accelerated RRT starts within 12 hours of full eligibility.

1. Notify the bedside ICU nurse that RRT will be started imminently. **The aim should be to start RRT as soon as possible**.

2. Contact the ICU and nephrology (at sites where nephrology is involved in RRT initiation) attendings/fellows/residents to advise them that RRT must commence within 12 hours of study eligibility (specify the exact time in your conversation with them) and that a dual lumen catheter needs to be placed as soon as possible.

3. Clarify the initial RRT modality that will be used to ensure that the appropriate nursing staff is available to provide timely therapy.

If CRRT is the chosen modality, the machine is generally set up and administered by ICU staff so no additional contacts are needed. However, depending on local policy, staff from the hemodialysis unit may need to set up the CRRT machine. *If IHD or SLED is chosen as the initial modality*, please ensure that the charge nurse in the hemodialysis unit is aware so that dialysis nursing staff is allocated to initiate dialysis as soon as possible. In situations where RRT cannot start within the protocol-defined window of 12 hours, (eg, patient was taken for a test or to the operative room, a dialysis machine is not available, difficulty obtaining vascular access) and the patient does not receive RRT within 12 hours of full eligibility, this should be documented as a protocol deviation**. Following that, all efforts should still continue for RRT should be initiated as soon as possible in order to be consistent with the spirit of the accelerated arm to which the patient was randomized.**

Ensure that RRT orders have been written by the appropriate service (Critical Care or Nephrology, depending on local practice).

Procedures to follow for patients randomized to standard RRT initiation

This arm of the trial specifically entails a strategy of watchful waiting, such that RRT is only started if and when a compelling reason arises. Specifically, RRT initiation will be DISCOURAGED unless one of the following is met:

a) Persistent severe AKI defined as serum creatinine that remains > 50% of the value recorded at randomization, (ie, patient has a baseline serum creatinine of 400µmol/L at time of randomization and maintains a serum creatinine of ≥ 200µmol/L) **AND**

b) **At least one of the following** indications for RRT initiation:

i. Serum potassium ≥ 6.0 mmol/L
ii. Serum bicarbonate ≤ 12 mmol/L or pH ≤ 7.20
iii. PaO_2/FiO_2 ≤ 200 and perception of volume overload as the cause of the impairment in oxygenation
iv. Persistent severe AKI (sCr remains > 50% the value recorded at randomization) for > 72 hours from randomization

While we discourage the initiation of RRT unless one of the above conditions is met, meeting any of the above criteria does not mandate the initiation of RRT. For example, if a patient in the standard arm develops a potassium concentration of 6.1 mmol/L 2 days after randomization, a physician may attempt maneuvers that do NOT involve RRT to lower the potassium concentration (e.g., diuretics).

****KEY POINT:** There is never an obligation to start RRT in the standard arm of the trial.

Notwithstanding the above, patients in the standard arm may be started on RRT at any time at the discretion of the attending clinician EVEN in the absence of the criteria above. However, all decisions to initiate RRT in the standard arm of the trial will have to be approved by the attending physician(s) involved in the patient's care and if applicable, the physician(s) will be asked to specify the primary reason for initiating RRT in the absence of meeting the trial-specified criteria above.

In the standard arm, initiation of RRT within 12 hours of eligibility will be considered a protocol violation and the clinician will be asked to provide the primary reason(s) for RRT commencement. For example, if RRT is initiated 11 hours and 45 minutes after the time of full eligibility in a patient randomized to the standard arm, this would be a protocol violation and should be entered as a deviation on the electronic case report form.

In the standard arm of the trial, it is expected that a proportion of participants may die before receiving RRT while others may experience recovery of kidney function, thus obviating the need for RRT.

Part 6: Principles of RRT Initiation in STARRT-AKI

RRT Delivery

Other than the study intervention (i.e., differential timing of RRT initiation), all RRT delivered to patients in both treatment arms will follow an identical set of recommended guidelines that is compatible with contemporary clinical practice. The STARRT-AKI team at the site will supervise and document the details of all RRT provided to patients in the first 14 days following randomization.

RRT Modality Choice

The three RRT modalities that are employed in usual practice may be used in this study: intermittent hemodialysis (IHD), sustained low efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT). The initial RRT modality may be guided by hemodynamic stability at the time the patient is ready to start RRT. If the cardiovascular component of the Sequential Organ Failure Assessment ($SOFA_{CV}$) score is ≥2 (see table below), based on the patient's clinical status at the time of randomization, it is recommended that CRRT or SLED be the chosen modality. If $SOFA_{CV}$ is <2 at the time of randomization, then IHD is a reasonable option.

The cardiovascular component of the Sequential Organ Failure Assessment (SOFA) score:

Score	Clinical condition
0	Mean arterial pressure ≥ 70 mmHg
1	Mean arterial pressure < 70 mmHg
2	Dopamine ≤ 5 µg/kg/min or any dose of dobutamine or milrinone
3	Dopamine 5.1-14.9 µg/kg/min or epinephrine/norepinephrine ≤ 0.1 µg/kg/min or vasopressin ≤ 0.03 U/min or phenylephrine
4	Dopamine > 15 µg/kg/min or epinephrine/norepinephrine > 0.1 µg/kg/min or vasopressin > 0.03 U/min or receipt of A-V extracorporeal life support

Following the initiation of RRT, modality switches are permissible and may be guided by the patient's hemodynamic profile. For patients receiving SLED or CRRT, a modality switch to IHD is reasonable if the patient has been off all continuous infusions of vasopressors and/or inotropes for the preceding 12 hours (i.e., $SOFA_{CV}$ has come down to < 2). For patients receiving IHD, it is recommended that SLED or CRRT be instituted if the patient's status changes and the continuous infusion of vasopressors or inotropes becomes necessary (i.e., $SOFA_{CV}$ has risen to ≥ 2). These suggestions are meant to provide general guidance, as we recognize that modality choices and transitions are often driven by local policies and practice.

Guidelines for RRT Prescription by Modality

The following table outlines the essential parameters around the prescription of RRT by modality:

	IHD	**SLED**	**CRRT**
Minimum session duration (hrs)	3	8	24
Minimum frequency	3 times/week	3 times/week	-
Blood flow target (mL/min)	200-400	200-300	100-250
Dialysate flow (mL/min)	500-800	100-400	-
Dose target, per session	KT/V > 1.2 or urea reduction ratio > 0.65	KT/V > 1.2 or urea reduction ratio > 0.65	≥ 20 mL/kg/hr effluent flow
Anticoagulation options	Heparin None Regional citrate anticoagulation	Heparin None Regional citrate anticoagulation	Heparin None Regional citrate anticoagulation

➢ Equipment

RRT machines and hemodiafilters that are in routine use at each study site will be acceptable for this study.

➢ Clearance Mode

In CRRT, the total hemofiltration dose (i.e., defined by the replacement fluid rate) and dialysis dose (i.e., defined by dialysate flow rate) will be combined and must equal at least 20 mL/kg/hr. Where technology permits and depending on local practice, hemofiltration may also be used in conjunction with IHD and SLED.

➢ Net Fluid Removal

Net fluid removal rate for each RRT session will be determined by the nephrologist and/or the critical care physician, according to the patient's hemodynamic status and the desired fluid balance.

➢ Hemodynamic Support

The administration of intravenous fluids, inotropes, and vasopressors will be at the discretion of the critical care team.

➢ Vital Signs and Routine Bloodwork

These will be performed and documented as per the usual protocols in place at the participating centres.

Cessation of RRT

Once started in either treatment arm, RRT will continue until one of the following circumstances is encountered:

1. Death
2. Withdrawal of life support in the context of a change in the philosophy of care
3. Kidney function recovery with no need for continued RRT

Kidney function recovery may be defined as fulfillment of ONE of the following three criteria:

1. Decline in serum creatinine by ≥ 50 µmol/L on 2 sets of bloodwork separated by > 12 hours with no intervening RRT
2. If a patient is receiving CRRT, urine output > 0.5 mL/kg/hr in the preceding 12 hours and most recent potassium < 5.5 mmol/L and most recent bicarbonate > 18 mmol/L.
3. Clinician discretion that kidney function has recovered adequately to permit withdrawal of RRT

In some circumstances, RRT may need to be restarted after a period during which RRT is halted. In that instance, RRT will be administered using the same principles delineated above.

Part 7: Safety Reporting

Safety Events

➢ Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or participant in clinical investigation administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment (the study therapy). An AE, therefore, can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study interventions.

➢ Serious Adverse Event (SAE)

An adverse event that meets at least one of the following conditions:

- is fatal (results in death)
- is felt to be life-threatening
- requires in-patient hospitalization or prolongation of an existing hospitalization
- results in significant disability or incapacity

Reportable Safety Events in STARRT-AKI

➢ Observation Period

Safety events will be collected from the time of patient randomization up to 14 days post-randomization or until the patient is discharged from ICU, whichever timepoint comes first.

All ***deaths that occur during the 14-day follow-up period should be reviewed by the Principal Investigators*** in coordination with attending clinicians in order to determine whether these may be linked to the trial interventions.

➢ What to Report

All safety events (AEs and SAEs) that are thought to be potentially related to the trial intervention (timing of RRT initiation) or complications of RRT should be reported. These include events related to the administration of RRT and associated need for vascular access or events that were felt to occur due to the delay in RRT initiation.
****See Data Completion Manual for detailed definitions of reportable AEs/SAEs***

Safety Events potentially related to RRT include:

- RRT-associated hypotension
- Sever hypophosphatemia
- Severe hypokalemia
- Severe hypocalcemia
- Arrhythmia during RRT
- Seizure
- Major bleeding
- Allergic reaction

Safety Events potentially related to the central venous catheter (CVC) used for RRT:

- Hemorrhage at the site of CVC insertion
- CVC-associated bloodstream infection
- Ultrasonographically-confirmed thrombus attributed to CVC
- Pneumothorax
- Hemothorax
- Air embolism
- Inadvertent arterial puncture at time of CVC insertion
- Other CVC-related safety events

➢ Reporting Procedures for Safety Events Relating to Trial Interventions

Adverse Events (AEs)

Reportable Adverse Events (non-serious) should be reported in the eCRF via the Adverse Event Details form within 7 days of the site becoming aware of the event.

Serious Adverse Events (SAEs)

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

i. an atypical event, defined as clinically significant and unexpected in the context of critical illness secondary to AKI, AND

ii. an event that is at least possibly related to study procedures.

For reportable SAEs that occur from the time of patient consent/enrollment until Day 14, the following reporting procedure applies:

- **Report the SAE within 1 business day of becoming aware of the event** using the Adverse Event Form of the eCRF
- Document in source records
- Follow up any SAE that is fatal or life threatening within 7 calendar days
- Follow up the outcome of SAEs until clinical recovery is complete and laboratory results have returned to baseline, or until progression has been stabilized. Follow-up will continue for the duration of the patient's study participation.

Safety Oversight

Safety events will be monitored throughout the study by a Data Safety and Monitoring Board (DSMB). A biostatistician will generate tabulations of AEs and SAEs and present a summary of all AEs and SAEs to the DSMB on a schedule set by the DSMB. The DSMB will monitor the primary endpoint at predetermined intervals and recommend to the investigators whether the trial should be stopped on grounds of efficacy based on pre-defined statistical criteria. Summary reports from the DSMB will be provided to the Ethics Committee at each participating site.

Figure 1: Safety Reporting Decision Tree

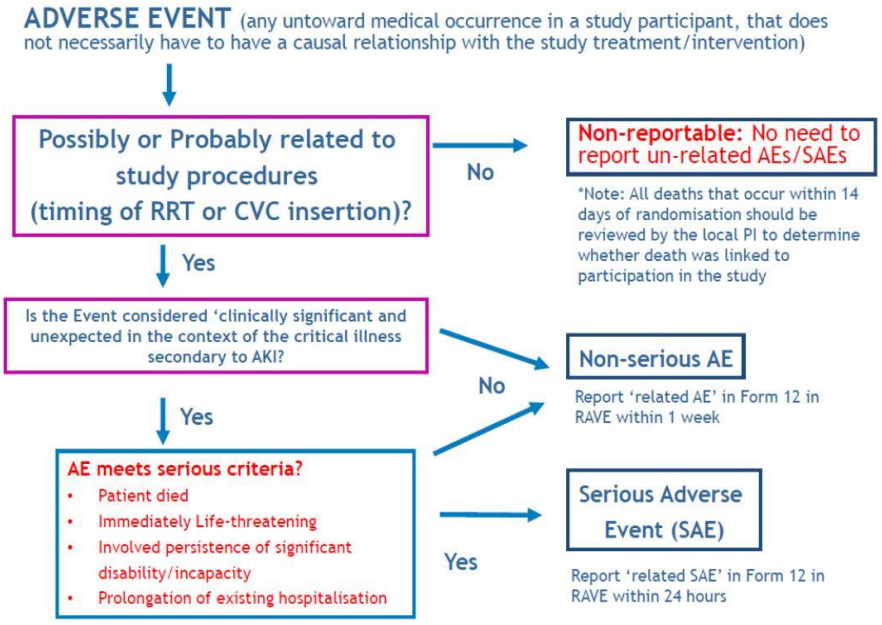


Figure 2: What to Report

RRT-related:

- RRT-associated hypotension
- Severe hypophosphatemia (<0.5 mmol/L)
- Severe hypokalemia (<3.0 mmol/L)
- Severe hypocalcemia (ionized calcium <0.90 mmol/L)
- Allergic reaction to RRT
- Arrhythmia during RRT
- Seizure
- Major bleeding
- Any event deemed to be the consequence of deliberate non-initiation of RT in the standard arm

CVC-related:

- Haemorrhage at the site of CVC insertion
- CVC associated bloodstream infection
- Ultrasonographically confirmed thrombus attributed to CVC
- Pneumothorax following CVC insertion
- Hemothorax following CVC insertion
- Inadvertent arterial puncture at the time of CVC insertion
- Other CVC-related safety events
- Any event deemed to be the consequence of deliberate non-initiation of RT in the standard arm

Report all related events (both serious and non-serious that occur within 14 days of randomization, in Form 12 on Medidata RAVE

Part 8: Data Completion Manual

Form 1: Eligibility

ENROLLING A PATIENT IN STARRT-AKI

Patients who meet all inclusion criteria and no exclusion criteria should be randomised. ***Only patients who will be randomized should be entered into the RAVE Database***.

GENERAL INFORMATION

IF THE PATIENT MEETS ALL THE INCLUSION CRITERIA AND NONE OF EXCLUSIONS 1-8, THEN THE PATIENT IS DEEMED *PROVISIONALLY ELIGIBLE* AND THE ATTENDING CLINICIANS WILL BE APPROACHED BY THE RESEARCH TEAM TO CONFIRM THEIR COMFORT WITH THE TRIAL ENROLMENT USING EXCLUSION CRITERIA 9 & 10. If the research team believes that either the immediate initiation of RRT is mandated or the deferral of RRT is mandated, the patient should be excluded. If a patient's eligibility is excluded by a clinician but RRT has not yet commenced at the subsequent screening round, the patient may be reconsidered for participation in the trial, and the clinician re-approached about the need to initiate/defer RRT, provided the patient still meets the other eligibility criteria.

INCLUSION CRITERIA

The patient is NOT eligible for randomisation if NO is selected for any of the inclusion criteria

No.	Question	Definition or explanation of question
1	Age ≥ 18 years	The patient's age on the day of eligibility screening must be 18 years or older.
2.	Admission to a critical care unit (ICU)	A critical care unit can be defined as any unit where there is capacity to administer invasive mechanical ventilation though the patient him/herself need not be ventilated for consideration in the trial. There is no limit for how long the patient needs to be in the ICU prior to enrolment in STARRT-AKI and there is no minimum duration for "expected" ICU stay.
3.	Evidence of kidney dysfunction defined as serum creatinine ≥100 µmol/L (1.13 mg/dL) in women and ≥130 µmol/L (1.47 mg/dL) in men.	Serum creatinine ≥100 µmol/L (1.13 mg/dl) [women] and ≥ 130 µmol/L (1.47 mg/dL) [men], based on most recent bloodwork available prior to screening and that has not declined by > 27 µmol/L compared to the highest value recorded in the preceding 48 hours.
4.	Evidence of severe AKI defined by at least ONE of the following three criteria? i) ≥2-fold increase in serum creatinine (sCR) from baseline (as defined on the right); **OR** ii) Achievement of a serum creatinine ≥ 354 µmol/L (4.0 mg/dL) with evidence of a minimum increase of 27 µmol/L (0.3 mg/dL) from a pre-morbid baseline or during the current hospitalization **OR**	 i) The baseline sCr is an *outpatient* reading within 365 days of the current admission date; if multiple pre-hospitalization values are available, the one closest to the date of hospital admission will be used. If an outpatient pre-hospitalization value is not available during the 365 days prior to admission date, the lowest creatinine value obtained during the current hospitalization should be taken as the baseline. This criterion is met if the current sCr is ≥ 100% (2x) higher than the baseline value. ii) If current sCr is ≥ 354 µmol/L and the patient has experienced an increase of ≥ 27 µmol/L from the documented baseline, based on the definition delineated in i) for baseline sCr.

	iii) Urine output < 6.0 mL/kg over the preceding 12 hours	iii) Urine output < 6.0 mL/kg over the preceding 12 hours. *Patient must be in the ICU for at least 12 hours prior to using this criterion. Weight should be earliest recorded weight during current hospital stay. If no weight is recorded, take the average weight estimated by bedside nurse and attending physician.
EXCLUSION CRITERIA		
The patient is NOT eligible for randomization if YES is selected for any of the exclusion criteria		
1.	Potassium > 5.5 mmol/L	Based on last available bloodwork from any source (serum, plasma, whole blood) using any available technology (laboratory analyser, point of care meter). This criterion is dynamic, so the patient may be re-assessed to verify if potassium subsequently enters the range for eligibility.
2.	Bicarbonate concentration < 15 mmol/L	Based on last available bloodwork from any source (serum, plasma, whole blood) using any available technology (laboratory analyzer, point of care meter). This criterion is dynamic, so the patient may be re-assessed to verify if bicarbonate subsequently enters range for eligibility.
3.	Presence of a drug overdose that necessitates initiation of RRT	Drug overdose is relevant if noted in the chart or directly from the treating team as the primary reason for administering RRT.
4.	Lack of commitment to ongoing life support including RRT?	Critical care team has deemed the patient not to be eligible for RRT as part of escalation of life support. A patient who has requested to not be resuscitated in case of cardiac arrest might still be considered for STARRT-AKI if RRT remains a viable treatment option.
5.	Any RRT within the previous two months (either acute or chronic RRT)	If recorded in the medical chart
6.	Kidney transplant within the last 365 days	As reflected in the medical chart
7.	Known pre-hospitalization advanced chronic kidney disease, defined by an eGFR <20 mL/min/1.73m^2	Pre-hospitalisation baseline serum creatinine values should be used to calculate eGFR, using the CKD-EPI formula (http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr). If patient does NOT have a **pre-hospitalization outpatient** serum creatinine available (and you are using a baseline serum creatinine from the current hospitalization), then this exclusion criteria does not have to be considered.
8.	Presence or strong clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy, or acute interstitial nephritis?	These conditions are only relevant if explicitly described in the medical chart and confirmed or strongly suspected as the cause of AKI by the clinicians following the patient.

PROVISIONAL ELIGIBILITY		
*A patient is considered Provisionally Eligible once they meet all inclusion criteria and exclusion criteria 1 through 8. Please document the date and time the patient was **FIRST considered provisionally eligible** on the screening log and in MEDIDATA RAVE.*		
a.	**Date of (first) Provisional Eligibility** DD-MMM-YYYY	Please enter the date that the patient was first considered provisionally eligible for STARRT-AKI.
b.	**Time of (first) Provisional Eligibility** (24-hr clock, local time)	Please enter the local time that the patient was first considered provisionally eligible for STARRT-AKI.
9.	Clinician(s) caring for the patient believe(s) that immediate RRT is mandated	The study team will speak to the Critical Care attending physician, (and at relevant sites, the Nephrology attending physician caring for the patient) and ask if he/she agrees with the statement: "Renal replacement therapy must be initiated immediately in this patient." If one of the clinicians answers "Yes", the patient is not eligible for enrolment into STARRT-AKI.
10.	Clinician(s) caring for patient believe(s) that deferral of RRT initiation is mandated	The study team will speak to the Critical Care (and, at relevant sites, the Nephrology) attending physician caring for the patient and ask if he/she agrees with the statement: "Renal replacement therapy must be deferred in this patient." If one of the clinicians answers "Yes", the patient is not eligible for enrolment into STARRT-AKI right now but may be re-screened for eligibility.
ELIGIBILITY		
11.	**According to the screening criteria above, is the patient eligible for the study?** Y/N	The patient must meet all inclusion criteria and no exclusion criteria to be eligible for STARRT-AKI. **Note: If patient does not meet all criteria, they should not be entered into the RAVE database.*
11a	**Date of full eligibility** (DD-MMM-YYYY)	Please enter the date that the patient meets all inclusion criteria and no exclusion criteria.
11b	**Time of full eligibility** (24-hr clock)	Please enter the time that the patient meets all inclusion and no exclusion criteria. **Note: This is the time that the 12-hour clock starts for the patient to be randomized and if they are randomized to the accelerated initiation arm, the patient should start RRT within the first 12 hours of full eligibility*.

Form 2: Consent

GENERAL INFORMATION

Study coordinators will be responsible for obtaining informed consent from the eligible patient or the substitute decision maker (SDM), if the patient is unable. If neither of these options is available, and the local ethics committee approves, a delayed or deferred consent model may be used whereby a decision is made by the clinical and research team to enrol the patient in the study. In these cases, consent from the patient and/or SDM will be sought as soon as reasonably possible. In some jurisdictions, waived consent has been approved and is acceptable for the implementation of STARRT-AKI. In all instances, please follow instructions for your region to complete this document.

No.	Question	Definition or explanation
1.	Was consent of any approved type (from patient or substitute decision maker) obtained OR was a decision taken to randomize the patient using a deferred/delayed consent mechanism (at sites where permitted)? *Note: Patient must be randomized within 12 hours of meeting full eligibility.*	The answer to this question must always be YES to randomise a patient. If the patient or SDM does not give consent prior to randomisation, the decision to randomise the patient using the deferred/delayed consent model should be documented.
2.a	Date of initial consent (from patient or SDM), OR documentation for use of deferred/delayed consent. DD-MMM-YYYY	Date that consent was obtained or date decision was made to enrol the patient using the deferred/delayed/waived consent model. **This date must be before or equal to the date of randomization.*
2.b	Time of initial consent (24h) OR documentation of use of deferred/delayed consent model.	Time of initial consent OR time decision was made to use deferred/delayed consent model (in 24-hour time format). **This time must be before the time of randomization.*
3.	What type of consent model was used for study entry (i.e. prior to randomization)? • Patient consent • SDM consent • Deferred/delayed consent model • Other, specify	Prior to randomization, what type of consent model was used for study entry? If patient or SDM assented after randomization, choose 'Deferred/delayed consent model'
4.	If SDM consent (in person or via telephone) was obtained for study entry, was consent ultimately obtained from the patient to continue participation in STARRT- AKI post randomization? • Yes • No • N/A	If a substitute decision maker consented on behalf of patient for study entry, was consent obtained from the patient to continue participation in STARRT-AKI?
4.a	If no, why not? • Patient did not regain capacity • Patient refused • N/A (Not applicable)	If a substitute decision maker consented on behalf of patient for study entry, and patient consent was ultimately not obtained to continue participation in STARRT-AKI, provide the reason why patient consent was not ultimately obtained. **If this is not required at your site, choose N/A.*

5.	If a deferred/delayed consent model was used, was consent obtained to continue participation in STARRT-AKI post- randomization? Yes → What type? • Patient continue • SDM continue • Other, specify No → Why declined or not obtained? • Patient declined • SDM declined • Patient died before consent • Patient lost to follow-up • Patient did not regain capacity and SDM could not be contacted • Language barrier with no translator available • Other, specify	If deferred/delayed consent model was used, please enter the type of consent that was ultimately obtained. If no consent was obtained, please choose the reason.

Form 4: Randomization

GENERAL INFORMATION

Once you complete the eligibility and consent page, you are ready to randomize.

No.	Question	Definition or explanation
1.	Do you wish to randomize this patient into the study? Y/N	This answer should always be YES. Patient who are NOT fully eligible and NOT ready to be randomized should NOT be entered into RAVE.
2	Is this patient randomized in the PLUS (Plasma-Lyte 148® versUs Saline) study? Y/N	The Plasma-Lyte 148® versUs Saline (PLUS) Study is being conducted in Australia and New Zealand only. Please answer YES if this patient has been enrolled in the PLUS study.
2a.	What is the PLUS Treatment Pack number for this patient? (LNNNNNN)	The PLUS Treatment Pack allocation is an L + 6-digit number, no spaces. This only needs to be entered if the patient has already been enrolled in the PLUS study.
2b.	Please verify the PLUS Treatment Pack number.	Ensure you are entering the correct PLUS Treatment Pack number.
3.	If your centre is NOT located in the Eastern Time Zone (Toronto, New York City, etc), enter the local date and time of randomization (24-hr clock)	If you are not located in the Eastern Time Zone (Eastern Standard Time), enter the local date and time of randomization. Date = DD-MMM-YYYY Time = 24-hour clock
4.	Randomization call date and time	This option is available if RAVE is down and a call is made in order to randomize a patient. This should not be completed if the patient is randomized on the on-line RAVE system. **Note: this option is only available in certain time zones.*
5.	Randomization group	The patient will be assigned to either **Accelerated RRT Initiation <u>OR</u> Standard/Delayed approach to RRT Initiation**. You should receive a Randomization e-mail detailing which arm the patient is assigned. The participant's randomization group/arm will be at the top of every eCRF page in RAVE from now on.

Forms 5-9: Baseline

GENERAL INFORMATION

Forms in the Baseline folder should reflect pre-randomization data
The forms include:
Form 5: Demographics & Details of Hospitalization
Form 6: Risk Factors
Form 7: Pre-randomization SOFA
Form 8: Pre-randomization Severity of Illness
Form 9: Pre-randomization data

Form 5: Demographics

No.	Question	Definition or explanation
1.	**Date of birth** DD-MMM-YYYY	If you are unsure of the specific date of birth, please enter the day as 01 and/or month as JAN. If your ethics committee does not permit collection of full date of birthday, please enter the day as 01, 15 or 30 per site requirements.
2.	**Sex** Male/Female	Record the person's biological sex.
3.	**Race** • First Nations • Asian • Black • Hawaiian/Pacific Islander • White • Multi-race • Other	Record the patient's race based on self-report or best judgement. Choose one.
4.	**Ethnicity** • Hispanic • Non-Hispanic	Record if patient is Hispanic or Non-Hispanic.
5.	**Earliest available weight since admission** Choose kgs or lbs	Record the patient's earliest recorded weight (in kgs or lbs) during the current hospitalization. If no weight is documented, please ask the bedside nurse and attending physician to estimate the patient's weight and take the average of the 2 estimates. **Note: this should be the same weight as the one used to assess oliguria in the screening phase.*

Form 5: Details of Hospitalization		
6.	**Patient transferred from another acute care hospital?** All dates are DD-MMM-YYYY All times are 24-hr clock Yes → • Date of Original hospital admission • Date of transfer (admission) to research site • Date of ICU admission at research site • Time of ICU admission at research site No → • Date of hospital admission at research site • Date of ICU admission • Time of ICU admission	If the patient was transferred from another hospital to the research site, please record the dates and times as requested. If the patient's hospitalization commenced at the research site, enter the relevant dates and times as requested.
7.	**Diagnostic Category** • Cardiovascular • Gastrointestinal/hepatic • Metabolic • Septic • Respiratory • Neurologic • Hematologic • Trauma • Other, specify____ **Please specify the other diagnostic category (ie. Orthopaedic)*	Choose the diagnostic category that is MOST responsible for the hospital admission. If there are multiple concurrent conditions driving the patient's hospitalization, choose the system most responsible for the patient's AKI. If the diagnostic category does not fit within those listed, please choose Other and specify a diagnostic category.
Form 6: Risk Factors		
1.	**Baseline serum creatinine** Choose: µmol/L or mg/dL **Value obtained from**: ➢ Inpatient setting ➢ Outpatient setting	Use the closest outpatient value prior to the present hospitalization that is obtained no more than 365 days before the admission date for the current hospitalization. If such a value is not available, the lowest creatinine obtained on the present hospitalization is the baseline. Creatinine values from previous hospitalizations should not be used as the baseline. Please document whether you are using an inpatient or outpatient creatinine for the baseline value. **Note: This value is the baseline creatinine used for determining eligibility.*

2.	**Baseline estimated GFR based on CKD-EPI formula**	Using the baseline sCr noted for the previous question, the patient's gender, age, and ethnicity (black or not black), determine the estimated GFR at baseline using the abbreviated CKD-EPI equation by going to the following link: http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr. *For accuracy, please ensure that the unit selected for creatinine on the calculator is correct.*
3.	**Pre-hospitalization urine albumin concentration** • mg/L or g/L • Exceeds upper Limit of Detection (LOD) • Not available	Use the closest outpatient value prior to the present hospitalization and no more than 365 days before the current admission date. Enter the value and the units being used. If value exceeds the upper limit of the local assay, choose "exceeds upper LOD." If unavailable, please tick "not available".
4.	**Pre-hospitalization urine protein concentration** (**if urine albumin concentration not available*) • mg/L or g/L • Exceeds upper Limit of Detection (LOD) • Not available	**Only needs to be entered if urine albumin concentration is not available.* Use the closest outpatient value prior to the present hospitalization and no more than 365 days before the current admission date. Enter the value and the units being used. If value exceeds the upper limit of the local assay, choose "exceeds upper LOD." If unavailable, please tick "not available".
5.	**Pre-hospitalization urine creatinine concentration** • mmol/L, mg/L or g/L • Exceeds upper Limit of Detection (LOD) • Not available	Use the closest outpatient value prior to the present hospitalization and no more than 365 days before the current admission date. Enter the value and the units being used. If value exceeds the upper limit of the local assay, choose "exceeds upper LOD." If unavailable, please tick "not available".
6.	**Pre-hospitalization urinalysis** (*if neither urine albumin nor urine protein concentration are available*) • None • 1+ • 2+ • 3+ • Not available	**Only needs to be entered if neither urine albumin or urine protein concentrations are available.* Use the closest outpatient value prior to the present hospitalization and no more than 365 days before the current admission date. If unavailable, please tick "not available". **Please note that urine dipstick values are semi-quantitative and sometimes expressed as concentrations. For values reported as "trace" or < 0.3 g/L, check "1+". For values reported between 0.3-3.0 g/L, check "2+". For values reported as > 3.0 g/L, check "3+".

Form 6: Pre-existing co-morbidities ***Note:** *All the following comorbidities are recorded based on their presence or absence on the ICU medical record (we suggest using the ICU admission note as it is most likely to contain the most comprehensive information regarding the patient's pre-existing conditions).*		
7.	**Hypertension** Y/N	Choose "Yes" if the patient is reported as having a history of hypertension on the ICU admission note.
8.	**Diabetes mellitus** Y/N	Choose "Yes" if the patient is reported as having a history of diabetes mellitus on the ICU admission note
9.	**Heart Failure** Y/N	Choose "Yes" if the patient is reported as having a history of congestive heart failure or heart failure on the ICU admission note
10.	**Coronary artery disease** Y/N	Choose "Yes" if the patient is reported as having a history of Coronary Artery Disease on the ICU admission note
11.	**Liver Disease** Y/N	Choose "Yes" if the patient is reported as having a history of Liver Disease on the ICU admission note
Form 6: Hospital Acquired Risk Factors ***Note:** *Provide a "yes" or "no" response for each field. To respond to each question, consider events/exposures in the 7 days prior to randomization. If the duration of hospital admission is < 7 days, only go back to the time of admission. Please note that if the patient was directly transferred from another acute care hospital, the date of admission is the date patient admitted at the initial (transferring) hospital.*		
12.	**Cardiopulmonary bypass in the preceding 7 days** Y/N	Defined as circulatory arrest and use of cardiopulmonary bypass to facilitate performance of cardiac or other major vascular surgery during the 7 days prior to randomization.
13.	**Aortic aneurysm repair in the preceding 7 days** Y/N	Defined as repair of an abdominal aortic aneurysm using open surgery or endovascular repair during the 7 days prior to trial randomization.
14.	**Other vascular surgery in the preceding 7 days** Y/N	Defined as any open or endovascular surgery involving major arteries (e.g., femoral-femoral bypass or common femoral angioplasty) other than the abdominal aorta during the 7 days prior to trial randomization.
15.	**Trauma in the preceding 7 days** Y/N	Defined as major trauma in the 7 days prior to randomization that is playing a major role in the patient's current critical illness.
16.	**IV contrast exposure in the preceding 7 days** Y/N	Check Yes if the patient was administered any intravenous or intra-arterial iodinated contrast for a diagnostic test (e.g., CT abdomen, coronary catheterization) or interventional procedure (e.g., endovascular aortic aneurysm repair, percutaneous coronary intervention) during the 7 days prior to randomization. *Gadolinium administered for an MRI study is NOT considered.*

17.	**Receipt of aminoglycoside in preceding 7 days** Y/N	Did the patient receive 1 or more doses of gentamicin, tobramycin or amikacin at the study hospital during the 7 days prior to randomization?
18.	**Receipt of amphotericin B in preceding 7 days** Y/N	Did the patient receive 1 or more doses of amphotericin B at the study hospital during the 7 days prior to randomization?
19.	**Obstetric complications in the preceding 7 days** Y/N	Did the patient deliver a baby in the preceding 7 days?
Form 6: Sepsis		
20.	**Has the patient met criteria for Sepsis in preceding 72 hours?** Y/N	Answer "Yes" if the patient has a proven or suspected infection at the time of randomization AND total SOFA score ≥ 2 based on data in Form 7. *By definition, all patients enrolled in STARRT-AKI will have a rise in SOFA score of at least 2 points.* (Note: As per the SEPSIS-3 guidelines released in 2016, the presence of a change in total SOFA score of ≥ 2 will enable the designation of "sepsis" in the presence of a proven or suspected infection.)

Form 7: Pre-Randomization SOFA ***Note**: Use the most extreme result for each component in the **24 hours preceding randomization**. If value is unavailable, assign a score of "0".*		
1.	**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)	Select all <u>arterial</u> 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 V-V or A-V 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.

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

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

Conversion Table for FiO_2 When Measured on Mask or Nasal Cannula

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.

2.	**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.
3.	**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 available prior to randomization, assign a score of 0.

4.	**Cardiovascular:** Blood Pressure and Support Requirements • Mean Arterial Pressure ≥ 70 mmHg (score 0) • Mean Arterial Pressure < 70 mmHg (score1) • 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 highest dose (even if patient was just on the drug for a brief period) and patient will get a score of 3 or 4. 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.

Score	Clinical condition
0	Mean arterial pressure ≥ 70 mmHg
1	Mean arterial pressure < 70 mmHg
2	Dopamine ≤ 5 µg/kg/min or any dose of dobutamine or milrinone
3	Dopamine 5.1-14.9 µg/kg/min or epinephrine/norepinephrine ≤ 0.1 µg/kg/min or vasopressin ≤ 0.03 U/min or phenylephrine
4	Dopamine > 15 µg/kg/min or epinephrine/norepinephrine > 0.1 µg/kg/min or vasopressin > 0.03 U/min or receipt of A-V extracorporeal life support

5.	**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. If patient intubated, assign a score "1" for verbal without making an assumption of their verbal capabilities had they not been intubated. DO NOT ACCOUNT FOR WHETHER PATIENT IS SEDATED OR RECEIVING PARALYTIC AGENTS WHEN ASSIGNING ANY COMPONENT OF THE GCS/SOFA Neurological SCORE. Patient's score should be based on *actual* abilities.

Glasgow Coma Scale (GCS) - (to be used as "CNS" component of SOFA score):

Category	Response	Points
Verbal	oriented	5
	confused	4
	inappropriate	3
	incomprehensible	2
	none	1
Motor	obeys commands	6
	localizes pain	5
	withdraws to pain	4
	flexion to pain	3
	extension to pain	2
	none	1
Eye opening	spontaneous	4
	to command	3
	to pain	2
	none	1
Total	Sum of above components	

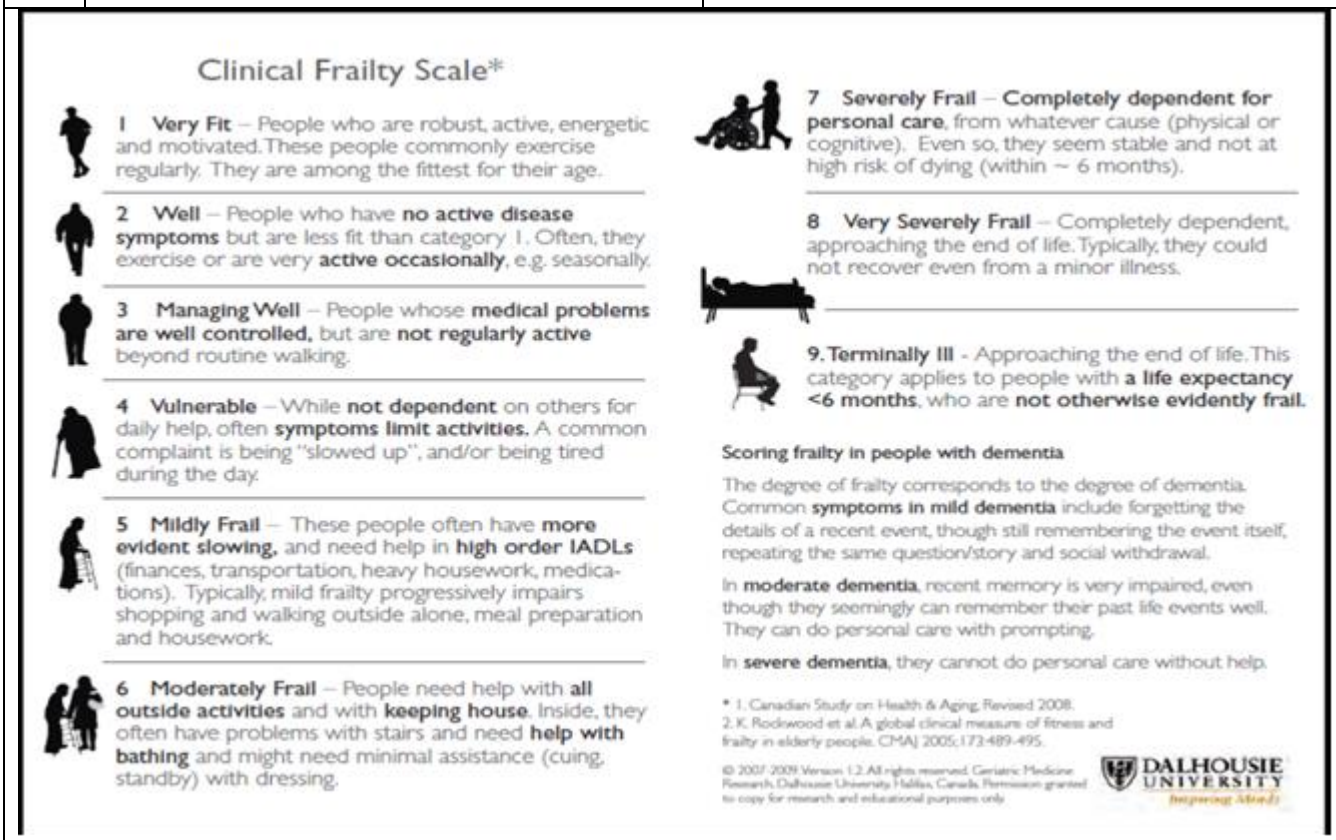
6.	**Renal:** Creatinine • ≤97 µmol/L (≤1.1 mg/dL) (score 0) • 98 - 168 µmol/L (1.2 - 1.9 mg/dL (score 1) • 169 - 299 µmol/L (2.0 - 3.4 mg/dL) (score 2) • 300 - 433 µmol/L (3.5 - 4.9 mg/dL) or urine output ≤ 500 mL/day (score 3) • ≥433 µmol/L (≥ 5.0 mg/dL) or urine output < 200 mL/d or patient receiving RRT (score 4)	Use the highest creatinine value during the 24 hour 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 creatinine places the patient in a higher (i.e., sicker) category.
7.	**TOTAL SOFA SCORE**	Automatically calculated
Form 8: Pre-Randomization Severity of Illness (Simplified Acute Physiology Score (SAPS) II) **Note: Use the worst value during 24 hours preceding randomization. If data is not available, select the Not Available option. Please only use the guidance as outlined below.*		
1.	**Age**	Age in years at time of randomization
2.	**Heart rate** (beats/min)	The *highest* recorded heart rate in the 24 hours preceding randomization.
3.	**Systolic blood pressure** (mmHg)	The *lowest* recorded systolic blood pressure in the 24 hours preceding randomization.

4.	**Temperature** (choose C or F)	Record the *highest* temperature in the 24 hours preceding randomization in degrees Celsius or Fahrenheit.
5.	**Glasgow Coma Scale**	The *lowest* value in the 24 hours preceding randomization (this information will also be used for determination of the pre-randomization SOFA – CNS component)
6.	**Mechanical ventilation or CPAP?** Y/N If yes, enter PaO_2/FiO_2 ratio	Indicate Yes or No. If yes, record PaO_2/FiO_2 ratio.
7.	**Urine Output in ICU over preceding 24 hours** (in mls)	If patient has been in ICU for under 24 hours, record urine output and specify the duration of collection in hours, rounding up or down to the nearest hour.
8.	**Blood urea nitrogen (BUN)** (choose mmol/L or mg/dL) **Please enter either BUN or Serum urea value, depending on what is collected at your site*	Record the *highest* value in the 24 hours preceding randomization. If your site collects serum urea instead of BUN, then you may tick the 'N/A' checkbox for BUN and enter the serum urea in the below field instead.
9.	**Serum urea** (choose mmol/L or mg/dL) **Please enter either BUN or Serum urea value, depending on what is collected at your site*	Record the *highest* value in the 24 hours preceding randomization. If your site collects BUN instead of serum urea, then you may tick the 'N/A' checkbox for serum urea and enter the BUN in the above field instead.
10.	**Serum sodium – Na^+** (mmol/L)	Record the *lowest* value in the 24 hours preceding randomization. Plasma values and results from point of care devices are acceptable.
11.	**Serum potassium – K^+** (mmol/L)	Record the *highest* value in the 24 hours preceding randomization. Plasma values and results from point of care devices are acceptable.
12.	**Serum bicarbonate - HCO_3** (mmol/L)	Record the *lowest* value in the 24 hours preceding randomization. Plasma values and results from point of care devices are acceptable.
13.	**Bilirubin** (µmol/L or mg/dL)	Record the *highest* value in the 24 hours preceding randomization.
14.	**WBC count** ($x10^9$/L)	Record the *highest* value in the 24 hours preceding randomization.
15.	**Metastatic Cancer** Yes/No	Record as Yes/No based on ICU admission note.
16.	**Hematologic malignancy** Yes/No	Record as Yes/No based on ICU admission note.
17.	**AIDS** Yes/No	Record as Yes/No based on ICU admission note. *For this to be YES, a patient must have HIV infection AND an AIDS-defining illness such as Kaposi's sarcoma, toxoplasmosis infection, PJP pneumonia, tuberculosis, lymphoma.*

18.	**Type of admission** • Scheduled surgical • Unscheduled surgical • Medical	Specify if admission type is for a scheduled surgery (patient had a pre-planned surgery as reason for hospital admission), unscheduled surgical (main reason for admission was for performance of urgent surgery), or Medical.
19.	**SAPS II Score**	This will be calculated at the end of the study
Form 9: Pre-Randomization Data		
Physiological Parameters ***Note:** *Enter the last available value prior to randomization. If value is not available, tick 'Not Available'*.		
1.	**Respiratory rate** (breaths/min)	Choose the value recorded closest to but preceding randomization.
2.	**Arterial pH**	Choose the value recorded closest to but preceding randomization.
3.	**Cumulative Fluid Balance** (since ICU admission) in mls	Record the value up to but not including the ICU day on which randomization occurred. For example, if the "ICU charting day" ended at midnight, but a patient was enrolled at 20:00 hrs, record the cumulative balance as of the preceding midnight.
Laboratory Data ***Note**: Enter the last available value prior to randomization. If value is not available, tick 'Not Available'.* *Information from point of care meters may be used.*		
4.	**Serum Creatinine** (choose µmol/L or mg/dL)	Enter the value recorded closest to but preceding randomization.
5.	**Hemoglobin - Hgb** (g/L or g/dL)	Enter the value recorded closest to but preceding randomization.
6.	**Platelet count** ($x10^9$/L)	Enter the value recorded closest to but preceding randomization.
Interventions at Time of Randomization ***Note:** If patient did not receive the intervention in the 24-hours prior to randomization, then tick 'Not Applicable.'*		
7.	**If receiving mechanical ventilation or CPAP, Maximum PEEP (Positive end-expiratory pressure)** (cmH_2O)	As recorded closest to but preceding randomization. *If not receiving mechanical ventilation or CPAP, tick Not Applicable.*

8.	**If receiving mechanical ventilation or CPAP, Mean Airway Pressure** (cmH_2O)	As recorded closest to but preceding randomization. *If not receiving mechanical ventilation or CPAP, tick Not Applicable.*
9.	**Dose of norepinephrine** (µg/kg/min)	Maximum dose based on values recorded in the 24 hours preceding randomization.
10.	**Dose of epinephrine** (µg/kg/min)	Maximum dose based on values recorded in the 24 hours preceding randomization.
11.	**Dose of vasopressin** (units/hr)	Maximum dose based on values recorded in the 24 hours preceding randomization.
12.	**Dose of phenylephrine** (µg/kg/min)	Maximum dose based on values recorded in the 24 hours preceding randomization.
13.	**Dose of dopamine** (µg/kg/min)	Maximum dose based on values recorded in the 24 hours preceding randomization.
14.	**Dose of dobutamine** (µg/kg/min)	Maximum dose based on values recorded in the 24 hours preceding randomization.
15.	**Dose of levosimendan** (µg/kg/min)	Maximum dose based on values recorded in the 24 hours preceding randomization.
16.	**Dose of milrinone** (µg/kg/min)	Maximum dose based on values recorded in the 24 hours preceding randomization.
17.	**Receipt of diuretic in the 24 hours preceding randomization?** Y/N	Indicate Yes or No based on whether patient received furosemide, bumetanide, ethacrynic acid (or any loop diuretic) or metolazone at ANY dose or ANY frequency during the 24 hours preceding randomization.
18.	**Receipt of total parenteral nutrition (TPN)?** Y/N	Indicate Yes or No based on whether patient received any TPN during the 24 hours preceding randomization.
19.	**Receipt of enteral nutrition?** Y/N	Indicate Yes or No based on whether patient received any enteral nutrition during the 24 hours preceding randomization.

20.	**Quality of Life Assessment at Baseline** • Mobility: (score 1-5; missing 9) • Self-care: (score 1-5; missing 9) • Usual activities: (score 1-5; missing 9) • Pain/discomfort: (score 1-5; missing 9) • Anxiety/depression: (score 1-5; missing 9) • EQ-VAS score: (score 0 - 100)	Use the EQ-5D-5L questionnaire provided (patient self-completed) for the baseline visit. All data will be collected in the QoL form directly and transcribed in the eCRF (Medidata Rave). This assessment should be done as soon as feasible after randomization. If a patient does not have capacity to complete the questionnaire at this time, the SDM can complete the questionnaire. If the questionnaire cannot be completed by the patient or the SDM, then please select "not done." ***The information recorded on the baseline quality of life assessment should reflect the patient's state of health PRIOR to the current hospitalization.***
21.	**Clinical Frailty Scale(CFS) Score** (score 1-9; missing 0)	Select the most appropriate option. **The chosen score on a scale of 1-9 is meant to reflect the patient's state of health before the illness that led to the current hospitalization.** Assignment of score is based on information gleaned from patient, family members and clinical notes. *Select 0 if this data is missing.* For more information on the CFS score, see: •https://www.youtube.com/watch?v=brIcorfx9Ts •https://www.youtube.com/watch?v=_3QKcuf-Mhs



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – 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,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – 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 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People 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 **Severely Frail** – **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 **Very Severely Frail** – Completely dependent, approaching the 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 evidently frail.**

Scoring frailty in people with dementia

The degree of frailty 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.

* 1. Canadian Study on Health & Aging. Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY

Form 10: Daily Data

Day 0 to Day 14 (while in ICU only)

GENERAL INFORMATION

This information is collected for 14 days following randomization, constituting Day 0 to 14. The same information will be collected each day while the patient is in the study ICU. Day 0 will usually be a partial day and represents the time from randomization to the end of that "ICU day".

The daily data are collected only **while patients are in the ICU**. A daily data form should be completed if the lpatient spent part of the day in the ICU. For example, a "partial day" may occur if a patient was out of ICU for tests or procedures or if he/she was discharged to the ward, another ICU or another hospital during an "ICU day". Please note that daily data is not required for patients that remain hospitalized but have been discharged from the study ICU (i.e., either discharged to the ward or sent to an ICU at a different hospital). If a patient is discharged from the study ICU and then returns to the study ICU within 14 days, daily data collection does NOT resume.

Assessment Day:

How is a "day" defined in STARRT-AKI?

This should coincide with the usual data collection in your 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, the "days" associated with data collection in the STARRT-AKI trial will correspond to the cutoffs for "days" used in your ICU.

For example, a given ICU collects its data from 08:00- 07:59. A patient is randomized at 22:00 hrs on April 18, 2016. Day 0 runs from 22:00 on April 18 to 07:59 on April 19. Day 1 runs from 08:00 on April 19 to 07:59 on April 20. Day 2 runs from 08:00 on April 20 to 07:59 on April 21 etc.

Form 10: Assessment Date		
No.	**Question**	**Definition or explanation**
1.	Assessment date	DD-MMM-YYYY This is the assessment date on which the ICU day commences. For example if a "day" runs from 08:00 on April 19 to 07:59 on April 20, record April 19 as the date. (Day 0 = Date of randomization)
Form 10: Laboratory and Physiological Parameters ***Note:** Lab values should come from the routine daily bloodwork which is typically the first available value during the ICU day. An exception for Day 0, which should be the first available value after randomization during the ICU day. If your ICU day starts at 8 am and routine morning bloodwork is drawn within 4 hours before this, you may use the information from this routinely drawn bloodwork even if the bloodwork was technically done on the previous ICU day.*		
2.	**Urine output on study day** (mL)	Provide the actual urine output in mL without "adjustment" for time even if a day lasts less than 24 hours.
3.	**Hours of urine collection** (hrs)	Indicate the duration of time for which urine collection is documented. For example, on Day 0, a patient randomized at 22:00, and the "ICU Day" ends at 0:759, record hours as 10. **Note: Round up or down to the nearest hour.*
4.	**Total fluid balance** (mL)	Indicate total fluid balance in milliliters for the 24-hour period that constitutes the ICU study day. This is the balance of all the ins and outs (from all sources) during the ICU day. Number may be positive or negative – if the number is negative, enter a "minus sign" in front of the number; if the number is positive,

		do not enter any sign in front of the number. Complete this even if patient was not in ICU for a full 24 hours.
5.	**Potassium** (mmol/L)	Record the value documented as part of the routine morning ICU bloodwork for that ICU day. The potassium value may be a non-serum value and/or recorded from point of care or blood gas machines if it is local practice to draw routine blood tests from those devices.
6.	**Serum phosphate** (mmol/L)	Record the value documented as part of the routine morning ICU bloodwork for that ICU day.
7.	**Serum bicarbonate** (mmol/L)	Record the value recorded as part of the routine morning ICU bloodwork for that ICU day. The bicarbonate value may also be a non-serum value and/or recorded from point of care or blood gas machines if it is local practice to draw routine blood tests from those devices.
8.	**Arterial pH**	Record the value recorded as part of the routine morning ICU bloodwork for that ICU day.
9.	**Ionized calcium** (mmol/L)	Record the value documented as part of the routine morning ICU bloodwork for that ICU day.
10.	**PaO_2/FiO_2**	Record the value documented as part of the routine morning ICU bloodwork for that ICU day.
11.	**Hemoglobin** (g/L or g/dL)	Record the value documented as part of the routine morning ICU bloodwork for that ICU day.
Form 10: RRT and Vascular Access		
12	**Received RRT on study day?** Y/N	If patient received any RRT on the study day, choose YES. If not, choose NO. Your answer to this question will trigger further questions. If you want to amend the answer to this question, you should delete the answers out of the triggered questions first. ****Note that for intermittent RRT modalities (IHD and SLED), an RRT session may overlap 2 ICU days (ie. A session can commence on one day and concludes on another). In this instance, please attribute the RRT session to the day on which the RRT <u>commenced</u>.*** DO not consider the patient to have received RRT on a given ICU day if you are dealing with a SLED or IHD session that merely concluded on a given day but was started on a previous day.

13	**If YES, was RRT initiated for the first time since randomization on study day?** • Yes • N/A – initiated on previous study day	Answer ***YES if the patient initiated RRT for the first time on the study day***. If Yes, and you will also be asked to specify the time at which the patient started his/her first RRT session. **Note: If yes, complete the RRT initiation data form (Form 11).* Choose ***N/A if RRT initiated on previous day but patient still received RRT on the study day*** (ie, it was not their first RRT session). For any participant who received ANY RRT on a given study day, whether it was the initial session or not, you will be asked to

		comment on RRT modality, duration, and anticoagulation and that were **prescribed**. Delivered therapy may differ from prescribed therapy but you are only asked to record that which was prescribed, EXCEPT for the ultrafiltration variable where we are asking for the ultrafiltration volume **achieved**. For example, if a patient was intended to receive RRT for a full 24 hours but this duration was curtailed due to unforeseen circumstance such as a filter clot, then the prescribed duration would be 24 hours. However, if a decision was consciously made to discontinue CRRT at 16 hours of the 24-hour period, then the duration prescribed would be 16 hours.
14	**If yes, RRT modality** • IHD • SLED • CRRT	Choose the first modality used that day if multiple modalities used. If CRRT, dose question is triggered.
15	**If CRRT, Dose prescribed** (mL/kg/hr)	If the RRT modality is CRRT, you will be asked to enter the dose prescribed in mL/kg/hr. If this value is not readily available on the patient's chart, then you may calculate this by using the formula: (Replacement fluid rate + Dialysate rate) divided by (patient's weight).
16	**If yes, duration prescribed** • Hour • Minutes	If CRRT was started, default duration is 24 hours. However, if a decision was consciously made to discontinue CRRT at 16 hours of the 24-hour period, then the duration prescribed would be 16 hours. If SLED or IHD started, state duration prescribed in hours:minutes.
17	**If yes, Anticoagulation** • IV heparin • Regional citrate • None • Other, specify _____	Specify type of anticoagulation used (IV heparin, regional citrate). Should the patient have started on one anticoagulant and then was changed to another, please enter the first used **for that day**. If anticoagulation was not used, select None. If a patient is receiving low molecular weight or unfractionated heparin prior to and during RRT, but the RRT orders specify that no anticoagulants are to be given to the patient, it depends on the intent of the low molecular weight heparin or unfractionated heparin. If these drugs were just being administered for DVT prophylaxis, and not for the purpose of preventing clots on dialysis, then answer "none" for anticoagulation type. But if the unfractionated or low molecular weight heparin was intended to "cover" dialysis-related anticoagulation please treat this situation as if the patient received heparin for RRT.
18	**Ultrafiltration achieved during RRT session** (mL)	Net ultrafiltration achieved during the RRT session, in milliliters. This value reflects the net volume removed by the RRT machine for that session. For an IHD or SLED session, this is the total volume of fluid removed during that session MINUS any flushes and boluses that the patient received during that session. For a CRRT session, record the NET ultrafiltration achieved by the CRRT machine over a 24 hr period (even if CRRT may not have been running for the entire 24 hr

		period). In a scenario where a patient receives more than one type of RRT modality on a given ICU day, the ultrafiltration achieved would be the sum of the values in milliliters from each modality received on that ICU day.
19.	**RRT vascular access inserted on study day?** Yes/No	If yes, site and side questions will be triggered.
20a	**If yes, Site**: • IJ (Internal jugular) • Subclavian • Femoral	
20b.	**If yes, Side**: • Right • Left	

Form 11: RRT Initiation Data

GENERAL INFORMATION

This form should only be completed if/**when the participant initiates RRT for the first time** from the time of randomization.

No.	Question	Definition or explanation
1.	**Date of RRT Initiation** (DD-MMM-YYYY)	Enter the date that the patient initiated RRT for the FIRST TIME since randomization.
2.	**Time of RRT Initiation** (24-hour clock)	Enter the time that the patient initiated RRT for the FIRST TIME since randomization.
Form 11: SOFA at RRT Initiation Indicate the value for each component of the SOFA score and the total SOFA score will be automatically calculated. Use the last available value prior to initiation of RRT to determine the value for each component at the time of RRT initiation. If the patient was randomized to the accelerated arm, the SOFA scores may be the same as the pre-randomization SOFA values. **Please see Pre-randomisation SOFA tables for reference.*		
3.	**Respiration**: PaO2/FiO2 • > 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)	Select the arterial partial pressure of oxygen (PaO_2) value that was last recorded prior to RRT initiation obtained from blood gas samples and the fractional inspired oxygen (FiO_2) that was being administered at the same time. Calculate the quotient PaO_2/FiO_2 and select the appropriate category. • Patients who are on V-V or V-A ECLS at time of RRT initiation should get an automatic score of 4. • In order to assign 3 or 4, the patient must be receiving invasive or non-invasive mechanical ventilation. • If a patient's PaO_2/FiO_2 is ≤ 200 but he/she is not receiving mechanical ventilation, the score is automatically 2; • In some cases, PaO_2 may not have been obtained; in that case, choose the lowest oxygen saturation

		(SaO_2) for the day and use the chart below to "translate" oxygen saturation (SaO_2) into PaO_2 In some cases, FiO_2 may not have been recorded; as an alternative, use Appendix 1 to "translate" O_2 flow rates through face mask or nasal cannula into an FiO2 value
4.	**Coagulation:** Platelets (x 10^9/L) • > 150 (score 0) • 101 - 150 (score 1) • 50 - 100 (score 2) • 20 - 49 (score 3) • < 20 (score 4)	The last platelet count prior to RRT initiation

5.	**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)	The last bilirubin available prior to the time of RRT initiation • If bilirubin is missing and the last bilirubin was normal (< 20), assign a score of 0; if missing within last 24 hours but last value on current hospitalization ≥ 20, use that value • If no bilirubin available, assign a score of 0
6.	**Cardiovascular:** Blood Pressure and Support Requirements • Mean Arterial Pressure >= 70 mmHg (score 0) • Mean Arterial Pressure < 70 mmHg (score1) • 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 dose at that time and patient will get a score of 3 or 4. 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.
7.	**CNS**: Glasgow Coma Scale • 15 (score 0) • 13 - 14 (score 1) • 10 - 12 (score 2) • 6 - 9 (score 3) • < 6 (score 4)	If patient intubated, assign a score "1" for verbal without making an assumption of their verbal capabilities had they not been intubated. DO NOT ACCOUNT FOR WHETHER PATIENT IS SEDATED OR RECEIVING PARALYTIC AGENTS WHEN ASSIGNING ANY COMPONENT OF THE GCS/SOFA Neurological SCORE. Patient's score should be based on actual abilities.
8.	**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)	Use the sCr value prior to the time of RRT initiation to determine the SOFA-Renal score. If urine output is < 200 mL in the 24 hours prior to RRT initiation, then an automatic score of 4 is assigned irrespective of sCr concentration. If urine output is 200-500 mL/day, crosscheck with highest sCr value and assign the score

	• >= 433 µmol/L (>= 5.0 mg/dL) or urine output < 200 mL/d (score 4)	based on whether the urine output or sCr places the patient in a higher (i.e., sicker) category.
9.	**Total SOFA Score**	Automatically calculated

Form 11: Physiological Parameters at RRT Initiation ***Note:** Please record the last available heart rate, systolic blood pressure, temperature, respiratory rate, and PaO_2/FiO_2 using the last available data prior to actual initiation of RRT.*		
10.	**Heart rate** (beats/min)	Use the last available data prior to actual initiation of RRT
11.	**Systolic blood pressure**	Use the last available data prior to actual initiation of RRT
12.	**Temperature** (C or F)	Use the last available data prior to actual initiation of RRT (you can record up to 1 decimal point).
13.	**Respiratory rate** (breaths/min)	Use the last available data prior to actual initiation of RRT
14.	**PaO_2/FiO_2**	Use the last available data prior to actual initiation of RRT
15.	**Urine output in preceding 24-hours** (mL)	Please record the *total urine output* during the 24-hour period preceding the actual initiation of RRT. For example, if RRT initiation took place at 20:00 on March 8, please calculate urine output from 20:00 on March 7 to 20:00 on March 8. If incomplete urine output data exists for the preceding 24 hours (e.g., patient was not in ICU for the entire period), record the urine volume from the available data.
16.	**Fluid balance up to time of RRT initiation** (mL)	Record the cumulative net fluid balance since the current ICU admission. This would encompass the time from admission to ICU and concluding at the end of the ICU day that precedes RRT initiation. Fluid balance assessment starts at the time of the current ICU admission and should not include fluid balance from wards or ICUs to which the patient may have been admitted prior to coming to the study ICU. For example, consider an ICU where daily charting concludes at 8:00 am. If a patient was admitted to that ICU on March 6 at 22:00 and RRT initiation took place at 20:00 on March 8, record the cumulative fluid balance from ICU admission until 08:00 on March 8.
Form 11: Laboratory Data at RRT Initiation ****Note**: Please record last available result prior to RRT initiation.*		
17.	**Serum creatinine** (µmol/L or mg/dL)	Record last available result prior to RRT initiation
18.	**Serum urea or blood urea nitrogen** (mmol/L for serum urea or mg/dL for blood urea nitrogen)	Record last available result prior to RRT initiation. Please enter either BUN or serum urea value depending on what is collected at your site. If your site collects BUN, then you may enter the BUN value and leave serum urea field blank and vice versa.
19.	**Potassium – K^+** (mmol/L)	Record last available result prior to RRT initiation; whole blood, plasma or serum values acceptable and may emanate from point of care monitors

20.	**Bicarbonate – $HCO3^-$** (mmol/L)	Record last available result prior to RRT initiation; whole blood, plasma or serum values acceptable and may emanate from point of care monitors

21.	**Arterial pH**	Record last available result prior to RRT initiation
22.	**Hemoglobin** (g/L or g/dL)	Record last available result prior to RRT initiation
Form 11: RRT Initiation		
23.	**If patient is in the Standard arm, were criteria for initiating RRT met?** • Yes • No • N/A Patient in the accelerated arm	For patients in the standard arm, this question aims to characterize the conditions under which RRT was actually commenced. For patients in the accelerated arm, answer "NA" to this question. ***Answer "Yes" if the following conditions were present at the time RRT was started in a patient in the standard arm***: a) Persistent severe AKI defined as sCr that remains > 50% of the value recorded at randomization. **AND** at least one of the following indications for RRT initiation: a) Serum potassium ≥ 6.0 mmol/L; **or** b) pH ≤ 7.20 or serum bicarbonate ≤ 12 mmol/L; **or** c) Evidence of severe respiratory failure, based on a PaO_2/FiO_2 ≤ 200 and clinical perception of volume overload; **or** d) Persistent severe AKI (sCr remains > 50% the value recorded at randomization) for > 72 hours from randomization. ***Answer "No" if a patient in the standard arm commenced RRT without the conditions above being present***.
23a	If NO, why was RRT initiated? Check all that apply: • Volume overload • Anuria/oliguria • Creatinine increasing / AKI worsening • Other, specify	A "No" response will prompt a question asking why RRT was commenced. This question should be answered by the attending clinician(s) (ICU and/or Nephrology) who made the decision to start RRT and more than one of the possible answers may be chosen. The ICU physician and nephrologist may report different reasons for initiating RRT and all responses should be recorded.

Form 12: Adverse Event Data

GENERAL INFORMATION

We define a ***reportable*** *adverse event* (AE) as any clinically important, untoward medical occurrence *that could potentially be associated with the study procedures*,* regardless of the "expectedness" of the event for the course of a patient with acute kidney injury.

**Adverse events will be considered study-related if the event follows a reasonable temporal sequence from a study procedure and could readily have been produced by the study procedure. Adverse events that are not study-related do not require reporting. Specifically, events related primarily to the underlying disease or to AKI and its sequelae should NOT be reported.*

*****Note****: ONLY enter/report AEs or SAEs if they are possibly related to the study procedures (dialysis or CVC insertion) or any event that is deemed to be at least possibly related to the study protocol.*

We define a *Serious Adverse Event* (SAE) as:

a) any adverse event that is fatal or immediately life-threatening, permanently disabling, severely incapacitating, or requires prolonged inpatient hospitalization; or
b) any adverse event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above.

Reporting:

AEs and SAEs will only be systematically collected for the first 14 days after randomization. However, any events occurring during the first 14 days after randomization will be followed until resolved or until Day 90 following randomization, whichever comes first.

Collection and evaluation of **adverse events** will include those non-serious adverse events (AEs) or SAEs related to the administration of RRT and the associated need for vascular access (i.e., potentially study-related), or any other AE or SAE that is possibly related to the patient's participation in STARRT-AKI.

New AEs/SAEs will only be systematically collected for the first 14 days after randomization AND while the patient is in the ICU. For example, an AE/SAE that takes place on Day 8 following randomization but after the patient has already been sent to the medical ward (ie, patient has been discharged from ICU) does not need to be recorded. Additionally, if a patient has a prolonged stay in the ICU and an event occurs on Day 20 of the trial, that event should not be reported as an AE/SAE.

All reportable AEs must be entered into the eCRF Adverse Event form within 1 week of the research team becoming aware of the event. Data can be added or edited as more information becomes available.

ALL SAEs must be entered by entering information into the eCRF within 1 business day of the research team becoming aware of the event. Data can be added or edited as more information becomes available. In addition, a copy of all relevant clinical notes should be forwarded to the coordinating centre, including all physicians' and nurses' notes, relevant diagnostic test results, and surgical and other intervention reports, within 3 business days of becoming aware of the SAE. **These notes will be previewed at both the site and the coordinating centre to ensure that they do not contain sensitive or confidential patient information**, before being forwarded to the DSMB for review. If required by the DSMB, additional information may be requested by the coordinating centre.

*****Note****: An Adverse Event Details form must be completed for each adverse event related to study procedures. Additional forms are added, as required, using the 'Add Event' menu on the patient's home page.*

No.	Question	Definition or explanation
1.	**Did the patient experience any of the following within the 14 days following randomization?** Y/N • RRT-associated hypotension • Severe hypophosphatemia (< 0.5 mmol/L) • Severe hypokalemia (< 3.0 mmol/L) • Severe hypocalcemia (Ionized calcium < 0.90 mmol/L) • Allergic reaction to RRT • Arrhythmia during RRT • Seizure • Major bleeding • Hemorrhage at site of CVC insertion • CVC-associated bloodstream infection • Ultrasonographically confirmed thrombus attributed to CVC • Pneumothorax following CVC insertion • Air embolism following CVC insertion • Hemothorax following CVC insertion • Inadvertent arterial puncture at time of CVC insertion • Other, specify	If the patient experienced one of the listed Adverse Events, select YES then complete the 'Adverse Event Details' form.
2.	**Event Number**	Enter Event number starting with 1. The next Event will be 2 then 3 and so on. The Event Number DOES NOT have to correspond to when the event occurred temporally.
Event Type (choose one)		
3.	**Event type**: • RRT - associated hypotension • Severe hypophosphatemia (< 0.5 mmol/L) • Severe hypokalemia (< 3.0 mmol/L) • Severe hypocalcemia (Ionized calcium < 0.90 mmol/L) • Allergic reaction to RRT • Arrhythmia during RRT • Seizure • Major bleeding • Hemorrhage at site of CVC insertion • CVC - associated bloodstream infection • Ultrasonographically confirmed thrombus attributed to CVC • Pneumothorax following CVC insertion • Air embolism following CVC insertion • Hemothorax following CVC insertion • Inadvertent arterial puncture at time of CVC insertion • Other, specify	If the patient has more than one of the listed Events, they should be listed as separate Events. • *RRT-associated hypotension:* defined as a drop in blood pressure drop of any magnitude requiring one of: initiation of a vasopressor during RRT session or need to escalate dose of a vasopressor during the RRT session or premature discontinuation of RRT session due to blood pressure drop. • *Severe hypophosphatemia:* defined as serum phosphorus < 0.5 mmol/L • *Severe hypokalemia:* defined as serum potassium < 3.0 mmol/L • *Severe hypocalcemia:* defined as serum total calcium (adjusted for albumin) < 1.90 mmol/L or any ionized calcium value < 0.90 mmol/L. *albumin-adjusted total calcium = measured calcium + [0.02 x (40-concurrent serum albumin)].

- *Allergic reaction to RRT:* defined as clinician suspicion of allergic reaction to one or more of the components of the RRT apparatus.
- *Arrhythmia during RRT:* defined as new atrial (excluding sinus tachycardia or sinus arrhythmia) or ventricular arrhythmia that develops during RRT and was not present prior to initiation of RRT.
- *Seizure:* defined as seizure that develops during RRT session and confirmed by attending clinician
- *Major Bleeding:* For this event to be reportable the "major bleeding" must be at least plausibly related to the RRT procedure (e.g., if patient was receiving systemic anticoagulation for RRT), the vascular access for RRT or any other aspect of the patient's participation in STARRT-AKI.

Bleeding will be classified as "major" if it was:

a) Life threatening bleeding due to hypovolemic shock (e.g., from ruptured abdominal aortic aneurysm or upper or lower gastrointestinal hemorrhage);

b) Life threatening bleeding at a critical site (e.g., intracranial, retroperitoneal, pericardial);

c) Overt, clinically important bleeding associated with one of the following within 24 hours of the bleed: decrease in hemoglobin >20 g/L or transfusion >2 packed red blood cell;

d) Bleeding at other critical sites (e.g., epidural, intraocular or intraarticular);

e) Bleeding requiring an invasive intervention (e.g., re-operation).

- *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.* • *Other, specify*
Event Details		
4.	**Event onset date**: DD-MMM-YYYY	Date the Event started
5.	**Event stop date**: DD-MMM-YYYY	Date the event resolved or indicate if AE/SAE is still ongoing at 90 days post-randomization
6.	**How was event related to study procedures?** Choose one: • RRT associated • CVC associated • Other, specify	This is not a Yes/No question. If the answer to this question is ever 'Not Related' then it should not be reported as an AE/SAE. Please choose RRT associated, CVC associated or Other. If you believe that the AE/SAE occurred for another trial-related reason, including delay in RRT, please check on "other" and specify.
7	**Was event classified as a serious adverse event (SAE)?** Y/N (*Check all that apply*) Serious due to: • Patient died • Life-threatening • Involved persistence of significant disability or incapacity • Involved prolongation of existing hospitalization	For this study, a ***reportable SAE*** must be considered: a. An atypical event, defined as clinically significant and unexpected in the context of critical illness and associated AKI, **AND** b. An event that is at least possibly related to study procedures. **Only choose YES if event is classified as a 'reportable Serious Adverse Event' as defined above.*

7a.	**Date when Investigator became aware of the SAE** DD-MMM-YYYY	Please enter the date when Site Investigator became aware of the SAE. **Note that study reporting requirements require you to report the SAE (on the database) within 24 hours of becoming aware of the SAE.*
7b.	**Describe SAE** (including any relevant tests/lab data, actions taken, etc)	Free text to describe the event and its resolution
7c.	**SAE resolution** (*choose one*) • Recovered • Recovered to previous baseline • Significant impairment • Death • Other, specify	Specify if the event Recovered, Recovered to previous baseline, Significant impairment, Death, or Other.

Form 13: Protocol Violations Regarding the Timing of RRT Initiation

GENERAL INFORMATION

Please complete this form only if there is a violation regarding the timing of RRT initiation based on randomization allocation.

A. <u>If randomized to Accelerated/Early RRT initiation arm</u>: Patient should start RRT within 12 hours of being fully eligible. ****If the patient does not start RRT within the first 12 hours or does not start at all, this is a protocol violation***.

B. <u>If randomized to Standard/Delayed Approach to RRT initiation arm</u>: RRT initiation is discouraged unless the conditions below (see REMINDER below) are met. However, clinician may start RRT at his/her discretion at all times if felt to be clinically necessary. ***It is only considered a protocol violation if a patient in the standard arm commences RRT within 12 hours of being fully eligible.**

<u>REMINDER</u> regarding philosophy of RRT initiation for patients randomized to the standard arm:
RRT Initiation in the Standard arm is *discouraged* unless the patient has:
a) Persistent severe AKI defined as sCr that remains > 50% of the value recorded at randomization.
<u>AND</u> <u>at least one of the following indications for RRT initiation:</u>
a) Serum potassium ≥ 6.0 mmol/L; **or**
b) pH ≤ 7.20 or bicarbonate ≤ 12 mmol/L; **or**
c) Evidence of severe respiratory failure, based on a PaO_2/FiO_2 ≤ 200 and clinical perception of volume overload as main driver of hypoxia; **or**
d) Persistent severe AKI (sCr remains > 50% the value recorded at randomization) for > 72 hours from randomization
If a patient allocated to standard RRT initiation, initiates RRT more than 12 hours after full eligibility but without one of the above criteria/indications for RRT initiation, this is NOT A PROTOCOL VIOLATION.

No.	Question	Definition or explanation
1.	Was RRT initiated within the specified time intervals mandated by the protocol? Y/N	The specified time intervals are: **Accelerated arm**: < 12 hours from full eligibility **Standard/Delayed arm**: ≥ 12 hours from full eligibility
2.	If NO and patient was randomized to <u>accelerated</u> RRT initiation, please clarify why RRT was not started within 12 hours of FULL eligibility.	Choose one: • Problem with vascular access • Dialysis machine not available • Change in patient goals of care

		• Clinical deterioration • Other, specify
3.	If NO and patient was randomised to standard RRT initiation, please clarify why RRT was started within 12 hours of determination of eligibility.	Choose one: • Volume overload • Anuria/Oliguria • sCr increasing • Severe acidosis • Severe hyperkalemia • Other, specify

Form 14: ICU and Hospital Discharge Data (Index Hospitalization Discharge)

GENERAL INFORMATION

Form should be completed for all patients.

Form 14: ICU Discharge Data/Death

No.	Question	Definition or explanation
1.	**Alive at ICU discharge?** • Yes • No • N/A, still in ICU at Day 90	If patient is discharged alive from the ICU indicate 'Yes' and subsequently provide the date of discharge. If patient dies in the ICU indicate 'No' and the date of death will need to be recorded on Death Form (Form 17). If patient is never discharged from the ICU during the course of their study participation (by 90 days) then indicate 'N/A still in ICU at Day 90'. *NOTE: This question applies to the initial ICU admission during which the patient was enrolled in the trial. For example, if a patient enrolled in the trial is discharged from the ICU to a general ward but then deteriorates on the ward and is readmitted to the ICU a few days later and then dies, the response to this question is "Yes". The patient's status at the end of the initial ICU stay is what determines the answer to this question*. If yes, complete further questions. If no, please complete the Death form.
2a	**If yes, Date of ICU discharge** DD-MMM-YYYY	Enter date of initial ICU discharge *NOTE: This question only applies to the patient's first discharge from the ICU after entering the trial. Subsequent ICU readmissions and discharges are not considered*.
2b	**If yes, disposition at time of ICU discharge** • General ward • Step-down unit • Chronic care facility • Palliative care ward • Other acute care hospital • Inpatient rehabilitation hospital or facility • Other, specify	Indicate if patient was discharged to the General Ward, Chronic Care Facility, Other Acute Care Hospital, Step-Down Unit, Palliative Care Ward, Inpatient Rehabilitation Hospital or Facility, or Other (specify). *NOTE: This question only applies to the patient's first discharge from the ICU after entering the trial. Subsequent ICU readmissions and discharges are not considered*.

2c.	**If yes, was RRT administered (≥ 1 session) in 7 days following ICU discharge?** Y/N	If alive at ICU discharge, indicate if patient received additional RRT in the 7 days following (initial) ICU discharge.
2d.	**ICU readmission(s) during the index hospitalization?** Y/N	During the index hospitalization, indicate whether the patient was ever readmitted to the ICU after having been discharged from the ICU to another location in the study hospital.

Form 14: Hospital Discharge data/Death		
3.	**Date of last RRT in Hospital** DD-MMM-YYYY or N/A, no RRT	Indicate the date of the last RRT session prior to hospital discharge but within the 90-day follow-up window OR indicate N/A if RRT was never administered. This RRT session could have taken place in any study hospital venue (ie, ICU or general ward).
4.	**Last serum creatinine recorded in the hospital** (µmol/L or mg/dL)	Indicate the last available sCr prior to hospital discharge but within the 90-day follow-up window. If patient is still in hospital at Day 90, please enter the patient's recorded serum creatinine on Day 90 or the value closest to but preceding Day 90. For example, if Day 90 for a given patient is May 16, 2017, but no creatinine value was available that day, take the last recorded value preceding May 16, 2017.
5.	**Date of last serum creatinine recorded in the hospital** DD-MMM-YYYY	Indicate the date of the last sCr recorded on the patient's chart prior to hospital discharge but within the 90-day follow-up window.
6.	**Alive at hospital discharge?** • Yes • No • N/A, still in hospital at Day 90	If patient was discharged alive from the hospital indicate 'Yes' and subsequently provide the date of discharge and disposition. This question applies only to the hospital admission on which the patient was enrolled in STARRT-AKI. If patient dies in the hospital (inside or outside of the ICU) indicate 'No' and the date of death will need to be recorded on the Death form (Form 17). If patient is never discharged from the hospital during the course of their study participation (by 90 days) then indicate 'N/A still in hospital at Day 90.' If 'yes', complete further questions. If 'no', please complete the Death form.
7a.	**If YES (alive), date of hospital discharge**: DD-MMM-YYYY	
7b.	**If YES (alive), disposition at time of hospital discharge**: • Home • Chronic care facility • Palliative care hospital or facility • Other acute care hospital • Inpatient rehabilitation hospital or facility • Other, specify	Indicate if patient was discharged to Home, Chronic Care Facility, Palliative care hospital or facility, Other acute care hospital, Inpatient Rehabilitation Hospital or Facility, or Other (specify). *NOTE: This question only applies to the patient's first discharge from the hospital after entering the trial. Subsequent hospital admissions and discharges are not considered.*
7c.	**Plan for further RRT at the time of hospital discharge?** Y/N	Indicate Yes or No based on whether there was a plan to continue RRT once the patient left the hospital.

Form 15: Resource Utilization Through Day 28

GENERAL INFORMATION

Data on this form includes all resource utilization, even if these took place during multiple ICU stays or multiple hospitalizations, from the day of randomization up to and including day 28. The maximum number of days in response to any of these questions would be 29.

No.	Question	Definition or explanation
1.	**Total number of ICU days**	An "ICU day" is defined as any 24-hour period during which a participant spent ≥ 2 hrs in ICU; definition of "ICU" is any unit with the capability of administering invasive mechanical ventilation.
2.	**Total number of in-hospital RRT days**	An "RRT day" is defined as any day on which the participant received ≥ 2 hours of RRT using any modality as an inpatient.
3.	**Number of days of mechanical ventilation**	A "mechanical ventilation day" is defined as any day on which the participant received ≥ 2 hours of invasive or non-invasive mechanical ventilation in a 24-hr day; time on CPAP and BiPAP should be included. Pressure support ventilation will count toward mechanical ventilation days.
4.	**Number of days of vasoactive therapy**	A "vasoactive therapy day" is defined as any day on which the participant received ≥ 2 hours of a vasoactive drug by continuous infusion; vasoactive drugs include norepinephrine, epinephrine, phenylephrine, vasopressin, dobutamine, milrinone, dopamine and levosimendan.
5.	**Was patient re-admitted to hospital following discharge from their index hospitalization?** • Yes • No • N/A, not discharged from index hospitalization.	If yes, record all hospital re-admissions (to any hospital) from the date of index hospitalization discharge **through Day 28**. If patient is still in the hospital (i.e., not discharged from index hospitalization), indicate 'N/A, not discharged from index hospitalization by Day 28'
Re-hospitalization Form (to Day 90) If patient was discharged from study hospital then re-admitted to hospital, go to separate Re-hospitalization form to enter admission and discharge dates.		
6.	If yes, please record all hospital re-admissions from the date of index hospitalization discharge to Day 90. • Re-admission date (DD-MMM-YYYY) • Discharge date (DD-MMM-YYYY) • Ongoing	Enter re-admission date, Discharge date, or ongoing

Form 16: Day 90 Outcome Data

GENERAL INFORMATION

Form should be completed for all patients and should reflect the patient's status at Day 90

Vital Status Data at 90 Days

No.	Question	Definition or explanation
1.	**How was 90-day vital status obtained?** • Medical record • Phone call to patient/SDM/family member • Phone call to other hospital/other care centre/family doctor • Other, specify • Not obtained, explain	Indicate the source used to determine patient's vital status at Day 90. If not obtained, provide an explanation.
2.	**Vital status at 90 days following randomization.** • Alive • Deceased	Indicate if patient is Alive or Deceased. If patient is alive, provide disposition at day 90. If deceased, complete the Death form (Form 17). **Note: Please try using all means possible to determine patient's vital status at Day 90. If you are unable to determine whether the patient is alive or deceased at Day 90, you can leave this answer blank and enter a comment into the query.*
3.	**If alive, disposition at 90 days** • Home • Chronic care facility • Study hospital • Other acute care hospital • Palliative care hospital or facility • Inpatient rehabilitation hospital or facility • Other, specify	Indicate where patient is staying/being cared for at Day 90.

Kidney Function at 90 Days

***Note**: Blood and urine tests should be done for ALL patients alive on Day 90 and NOT on RRT. The purpose is to assess residual kidney damage among survivors. These are *clinically recommended* tests as per the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines for AKI. *They should be done as part of routine care in all patients who experience AKI*. Though we are collecting these data as part of STARRT-AKI follow-up, the blood and urine sample being requested are part of usual clinical care.

4.	**Requirement for RRT at 90 days following randomization?** • Yes • No • Not applicable • Not available/Unknown	Indicate **Yes** if patient is receiving RRT at 90 days, regardless of whether it was withdrawn for some portion of the 90-day follow-up period. Note that it is not necessary for patient to receive RRT ON DAY 90 as dialysis often occurs on alternate days. If a patient last received dialysis within 7 days of Day 90 with the intention of continuing beyond Day 90, please answer YES.

		Indicate **No** if the patient is alive but not receiving RRT at 90 days. Indicate **Not Applicable**, if patient is deceased at 90 days. Indicate **Not available/unknown** if the patient is alive but this information is not known.
5.	**Date of last RRT session prior to or on Day 90** • DD-MMM-YYYY OR • Not applicable, no RRT OR • Not available/Unknown	Indicate the date that RRT (dialysis) was last performed prior to Day 90 following randomization. Indicate 'N/A, no RRT' if RRT was never initiated.
6.	**Date blood sample collected** • DD-MMM-YYYY OR • Not available	Blood sample should be collected within 76 days and 132 days from date of randomization (or Day 90 -14 days/+42 days). If there are multiple results available, choose the one closest to the Day 90 date. Indicate N/A if data is not available.
7.	**Day 90 serum creatinine** • (µmol/L or mg/dL) • Not available	Indicate the serum creatinine result obtained between 76 days and 132 days from randomization. If there are multiple results available, choose the one closest to the Day 90 date. Indicate N/A if data is not available.
8.	**Day 90 eGFR** (using CKD-EPI formula) • mL/min/1.73m^2 • Not available	Indicate eGFR result using CKD-EPI formula, based on serum creatinine value listed above. Often the eGFR from the CKD-EPI formula will be provided by the lab provider but if not available, the CKD-EPI eGFR can be calculated by entering the relevant information at this website: http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr Indicate N/A if data is not available.
9.	**Date urine sample collected**: • DD-MMM-YYYY • Not available	Urine sample can be collected within 76 days and 132 days from date of randomization (or Day 90 -14 days/+42 days). Indicate N/A if data is not available.
10.	**Day 90 Urine Albumin Concentration** • mmol/L or mg/L or g/L (choose one) • Exceeds upper LOD • Not available	Indicate the urine albumin concentration between 76 days and 132 days from randomization. If there are multiple results available, choose the one closest to the Day 90 date. Indicate Exceeds upper LOD if concentration is above upper limit of detection or N/A if data is not available.
11.	**Day 90 Urine Creatinine concentration** • mmol/L or mg/L or g/L (choose one) • Exceeds upper LOD • Not available	Indicate the urine creatinine concentration between 76 days and 132 days from randomization. If there are multiple results available, choose the one closest to the Day 90 date. Indicate Exceeds upper LOD if concentration is above upper limit of detection or N/A if data is not available.

Hospital Re-Admission (Day 29 to Day 90) ***Note:** All re-admissions from Day 0 to Day 90 should be entered on the Hospital Re-Admissions form.*		
12a.	**Was patient re-admitted to hospital between Day 29 and Day 90?** • Yes • No • Not applicable, not discharged from prior hospitalization by day 90 • Not available/Unknown	Indicate '**Yes**' if patient was hospitalized between Days 29 to 90 following randomization and record all hospital re-admissions from Day 29-Day 90 on the re-hospitalization form. If patient was not discharged from index hospitalization by day 90, indicate 'N/A, not discharged from prior hospitalization by day 90'. If this information is not known, indicate 'Not available/Unknown.'
12b.	**If yes, please record all hospital re-admissions from the date of index hospitalization discharge to day 90**. • Re-admission date (DD-MMM-YYYY) • Discharge date (DD-MMM-YYYY) • Ongoing	Enter re-admission date, Discharge date, or ongoing (to any hospital)
Quality of Life Assessment at 90 Days		
13.	**EQ-5D-5L Assessment completed by:** • Patient • SDM/Other • Not done	Indicate whether it was possible to administer the EQ-5D (found in Appendix 3) to the patient at 90 days and provide the scores for each component of the assessment as well as the visual analog scale (VAS). The window range for the EQ-5D-5L Assessment is 76 to 132 days post randomization. **Note: this assessment can be completed over the phone or in person. Ideally, the patient will answer the questions, but if this is not possible, a Substitute Decision Maker/other family/friend may complete the assessment.* If the assessment could not be completed, choose "Not done."
14a.	Mobility (score 1-5, missing 9)	
14b.	Self-care (score 1-5, missing 9)	
14c.	Usual activities (score 1-5, missing 9)	
14d.	Pain/discomfort (score 1-5, missing 9)	

14e.	Anxiety/depression (score 1-5, missing 9)	**Anxiety/Depression Component of the EQ-5D:** One of the items on the EQ-5D questionnaire asks participants to rank the level of anxiety/depression that they are experiencing. While the EQ-5D is not a detailed depression tool, it is still important to remain alert to possible indications that a participant is suffering from anxiety/depression of a more serious nature and to have a strategy in place whereby additional support can be offered. The following procedure has been developed with this in mind: • Any time that a participant indicates that they are feeling either "severely" or "extremely" anxious or depressed during the administration of the EQ-5D, the research coordinator will notify the site PI. Similarly, the research coordinator will inform the site PI of any other comments volunteered during the follow-up interview that could be cause for concern (e.g., comments like "I wish I were dead" or "I've been thinking a lot about how to end my life"). • The site PI will contact the participant and offer them a referral to either a general practitioner or a psychiatrist. • The participant encounter(s) will be documented in the patient record along with the services offered and/or actions taken.
14f.	EQ-VAS score (score 0-100)	Visual Analog Scale Assessment as part of the EQ-5D.
Clinical Frailty Scale (CFS)		
15.	Clinical Frailty Scale (CFS) Score (score 1-9, missing = 0)	Choose one that best reflects the ***patient's condition at Day 90***: 0 - Missing / Not Available / Not applicable 1 - Very Fit - robust, active, energetic and motivated 2 - Well –no active disease symptoms but are less fit, active occasionally 3 - Managing Well –well controlled medical problems, not regularly active 4 - Vulnerable – not dependent, symptoms limit activities 5 - Mildly Frail – more evident slowing, need help with high order independent activities of daily living 6 - Moderately Frail – need help with all outside activities, keeping house, bathing, and often have problems with stairs 7 - Severely Frail – complete dependence for personal care (physical or cognitive) 8 - Very Severely Frail –approaching end of life, unlikely to recover from minor illness 9 - Terminally Ill – life expectancy <6 months who are not otherwise evidently frail

Form 17: Death- General Information

Use this form for patients that died between Day 0 and Day 90.
**If the patient died at any time following randomization up to and including day 90, add a Death form using the Add Event menu on the patient home page. This will unlock the death form and allow you to add the death details.*

No.	Question	Definition or explanation
1.	**Date of death** DD-MMM-YYYY	Indicate the date of death.
2.	**Death category** • Neurological • Cardiovascular • Respiratory • Metabolic	Select **one category** reflecting the most appropriate explanation underlying the participant's death.
3.	**Cause of death: (select ONE)** **Neurological** • Brain death • Hypoxic encephalopathy • Intracranial hemorrhage • Ischemic stroke **Cardiovascular** • Primary arrhythmia • Refractory cardiogenic shock including pulmonary edema • Cardiac tamponade • Hypovolemic (uncontrollable bleeding) • Septic Shock • Massive pulmonary embolism • Anaphylaxis **Respiratory** • Refractory hypoxia due to ARDS • COPD • Asthma • Pulmonary hemorrhage • Pneumothorax **Metabolic** • Hypoglycemia • Hyperkalemia • Hypothermia • Liver failure	You will be able to choose the cause based on the category you selected in the previous question. Select one cause.
4.	**Withdrawal of life support?** Y/N	

Form 18: Retrospective Amendment of Eligibility

General Information

This form will be completed if there were any retrospective changes to the screening eligibility criteria (i.e., site became aware that patient did not meet one or more eligibility criteria post randomization). Note that the study will not exclude or withdraw any patients that may be 'ineligible' retrospectively, however, sites will be required to collect this information on Form 18 and entered into the database.

***Note**: In order to unlock this form, you must go to the patient's home page and Add Event: Retrospective Amendment to Eligibility Criteria*.

No.	Question	Definition or explanation
1.	**Date site first became aware of change in eligibility** DD-MMM-YYYY	Indicate the date site became aware of the change in patient's eligibility criteria.
2.	**Check all that apply:** **<u>Inclusion criteria</u>** 1. Age ≥ 18 years 2. Admission to a critical care unit 3. Evidence of kidney dysfunction 4. ≥2-fold increase in serum creatinine (sCr) from baseline 5. If the current serum creatinine is ≥354 µmol/L (4.0 mg/dL) this must be accompanied by evidence of a minimum increase of 27 µmol/L (0.3 mg/dL) from the baseline serum creatinine. 6. Urine output < 6.0 mL/kg over the preceding 12 hours **<u>Exclusion Criteria</u>** 1. Serum potassium concentration > 5.5 mmol/L 2. Serum bicarbonate concentration < 15 mmol/L 3. Presence of drug overdose that necessitates initiation of RRT 4. Lack of commitment to provide RRT as part of limitation of ongoing life support 5. Any RRT within the previous 2 months 6. Kidney transplant within the past 365 days 7. Known pre-hospitalization advanced chronic kidney disease, estimated by an eGFR <20 mL/min/1.73m^2 in a patient who is not on chronic RRT 8. Presence or strong clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, scleroderma renal crisis) or acute interstitial nephritis. 9. Clinician(s) caring for the patient believe(s) that immediate renal replacement therapy is mandated 10. Clinician(s) caring for the patient believe(s) that deferral of renal replacement therapy initiation is mandated.	You will have an option to add additional comments for any inclusion or exclusion criteria checked off in this section. You can select as many as are relevant.

Form 19: Study Completion/Early Discontinuation

General Information

This form should be completed for all patients.

No.	Question	Definition or explanation
1.	**Did the patient complete the full study to 90 days?** Y/N **Yes** Date of study completion: DD-MMM-YYYY **No** • Patient or SDM withdrew consent • Lost to follow-up • Other, specify	Select **YES** if you are able to determine patient vital status at Day 90. Date of study completion should be recorded as the Day 90 date (Randomization date +90 days). If patient died prior to Day 90, the date of death is the date of study completion. Select **NO** if patient did not complete the study. This option should only be selected if patient or SDM withdrew consent or the patient is Lost to follow-up. If the patient dies prior to day 90, the patient is still considered to have reached full study completion.
2a.	**If no and patient or SDM withdrew consent, enter Date of withdrawal**. DD-MMM-YYYY	If the patient or SDM withdrew consent, ensure this is documented in either a withdrawal of consent form or in the patient's medical records/study files.
2b.	**If no and the patient is Lost to follow-up, enter the Date of Last Contact**. DD-MMM-YYYY	Date of last contact should be at/around Day 90. Note that if you are unable to contact the patient or SDM at/around Day 90, you may consider trying to contact the patient's GP to ascertain vital status and/or to see if laboratory results are available for Day 90 kidney function.
2c.	**If no, and OTHER, please specify other reason and enter date of Early Discontinuation** DD-MMM-YYYY	
3.	**Was consent obtained for the linkage of personal information with administrative data for the purpose of long-term follow-up (vital status, RRT dependence) at 365 days?** • Yes • No • Not applicable, site not participating in sub-study	Did patient consent to data linkage on their informed consent form? *Note: some sites are either not participating in this sub-study, are not able to collect this administrative data on patients, or do not have consent to collect this data for certain patients.*

Form 20: Day 365 Outcome Data

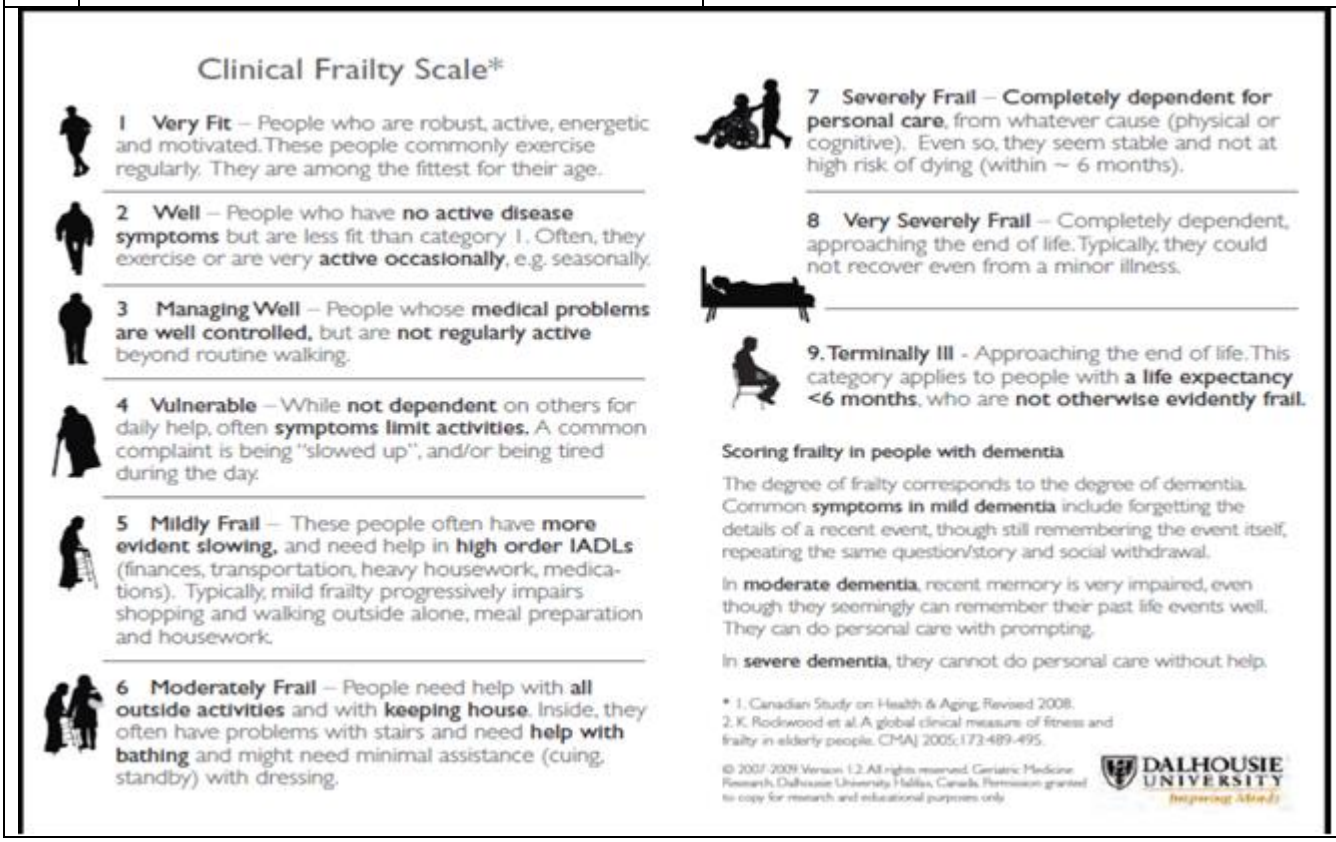
General Information

Data may be collected by calling the patients or by linking to government (i.e., provincial, state or national) health registries. For data linkages, collection of a unique personal health information will be required. Not all sites/patients will be participating in this component (ie, follow-up from day 91-365) of the study.

**Note: Site staff may not be required to enter this data if the data linkage will be done centrally at the end of the study. Check with the study manager in your region if you are unsure.*

No.	Question	Definition or explanation
1.	**Vital status at 365 days following randomization** • Alive • Deceased, Date of Death (DD-MMM-YYYY)	Answer should reflect vital status 365 days after randomization or as close as reasonably possible.
2.	**Requirement for RRT at 365 days following randomization** • Yes • No • Not applicable (if deceased) • Not available, Unknown	If patient received at least one session of RRT within 7 days before or after Day 365, then the answer is YES. If deceased at 365 days, select N/A
Quality of Life Assessment at 365 days **Note: This is a sub-study and will only be completed at sites that will be contacting the patient at Day 365. Definitions are the same as Quality of Life Assessments done at Day 0 and Day 90.*		
3.	EQ-5D-5L Assessment completed by: • Patient • SDM/Other • Not done	
4a.	Mobility (score 1-5, missing 9)	
4b.	Self-care (score 1-5, missing 9)	
4c.	Usual activities (score 1-5, missing 9)	
4d.	Pain/discomfort (score 1-5, missing 9)	
4e.	Anxiety/depression (score 1-5, missing 9)	
4f.	EQ-VAS score (score 1-100)	

Clinical Frailty Score (CFS)		
5.	Clinical Frailty Scale (CFS) Score (score 1-9, missing = 0)	Choose one that best reflects the patient's condition at Day 365: 0 - Missing 1 - Very Fit - robust, active, energetic and motivated 2 - Well –no active disease symptoms but are less fit, active occasionally 3 - Managing Well –well controlled medical problems, not regularly active 4 - Vulnerable – not dependent, symptoms limit activities 5 - Mildly Frail – more evident slowing, need help with high order independent activities of daily living 6 - Moderately Frail – need help with all outside activities, keeping house, bathing, and often have problems with stairs 7 - Severely Frail – complete dependence for personal care (physical or cognitive) 8 - Very Severely Frail –approaching end of life, unlikely to recover from minor illness 9 - Terminally Ill – life expectancy <6 months who are not otherwise evidently frail



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – 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,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – 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 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People 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 **Severely Frail** – **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 **Very Severely Frail** – Completely dependent, approaching the 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 evidently frail.**

Scoring frailty in people with dementia

The degree of frailty 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.

* 1. Canadian Study on Health & Aging. Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY

APPENDIX

A: Furosemide Stress Test

Furosemide Stress Test Protocol

Primary Assessment

1. Patient should be clinically assessed to be optimally resuscitated
2. Indwelling urinary catheter is preferred but not absolutely necessary
3. Heart rate, blood pressure, and urine output monitoring every 30 minutes is required as a minimum. Presence in an intensive care unit is preferred.
4. Assess whether patients have been exposed to loop diuretic in the past 7 days
5. Patient should be KDIGO Stage I or II

Contraindications

a. Sensitivity or allergy to loop diuretics
b. Pregnancy
c. Patients with nephrostomy tubes or any type of urinary diversion
d. Urinary obstruction
e. Patients concurrently on a loop diuretic continuous infusion

Intervention

1. Infusion of furosemide at 1.0 mg/kg over 5-15 minutes (For patients who are NOT loop diuretic naïve, the dose is 1.5 mg/kg)
2. Replace urine output milliliter for milliliter with crystalloid unless it is clinically desirable to diurese the patient.
3. Volume replacement should be conducted for 6 hours after the infusion

Interpretation

1. Urine output of less than 200 cc over 2 hours after loop diuretic infusion is associated with 85-90% likelihood of progression to KDIGO Stage III and/or need for RRT.

Sensitivity/Specificity Range

Table 4 Sensitivity and specificity of two hour urine thresholds for progression to AKIN stage III

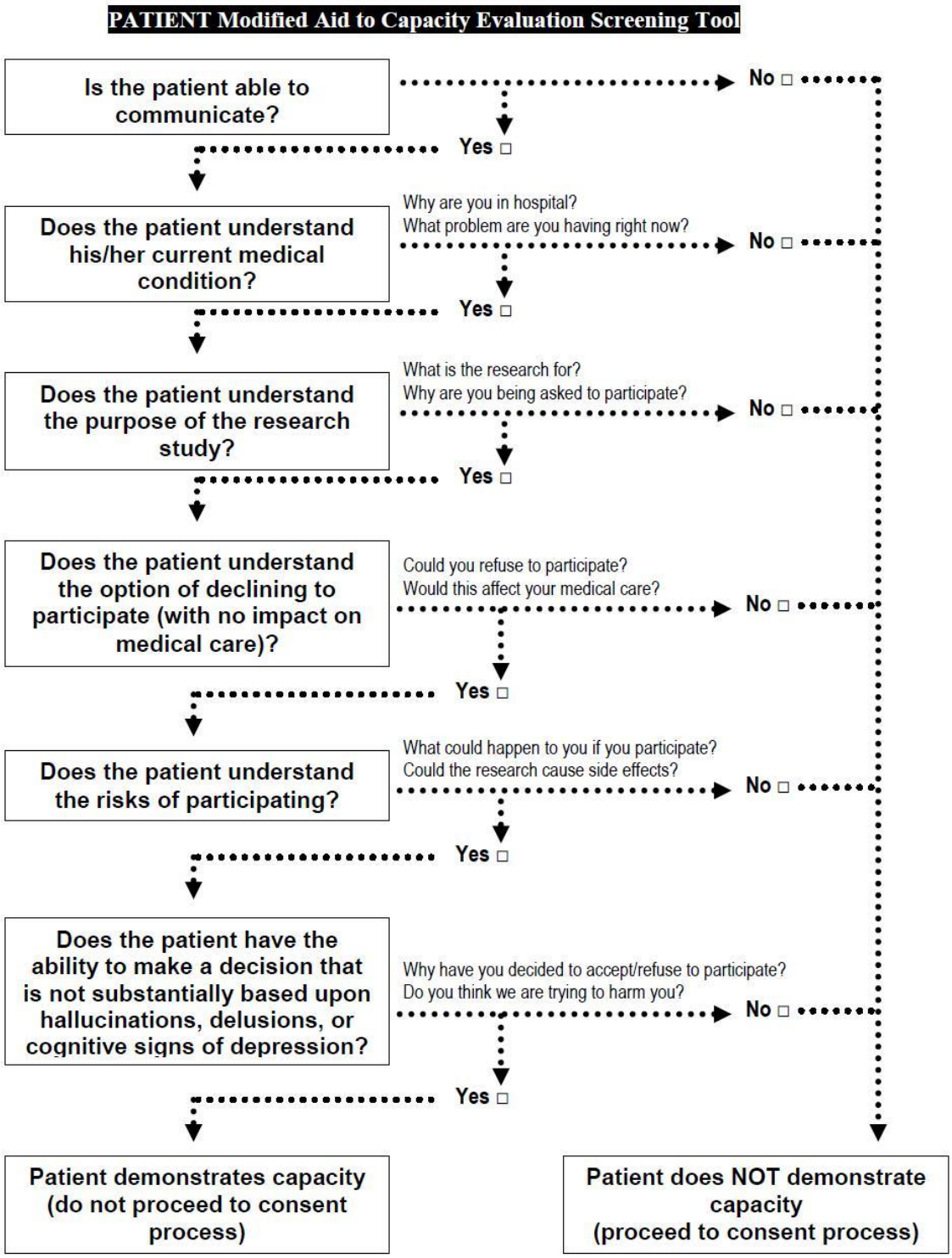
A

	Combined cohort	
Total urine output over 2 hours	Sensitivity	Specificity
≤100 ml	90.2%	60.0%
<200 ml	87.1%	84.1%
<300 ml	85.3%	88.0%
<400 ml	66.7%	88.0%
<500 ml	50.5%	88.0%

References

- Chawla LS, Davison DL, Brasha-Mitchell E, Koyner JL, Arthur JM, Shaw AD, Tumlin JA, Trevino SA, Kimmel PL, Seneff MG: Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Crit Care 17: R207, 2013
- Koyner JL, Davison DL, Brasha-Mitchell E, Chalikonda DM, Arthur JM, Shaw AD, Tumlin JA, Trevino SA, Bennett MR, Kimmel PL, Seneff MG, Chawla LS: Furosemide stress test and biomarkers for the prediction of AKI severity. J Am Soc Nephrol 26(8): 2023-31, 2015

B: Aid to Capacity Evaluation (ACE)



C: Calculate by QxMD – Screening Tool for STARRT-AKI

In collaboration with QxMD and Dr. Daniel Schwartz, we have developed a screening tool which Coordinators and Site Investigators will be able to access from their mobile devices! This screening tool will allow site members to determine patient's eligibility for the trial by simply answering eligibility questions on their phone. Please follow the instructions below to download and use this app:

1. To use the STARRT-AKI screening tool, download 'Calculate by QxMD' on your phone.
2. Search for "STARRT-AKI Enrollment Criteria" to access the STARRT-AKI screening tool.
3. For each patient, provide a response to Questions 1 to 10 on the screening tool
4. After you have entered responses for all the questions, the app will generate a result whether the patients is eligible for the trial at present, or if a reassessment at next screen is required.

Additional Features:

- **Randomize a patient:** If a patient if fully eligible for the trial, you can tap on "Randomize Fully Eligible Patients." This will take you to Medidata RAVE login page, where you will be able to randomize the patient to the trial. Please refer to Data Entry Guidelines for instructions on how to randomize a patient on Medidata RAVE.

- **Enrollment Flowchart:** Tap on "Enrolment Flowchart" to access the digital version of the pocket cards. The enrolment pocket cards provide an overview of STARRT-AKI enrolment and post-randomization procedures.

- **Trial Prescription Card and Study Contacts:** Tap on "Trial Prescription Card and Study Contacts" to access the digital version of the prescription pocket cards. These pocket cards provide guidance on RRT prescription and contact information for the Coordinating Centre as well as the Principal Investigators.

Appendix 3: STARRT-AKI sites, investigators and study personnel

Site Name	Site Principal Investigator(s)	Site Coordinator(s)
NORTH AMERICA		
CANADA		
University of Alberta Hospital (042)	Sean Bagshaw	Nadia Baig
Mazankowski Alberta Heart Institute (274)		
Grey Nuns Community Hospital (141)	Shelley Duggan	Jennifer Barchard
Misericordia Community Hospital (409)	Erika MacIntyre	Robin Scheelar
Red Deer Regional Hospital (410)	Michael Russell	Gillian Brown
Sturgeon Community Hospital (408)	Gabriel Suen	Aysha Shami
Foothills Hospital (002)	Thomas Stelfox	Joshua Booth
Peter Lougheed Centre (067)	Daniel Niven	
Royal Alexandra Hospital (051)	Jim Kutsogiannis	Patrica Thompson
Fraser Health - Surrey Memorial Hospital (402)	Greg Haljan	Christopher Condin
St. Paul's Hospital (044)	Peter Dodek	Victoria Alcuaz
Victoria General Hospital (057)	Gordon Wood	Fiona Auld
Royal Jubilee Hospital (063)		
Lakeridge Health (064)	Randy Wax	Kelly Fusco
Hamilton General (070)	Richard Whitlock	Nevena Savija Lisa Tittley
Health Sciences North (214)	John Harmon	Nicole Haslam Sarah Charette
Juravinski Hospital (377)	Bram Rochwerg Timothy Karachi	Tina Millen
Kingston General Hospital (035)	John Muscedere	Miranda Hunt
London Health Sciences Centre – University Hospital	Matthew Weir	Tracey Bentall

(384)		
London Health Sciences Centre – Victoria Hospital (385)	Ian Ball	Eileen Campbell
Mount Sinai Hospital (215)	Stephen Lapinsky	Sumesh Shah
St. Joseph's Healthcare (052)	Mark Soth	France Clarke
St. Michael's Hospital (010)	Ron Wald	Orla Smith
Sunnybrook Health Sciences Centre (011)	Neil Adhikari	Nicole Marinoff
The Ottawa Hospital - Civic Campus (012)	Lauralyn McIntyre	Rebecca Porteous Irene Watpool
The Ottawa Hospital - General Campus (216)		
Toronto Western Hospital – UHN (015)	Elizabeth Wilcox	Karolina Walczak
Toronto General Hospital – UHN (095)	Margaret Herridge	Felicity Backhouse
Centre Hospitalier Universitaire de Sherbrooke (CHUS) (048)	Francois Lamontagne	Elaine Carbonneau
CHU de Québec (CHUQ) - Université Laval (379)	Alexis Turgeon	Marie-Claude Tremblay
CHUM (345)	Francois Cailhier	Ali Ghamraoui
CIUSSS MCQ (387)	Ying Tung Sia	Patricia Alarie
Hopital Maisonneuve-Rosemont (026)	Jean-Philippe Lafrance	Emilie Rene
Institut Universitaire de cardiologie et de pneumologie de Quebec (IUCPQ) (028)	Francois Lellouche	Patricia Lizotte
McGill University Health Centre (386)	Sheldon Magder	Josie Campizi
Regina Qu'Appelle Health Authority (388)	Bhanu Prasad	Shelley Giebel Denyse Vanchu
Memorial University of Newfoundland (407)	Brandon Barrett	AnneMarie Whelan
Health Sciences Centre (411)	Claudio Rigatto	Anna Glybina
Trillium Health Partners - Credit Valley Hospital (491)	Vincent Ki	Martin Romano
Trillium Health Partners - Mississauga Hospital (014)		
St. Joseph's Health Centre Toronto (472)	Robert Cirone	Kanthi Kavikondala
USA		
Mayo Clinic (102)	Kianoush Kashani	Amy Amshbaugh
University of Alabama at Birmingham (205)	Ashita Tolwani	Anita (Laura) Latta

University of Florida (506)	Azra Bihorac	Sherry Brown
University of Kentucky (505)	Javier Lozano	Madona Elias
Rhode Island Authority (509)	Matthew Lynch Matthew Lynch	Ann O'Mara
The Miriam Hospital (516)		Ann O'Mara
SOUTH AMERICA		
BRAZIL		
Hospital de CLinicas de Porto Alegre (542)	Fernando Thome	Bianca Mentz Bruna Azevedo
AUSTRALIA		
AUSTRALIA		
Austin Hospital (359)	Rinaldo Bellomo	Glenn Eastwood
Princess Alexandra Hospital (283)	Peter Kruger	Emma Saylor Jason Meyer
Western Health (Footscray Hospital) (318)	Dashiell Gantner	Anna Tippett Samantha Bates
The Alfred Hospital (227)	Andrew Udy	Phoebe McCracken
Royal Prince Alfred Hospital (373)	David Gattas	Heidi Buhr
Nepean Hospital (374)	Louise Cole	Christina Whitehead
Sunshine Coast University Hospital (formerly Nambour) (317)	Victoria Campbell	Jane Brailsford
Geelong Hospital (468)	Neil Orford	Allison Bone
Bendigo Hospital (464)	Timothy Chimunda	Julie Smith
Ballarat Hospital (463)	Angus Richardson	Diane Hill
Eastern Hospital (Box Hill and Maroondah Hospital) (474)	Graeme Duke	Deborah Welsh
Flinder Medical Centre (397)	Alpesh Patel Shailesh Bihari	Elisha Matheson
Royal North Shore Hospital (257)	Celia Bradford	Anne O'Connor
St. Vincent's Hospital (259)	Priya Nair	Claire Reynolds
The Northern Hospital (469)	Angaj Ghosh	Simone Said

Concord Hospital (466)	Martin Gallagher Rosalba Cross	Helen Wong
NEW ZEALAND		
Wellington Hospital (261)	Paul Young	Anna Hunt
Auckland City Hospital (250)	Shay McGuinness	Madgalena Butler Rachael Parke
Christchurch Hospital (276)	David Knight	Jan Mehrtens
Auckland Hospital DCCM (467)	Colin McArthur	Lynette Newby
Hawke's Bay Hospital (494)	Matthew Bailey	Lesley Chadwick
Rotorua Hospital (507)	Ulrike Buehner	Erin Williams
Taranaki Hospital (530)	Jonathan Albrett	Simon Kirkham Carolyn Jackson
Whangarei Hospital (534)	Ryan Jang	Daniel Owens
Tauranga Hospital (548)	Troy Browne	Jennifer Goodson
EUROPE		
FRANCE		
Hôpital Louis Mourier (419)	Didier Dreyfuss Stéphane Gaudry	Coralie Gernez
Centre Hospitalier Départemental La Roche-Sur-Yon (425)	Martin Lefevre	
CHU D'Amiens (428)	Julien Maizel	Marie Laurence Lepilliez
Hôpital Pitiè Salpêtrière	Julien Mayaux	Laura Morizot
Hôpital Avicenne	Yves Cohen	
Hôpital Edouard Herriot	Laurent Argaud	Sylvie De La Salle
CH De Bourg-en-Bresse – Fleyriat	Remi Bruyere	
CHRU de Nîmes - Service de Réanimation	Saber Barbar	Audrey Ambert Solenne Villot
CHU De Rouen	Fabienne Tamion	Pauline Enguerrand
CH Sud Francilien	Guillaume Chevrel	
CHU Dijon Bourgogne	Jean-Pierre Quenot	

CH Le Mans	Nicolas Chudeau	Alain Robert
Hotel Dieu - Service d'Anesthesie	Karim Asehnoune	
CH de Béthune Beuvry – Germont et Gauthier	Christophe Vinsonneau	Mélanie Verlay
Hopital G. Montpied	Bertrand Souweine	Mireille Adda Frederic Duee
CH de Dieppe	Jean-Philippe Rigaud	
Hôpital Henri Mondor	Nicolas Prost	Sadaoui Thiziri
Hôpital Civil	Ferhat Meziani	Samir Chenaf
CHU de Pointe à Pitre	Bertrand Pons	
André Mignot	Benjamin Zuber	Sebastien Cavelot
Centre Hospitalier Dr. Schaffner (Lens)	Christophe Vinsonneau	
Hôpital Nord Laennec	Karim Lakhal	Laurence Pacaud
Groupe Hospitalier Carnelle-Portes de l'Oise	Eric Boulet	Mathilde Sampaio
Hotel Dieu – Service de Médicale	Laurent Nicolet	
Hôpital de la Source - CHR d'Orléans	Thierry Boulain	Lucie Muller
CH René DUBOS – Pontoise	Eric Boulet	Nathanael Charrier
CH Lyon Sud – Pierre Benite	Guillaume Thiery	
HEGP : Hôpital Européen Georges-Pompidou	Philippe Markowicz	
Service de reanimation medicale – Hopital Pitie Salpetriere	Allen Combes	
AUSTRIA		
Medical University Innsbruck (476)	Michael Joannidis	Klemens Zotter
Medical University Graz (492)	Philipp Eller	Gerald Hackl Gernot Schilcher
Medical University Innsbruck, General and Surgical ICU (515)	Dietman Fries	Mirjam Bachler
Medical University of Vienna (477)	Thomas Staudinger	Esther Tiller
BELGIUM		
Ghent University Hospital (414)	Eric Hoste	Stephanie Bracke
FINLAND		

Helsinki University Hospital (372)	Ville Pettila	Sari Sutinen
Tampere University Hospital (418)	Sari Karlsson	Sanna Ristimaki
Turku University Hospital (403)	Mikko Jarvisalo	Satu Kentala
GERMANY		
University Hospital Munster (405)	Alex Zarbock	Nadine Rosenow
Klinikum Coburg (508)	Orfeas Liangos	Monika Wittig
IRELAND		
St. Vincent's University Hospital (398)	Alistair Nichol	Ciara Fahey Kathy Brickel
SWITZERLAND		
Centre Hospitalier Universitaire Vaudois (CHUV) (521)	Antoine Schneider	Marco Altarelli Samia Abed
UK *(ENGLAND)*		
Guy's and St. Thomas NHS Foundation (475)	Marlies Ostermann	Arbane Gill Aneta Bociek
Nottingham University Hospital (499)	Andrew Sharman	Lucy Ryan
Buckinghamshire Healthcare: Stoke Mandeville Hospital (498)	Pradeep Shanmuga	Judith Abrams Katarina Manso
Buckinghamshire Healthcare: Wycombe Hospital (497)		
Milton Keynes Hospital (514)	Richard Stewart	Joanne Turner Esther Mwaura
Leeds Teaching Hospital (501)	James Beck	Clare Howcroft
East Kent University Hospitals NHS Trust (517)	Ritoo Kapoor	Janine Musselwhite Tracy Hazelton Angela Moon
Lewisham and Greenwich NHS Trust - University Hospital Lewisham (502)	Oliver Rose	Rosie-Reese Anthony
Liverpool University Hospital (500)	Ingeborg Welters	Karen Williams
King's College Hospital (503)	Philip Hopkins	Clare Finney John Smith

Lewisham and Greenwich Trust - Queen Elizabeth Hospital (518)	Ashraf Roshdy	Amy Collins
Western Sussex Hospitals NHS Foundation Trust: Worthing Hospital and St. Richard's (526 and 527)	Luke Hodgson	Indra Chadbourn
York Teaching Hospitals NHS Foundation Trust (544)	Rinus Pretorius	Lisa Carr
Warwick Hospital - South Warwickshire (537)	Ben Attwood	Penny Parsons
St. Helens & Knowsley Teaching Hospital (525)	Ascanio Tridente	Clare Harrop Susan Dowling
Royal Bornemouth & Christchurch Hospitals NHS Trust (546)	Nigel Chee	Sally Pitts
St. George's University Hospital (550)	Jonathan Ball	Sarah Farnell-Ward Susannah Leaver
University Hospital of North Tees (554)	Vijay Jagannathan	Michele Clark Sarah Purvis
UK *(SCOTLAND)*		
Queen Elizabeth University Hospital (531)	Malcolm Sim	Steven Henderson
Aberdeen Royal Infirmary (532)	Callum Kaye	Teresa Scott
Golden Jubilee National Hospital (536)	Ben Shelley	Elizabeth Boyd
University Hospital Ayr (545)	Derek McLaughlan	Natalie McLuckie
ITALY		
San Raffaele Hospital (512)	Giovanni Landoni	Rosalba Lembo Lara Sussani Paola Zuppeli
Ospedale San Carlo	Gianluca Paternsoter	Michelangelo Vitiello
ASIA		
CHINA		
Beijing Friendship Hospital, Capital Medical University (479)	Meili Duan	Xiaojun Ji Zhili Qi
Guizhou Provincial People's Hospital (483)	Xianqing Shi	Baning Ye
Henan Provincial People's Hospital (489)	Bingyu Qin	

Renmin Hospital of Wuhan University (490)	Zhui Yu	Song Xu
Shandong Provincial Hospital (486)	Chunting Wang	Ruiqi Ding
The First Affiliated Hospital of Xi'An Jiaotong University (488)	Xue Wang	Jingjing Sun
The First Hospital of Jilin University (482)	Zhong Liu	Xingang Liu
Xiangya Hospital Central South University (485)	Shuangping Zhao	Chenghuan Hu
Zhongda Hospital Southeast University (480)	Yi Yang	Yingzi Huang
Peking Union Medical College Hospital (481)	Bin Du	Chunyao Wang
The First Affiliated Hospital of Bengbu Medical College (511)	Xiandi He	Rui Li
Wuxi People's Hospital (510)	Jie Yang	Yifeng Weng
The First Affiliated Hospital of Xiamen University (484)	Minwei Zhang	Zhenzhu Fan
Peking University First Hospital (538)	Bin Du	Nan Li

Data Safety Monitoring Board (DSMB) Charter

STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury

Principal Investigators (PIs):

Sean Bagshaw MD MSc, University of Alberta
Ron Wald MD MPH, St. Michael's Hospital and University of Toronto

Sean Bagshaw and Ron Wald are PIs conducting the STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) randomized clinical trial.

The PIs, selected co-investigators (Neill Adhikari, Rinaldo Bellomo, Didier Dreyfuss, Bin Du, Martin Gallagher, Stephane Gaudry, Eric Hoste, Michael Joannidis, François Lamontagne, Kathleen Liu, Shay McGuiness, Alistair Nichol, Marlies Ostermann, Paul Palevsky, Ville Pettila, Haibo Qui, Orla Smith, Antoine Schneider, Matthew Weir) and the trial manager constitute the Steering Committee (SC**).**

DSMB Members Signature Page

Study Name:	**ST**andard versus **A**ccelerated initiation of **R**enal **R**eplacement **T**herapy in **A**cute **K**idney **I**njury (STARRT-AKI): A Multi-Centre, Randomized, Controlled Trial
Sponsor/Principal Investigators:	Dr. Ron Wald and Dr. Sean Bagshaw

I agree to be a part of the Data Safety Monitoring Board for the STARRT-AKI study. I understand and agree to all the terms and conditions outlined in the DSMB charter for the above named study. I confirm that I am not a part-time or full-time, paid or unpaid employee of any organizations that are involved in the STARRT-AKI trial. I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement. I have no conflicts of interests to disclose that make me ineligible to sit on this committee. I agree that in the event that the above may change during my tenure as a member of the DSMB I will disclose and discuss the risk with the Sponsor/Principal Investigators upon discovery of a risk and sign a new Conflict of Interest and Disclosure Statement form, and will include a description of the conflict. This includes the discovery that an organization with which I am affiliated meets the criteria for a conflict of interest.

DSMB Members:

Signature: _____ Date: 16/10/18
Name: Prof. Kathy Rowan

Signature: _____ Date: 15 Oct 2018
Name: Dr. Stuart Goldstein

Signature: _____ Date: Oct 17, 2018
Name: Dr. Dean Fergusson

Signature: _____ Date: 16/10/2018.
Name: Prof. Timothy Walsh

Signature: _____ Date: 16/10/2018
Name: Prof. David Harrison

Principal Investigators:

Signature: _____ Date: October 15, 2018
Name: Dr. Ron Wald

Signature: _____ Date: October 15, 2018
Name: Dr. Sean Bagshaw

Table of Contents

Introduction

The following outlines the Data Safety Monitoring Board (DSMB)'s terms of reference for the STARRT-AKI study. These terms of reference will govern the review of data on participants enrolled and treated under this protocol.

The DSMB is an independent group, appointed in an advisory capacity to the **Steering Committee** (SC) of the STARRT-AKI study. The DSMB will remain standing until the end of trial accrual. All DSMB members are expected to remain free from perceived or actual conflict of interest throughout their involvement in the trial, and will be asked to complete a conflict of interest form at the start of their participation in the DSMB.

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedures are needed.

Protocol Overview

Background: Acute kidney injury (AKI) is a common and devastating complication of critical illness. Once AKI is established, treatment is largely supportive and no intervention has been found to restore kidney function or improve overall survival. Renal replacement therapy (RRT), usually in the form of hemodialysis, hemofiltration, or a combination of these, is frequently needed to manage patients with severe AKI. Such patients have an in-hospital mortality that consistently exceeds 50% with delays in RRT initiation implicated as a possible contributor. A recent meta-analysis suggested that earlier initiation of RRT may improve survival, but this is based on data derived overwhelmingly from observational studies. Our group recently completed a multi-centre pilot randomized controlled trial that confirmed the feasibility of allocating patients to two different strategies of RRT initiation. Patient recruitment and follow-up, as well as patient safety, were successfully demonstrated during the pilot phase of this research program.
Objectives: The objectives of this trial are to determine whether, in critically ill patients with severe AKI, randomization to accelerated initiation of RRT, compared to a conservative strategy consistent with standard care, leads to: 1. *Improved survival* (primary outcome) at 90 days; and 2. *Recovery of kidney function* (*principal* secondary outcome), defined as independence from RRT at 90 days
Study Population: We will enroll 2,866 critically ill patients with severe AKI who do not have an urgent indication for RRT initiation at the time of screening but who have a reasonable likelihood of ultimately requiring RRT. Recruitment will occur at centres in Canada, the USA, Australia, New Zealand, the UK, Austria, and potentially several other countries.
Eligibility Criteria ***Inclusion criteria (all need to be fulfilled for eligibility):*** 1- Age ≥ 18 years 2- Admission to an intensive care unit (ICU)

3- Evidence of kidney dysfunction [serum creatinine ≥100 µmol/L (women) and ≥ 130 µmol/L (men)]
4- Evidence of severe AKI defined by at least 1 of the following 3 criteria:
    i) ≥ 2-fold increase in serum creatinine from a known pre-morbid baseline or during the current hospitalization; OR
    ii) Achievement of a serum creatinine ≥ 354 µmol/L with evidence of a minimum increase of 27 µmol/L from pre-morbid baseline or during the current hospitalization; OR
    iii) Urine output < 6.0 mL/kg over the preceding 12 hours

Exclusion criteria (any of the following factors will result in ineligibility):
1- Serum potassium > 5.5 mmol/L
2- Serum bicarbonate < 15 mmol/L
3- Presence of a drug overdose that necessitates initiation of RRT
4- Lack of commitment to ongoing life support (including RRT)
5- Any RRT within the previous 2 months (either acute or chronic RRT)
6- Kidney transplant within the past 365 days
7- Known pre-hospitalization advanced chronic kidney disease, defined by an estimated glomerular filtration rate < 20 mL/min/1.73 m2
8- Presence or clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy or acute interstitial nephritis
9- Clinician(s) caring for patient believe(s) that immediate RRT is absolutely mandated
10- Clinician(s) caring for patient believe(s) that deferral of RRT initiation is mandated

The patient or substitute decision maker will be asked to provide consent within 12 hours of the above criteria being met. Alternatively, in the absence of a substitute decision maker and where approved by the local Ethics Board, enrollment by deferred/delayed consent will need to be documented within 12 hours of the above criteria being met. The patient will be excluded if consent cannot be obtained (or enrollment by deferred/delayed consent cannot be documented) during this time window.

Interventions

Accelerated RRT initiation (experimental arm): A dialysis catheter will be placed and RRT initiated as soon as possible and no more than 12 hours after the patient became fully eligible.

Standard RRT initiation (control arm): In the absence of kidney function recovery, the initiation of RRT will be discouraged unless one of the following develops:

- serum potassium ≥ 6.0 mmol/L;
- pH ≤ 7.20 or serum bicarbonate ≤ 12 mmol/L;
- evidence of severe respiratory failure, based on a PaO_2/FiO_2 ≤ 200 and clinical perception of volume overload; and/or
- persistent AKI > 72 hours following the time of randomization.

Once a decision is made to start RRT, a dialysis catheter will be placed and RRT initiated as soon as possible.

All aspects of RRT (i.e. RRT modality, dose, anticoagulation) administered to patients in both treatment arms will follow guidelines that reflect local practice and usual standards of care.

Outcomes

Primary outcome:

1- All-cause mortality at 90 days.

Secondary outcomes:

1- RRT dependence at 90 days among surviving patients.
2- Composite of death or RRT dependence at 90 days.
3- Estimated glomerular filtration rate among patients alive at Day 90.
4- Albuminuria at Day 90. STARRT-AKI
5- Major adverse kidney outcomes, defined as death, RRT dependence or sustained reduction in kidney function (defined as eGFR < 75% baseline eGFR) at 90 days.
6- Mechanical ventilation-free days through day 28.
7- Vasoactive therapy-free days through day 28.
8- ICU-free days through day 28.
9- Hospitalization-free days through day 90.
10- Death in ICU, at 28 days, and in-hospital.
11- EuroQoL EQ-5D-5L (a measure of health-related quality of life and patient utility) at day 90 and at 1 year among survivors.
12- Health care costs through day 365.
13- Vital status and RRT dependence at 365 days among survivors.

Implications:

The optimal timing of RRT initiation is an existing knowledge gap and a clear priority for investigation. With the successful completion of the STARRT-AKI pilot trial, the feasibility and relevance of the proposed interventions has been established. It is now time to definitively evaluate whether earlier/pre-emptive/accelerated RRT initiation is associated with enhanced survival as compared to a conservative strategy

DSMB Aims and Roles

The DSMB is responsible for safeguarding the interests of study participants, and assessing the safety of study procedures, and is required to provide recommendations about continuing or stopping the study, based on safety considerations.

Specific roles: **Upon enrolment of every 300 patients**, the DSMB will:

- Assess data quality, including timeliness and completeness
- Monitor compliance with the protocol
- Monitor participant recruitment, accrual and retention
- Review adverse event and serious adverse event data
- Review protocol modifications, if applicable
- Assess the impact and relevance of external data that may affect the safety of the participants or the ethics of the trial
- Monitor compliance with previous DSMB recommendations

The DSMB will monitor serious adverse events as they occur (see below), and at the above stated intervals.

As per the protocol, interim analyses will take place after 25%, 50% and 75% of the trial cohort has completed 90-day follow-up. Thus, DSMB meetings to review data emanating from these analyses

will coincide with DSMB meetings corresponding to the enrollment of 900, 1500 and 2400 patients, respectively.

The agenda for DSMB meetings will be drafted by the Data Management and Coordinating Centre, The Applied Health Research Centre (AHRC), in consultation with the sponsor/SC. AHRC will finalize the agenda after consultation with the DSMB Chair. The agenda and data reports will be distributed by the AHRC at least 10 business days before each meeting.

Serious Adverse Events

1. Definition

For this trial, a reportable SAE is defined as any adverse event that meets at least one of the following conditions:

- is fatal (results in death)
- is felt to be life-threatening
- requires in-patient hospitalization or prolongation of an existing hospitalization
- results in significant disability or incapacity

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

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

In light of this and given the nature of the trial intervention, only SAEs occurring in the first 14 days following randomization will be reportable.

All SAEs must be reported to the DSMB in aggregate form at least 10 days in advance of a scheduled meeting. All SAEs should be reported to the DSMB chair in an expedited fashion as per the procedures described below.

*Note: An SAE will be considered to be study-related if the event follows a reasonable temporal sequence from a study procedure and could readily have been produced by the study procedure. Adverse events are considered to not be study-related, and need not be reported, if they are related primarily to the underlying disease or to AKI and its sequelae.

2. Procedures for Reporting a SAE

Each site research coordinator will liaise with the clinical team and review the medical records of study participants to identify potential SAEs. The site research coordinator will notify the site investigator and the local Ethics Board (according to local requirements) about each local SAE. Clinicians will treat the study patient affected by an SAE as per the usual standard of care.

The site investigator has primary responsibility for the safety of individual study patients at his/her study site. Upon recognition of an SAE, the site research coordinator or site investigator will notify the STARRT-AKI Data Management and Coordinating Centre within 1 business day of becoming aware of the SAE. Follow-up of any SAE that is fatal or life threatening should be provided within 7 calendar days. Follow-up of the outcome of SAEs will continue until clinical recovery is complete and laboratory results have returned to baseline, or until progression has been stabilized. Follow-up will continue for the duration of the patient's study participation. Any documents relating to SAEs

will be reviewed at the Data Management and Coordinating Centre to ensure that they do not contain sensitive or confidential patient information, in accordance with privacy requirements.

In the event of a reported SAE, the study manager will contact the PIs (Sean Bagshaw and Ron Wald) and the DSMB Chair (Dr. Kathy Rowan) to alert them of the forthcoming documentation regarding the SAE. Upon receiving all relevant clinical notes and case report forms from the site, research personnel at the Data Management and Coordinating Centre will collate this material into a detailed report for distribution to the PIs and the DSMB Chair within 5 business days of the original notification to the Data Management and Coordinating Centre.

After reviewing the clinical notes and CRFs, the DSMB chair will determine whether immediate input from other DSMB members is required and will contact them as needed. The DSMB will send its determinations to the PIs.

The DSMB will also review aggregate SAEs and AEs upon enrollment of every 300 patients and following each interim analysis. At this time, the DSMB will recommend to the SC whether to

a. continue patient enrolment,
b. suspend enrolment until careful review by the SC, or
c. request additional information before making a recommendation.

Membership

The DSMB consists of members who are experts in nephrology, critical care and trial methodology. Members are independent of the investigators and have no financial, scientific, or other conflict of interest with the trial, as noted in written documentation on file with the Data Management and Coordinating Centre at St. Michael's Hospital.

Dr. Kathy Rowan (ICNARC, UK) is the Chair, responsible for overseeing the meetings and the contact person for the DSMB.

Other members include Drs. Stuart Goldstein (Cincinnati Children's Hospital Medical Center, USA), Timothy Walsh (University of Edinburgh, Scotland), Dean Fergusson (Ottawa Hospital Research Institute, Canada), and David Harrison (ICNARC, UK).

The DSMB is independent of the PIs and SC with respect to recommendations made, but is supportive of the aims and methods of the trial. The DSMB serves in an advisory role. The DSMB, PIs, and SC will work collaboratively to ensure rigorous, safe, and timely conduct of the trial.

Quorum

It is expected that all DSMB members will attend every meeting. At minimum, the chair and three members must participate in order for a quorum to exist. If one member is unable to attend the meeting, the DSMB Chair will follow up by phone or email afterwards, as feasible. The sponsor or designated representative must always be available for the open session as well. If voting is required, then all members must participate.

Meeting Format

Each meeting will start with an **open session** that may be attended by 1-2 SC members (including one of the PIs) and selected trial staff. Issues discussed will include conduct and progress of the study, including patient accrual, compliance with the protocol, and any problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

Only DSMB members will attend the **closed session**; others (e.g., study statistician) may attend by invitation. All safety data will be presented at this session. The discussion at the closed session is confidential.

After each meeting, the DSMB will recommend whether to:

a. continue enrollment;
b. consult immediately with the PIs and SC with a view to terminating enrollment; or
c. request additional information before making a recommendation.

Results from the interim analyses will also be submitted to the DSMB to assist in forming their recommendations for continuation of the trial. The DSMB will inform the PIs if, in their view, major safety issues have arisen that are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that on balance, continued use of one of the study interventions in a particular group or sub-group would be widely seen as unethical, BOTH for clinical care AND for any further investigation.

The DSMB will follow these guidelines in formulating a recommendation:

- the Chair will encourage consensus and all members will attempt to achieve consensus
- members will consider the ethical, scientific, statistical, practical, and financial implications for the trial in making recommendations.

Stopping Rules

Should the DSMB contemplate a recommendation to terminate the study, they will provide the SC with the opportunity to halt enrollment (without terminating the trial) and investigate any concerns during the halt period. If the DSMB subsequently decides to recommend termination, after considering the SC's report of the issues raised, a vote of all DSMB members will be required. The DSMB will attempt to come to a consensus before taking a vote. In the event of a divided vote, majority will rule and a minority report should be appended.

Payments

DSMB members will receive a stipend, in Canadian dollars, for the contribution of their time and professional expertise as part of the DSMB.

<u>Stipend breakdown per meeting:</u>

- DSMB Chair: $500
- Other members: $250

Reports

1. **Interim Reports:** Interim reports are distributed to the DSMB membership at least 10 days before a scheduled meeting. These interim reports will be numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB member prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts:

    I. Part 1 (Open Session Report) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status, including protocol amendments.

II. Part 2 (Closed Session Report) will include safety data. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting.

2. **Reports from the DSMB:** A formal report containing recommendations for continuation or modifications of the study from the DSMB Chair will be sent to the full DSMB within 4 weeks of the meeting. It is the responsibility of the PI to distribute the formal DSMB recommendation report to all co-investigators (and funding agencies, if required) and to ensure that sites are advised to submit the reports to their local Ethics Board.

   The formal DSMB report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote after an attempt is made to reach consensus. A termination recommendation may be made by the DSMB at any time by majority vote. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the PIs of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry or evaluation.

Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Archiving of DSMB Activities and Related Documents

All DSMB documentation and records will be retained by the Applied Health Research Centre (AHRC) until the completion of the study, at which point they will be transferred to and stored by the PI, for a time period of minimum of 5 years after completion of the study. Access to archived data will be controlled by the AHRC until the completion of the study, at which point they will be transferred to and stored by the PI, and will be released only as specified in this charter or as required by law.