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

Operations Manual

Version 2.0

Date: July 5, 2016
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### Glossary of Terms

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>ACE</td>
<td>Aid to Capacity Evaluation</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute Kidney Injury</td>
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<tr>
<td>CRRT</td>
<td>Continuous renal replacement therapy</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized Tomography</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DMCC</td>
<td>Data Management Coordinating Centre</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>FiO₂</td>
<td>Fraction of Inspired Oxygen</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>Hr</td>
<td>Hour</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IHD</td>
<td>Intermittent hemodialysis</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
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<tr>
<td>mL/min</td>
<td>Milliliter per minute</td>
</tr>
<tr>
<td>mm³</td>
<td>Cubic milliliter</td>
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<tr>
<td>mmol/L</td>
<td>Millimoles per litre</td>
</tr>
<tr>
<td>mcmol/L</td>
<td>Micromoles per litre</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Partial pressure arterial oxygen</td>
</tr>
<tr>
<td>RRT</td>
<td>Renal Replacement Therapy</td>
</tr>
<tr>
<td>SaO₂</td>
<td>Arterial oxygen saturation</td>
</tr>
<tr>
<td>sCr</td>
<td>Serum Creatinine</td>
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<tr>
<td>SDM</td>
<td>Substitute Decision Maker</td>
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<tr>
<td>SLED</td>
<td>Sustained low efficiency dialysis</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
</tr>
<tr>
<td>µg</td>
<td>Microgram</td>
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Part 1: General Information

Study Chairs

<table>
<thead>
<tr>
<th>Name and Institution</th>
<th>Address, Phone, Email</th>
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</thead>
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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:

<table>
<thead>
<tr>
<th>Ron Wald, MDCM</th>
<th>Sean Bagshaw, MD MSc</th>
<th>Marlies Ostermann, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neill Adhikari, MDCM</td>
<td>François Lamontagne, MD</td>
<td>Paul Palevsky, MD</td>
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<td>Rinaldo Bellomo, MD</td>
<td>Kathleen Liu, MD</td>
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</tr>
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<td>Martin Gallagher, MD PhD</td>
<td>Shay McGuinness, MD</td>
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<tr>
<td>Michael Joannidis, MD</td>
<td>Alistair Nichol, MD</td>
<td>Matthew Weir, MD</td>
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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:

<table>
<thead>
<tr>
<th>Kathy Rowan, PhD (Chair)</th>
<th>Dean Fergusson, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stuart Goldstein, MD</td>
<td>David Harrison, PhD</td>
</tr>
<tr>
<td>Timothy Walsh, MD</td>
<td></td>
</tr>
</tbody>
</table>
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:
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Part 2: Screening and Eligibility

Philosophy of screening
The over-arching goal is to identify patients with severe AKI 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. 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 mcmol/L at time of screening from baseline of 100 mcmol/L) but at a later time, he/she may become eligible when his/her creatinine is found to be 210 mcmol/L; 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. By the same token, if exclusion 9 is invoked (clinician(s) feels that immediate RRT is mandated), the patient may be re-screened if RRT did not actually commence. More commonly, when a clinician excludes a patient due to the perception that deferral of RRT is mandated (exclusion 10), this is because of the perception that the patient is either not sick enough or that the AKI is about to recover. However, such patients must be rescreened. For example, 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 3-8 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 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**

Screened patients who meet all the conditions for inclusion should be entered in the screening log. If a patient does not meet ALL of the inclusion criteria, he/she should not be entered in 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.

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.

**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 of 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. Briefly, 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. Moreover, 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.

3. **Evidence of kidney dysfunction.**
   
   *Operational definition:* serum creatinine** ≥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. Serum creatinine will often fluctuate during a hospitalization and slight increases or decreases in sCr may be of little clinical relevance. However, for this trial we want to avoid enrolling patients who might have evidence of kidney recovery. A sCr drop of 27 µmol/L or more 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.

   ** creatinine values 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 serum creatinine (sCr) from baseline;**
      
      *Operational definition:* 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 sCr value obtained during the current hospitalization should be taken as the baseline. This criterion is met if the current sCr is ≥ 100% higher than the baseline value. There should always be a baseline sCr. Please refer to the Determining Baseline Serum Creatinine flow chart below.

   ii. If current sCr 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 sCr;
      
      *Operational definition:* If current sCr 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
sCr. 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; 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.

**Determining baseline sCr**

![Flow chart for determining baseline sCr](chart)

### 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, 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 > 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 concentration from point of care meters; these values are acceptable. The only thing that matters is that the last available serum potassium concentration is used for screening purposes.)
2. Bicarbonate concentration < 15 mmol/L.  
Operational definition: Based on last available bloodwork which may be derived from routine biochemistry or a arterial or venous blood gas. 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 as the primary reason for administering RRT.

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, including the initiation of RRT, or substitute decision makers have declined offer of same. However, there may be a patient who is “DNR” or for whom CPR in the event of cardiac arrest has been declined but if patient/SDM still consider 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 responding to this exclusion criterion.

6. Kidney transplant within the past 365 days.  
Operational definition: As reflected in the medical record.

7. Known pre-hospitalization advanced chronic kidney disease, defined by an estimated glomerular filtration rate < 20 mL/min/1.73 m².  
Operational definition: The coordinator will review all readily available sCr values within 365 days prior to the date of admission for the current hospitalization. The value closest to the admission date will be considered as the “baseline” and will be used to calculate the corresponding estimated glomerular filtration rate using an online calculator. A value of < 20 mL/min/1.73 m² derived from the CKD-EPI equation will be grounds for exclusion.

The sCr, 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 sCr data. In the case of a missing outpatient sCr, this exclusion criterion will be considered to have been NOT met.
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 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 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.

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.

**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 one 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. In
summary, invoking of 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 met. More commonly, a clinician
may have the impression that a given patient will likely recover imminently and invoke exclusion 10
(RRT deferral is mandated). On a subsequent screen, 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 criteria remain intact.
The following algorithm has been created to assist with determination of eligibility:

1. Age ≥18 and admitted to ICU
2. Current serum creatinine ≥130 μmol/L (men) ≥100 μmol/L (women)
3. At least one of:
   - ≥2-fold increase in serum creatinine from baseline
   - Serum creatinine ≥354 μmol/L with minimum increase of 27 μmol/L
   - Urine output <60 mL/kg over preceding 12 hours

Assess exclusion criteria:
1. Serum potassium >5.5 mmol/L
2. Serum bicarbonate <15 mmol/L

Continue assessing exclusion criteria:
3. Drug overdose requiring RRT?
4. Lack of commitment to life support?
5. Any RRT in previous 2 months?
6. Kidney transplant in past 365 days?
7. Known pre-hospitalization CKD with eGFR <20 mL/min/1.73m²?
8. Presence/suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy, or acute interstitial nephritis?

Does/Do the attending clinician(s) agree with either of the following:
9. RRT must be initiated immediately in this patient?
10. RRT must be deferred in this patient?

Provisionally eligible

Exclude if one or more criteria are met

FULLY ELIGIBLE

Exclude; reassess if clinician reconsiders and RRT has not been started
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 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?**

The exact time of eligibility should be noted and the consent process must start immediately in order to secure consent and potentially facilitate the start of RRT within the next 12 hours. The 12 hour window during which consent must be secured commences at the time of the patient meeting full trial eligibility. Usually, the clinician(s) assent to patient enrollment (i.e., answering “No” to both questions 9 and 10) are the last 2 eligibility criteria that are met prior to full eligibility being established. The 12-hour window has no relation to the sCr doubling or to any other biochemical index of AKI. It is only related to when all the eligibility criteria were finally met. It is during these 12 hours that follow the onset of FULL ELIGIBILITY that consent must take place, and if a patient is randomized to accelerated RRT, RRT MUST start during this 12-hour interval. Once again, Time 0 for this 12-hour interval is the time of full trial eligibility. For example, if a patient is found to be fully eligible at 09:06 on June 17, consent from the patient/SDM (or alternative forms of consent) must be obtained by 21:06 on June 17. If the patient cannot be enrolled during this 12-hour window, he/she is considered to be “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 for whom consent is obtained within 12 hours of becoming fully eligible 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.).

**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/coordinaor 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
STARRT-AKI Study: Operations Manual

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). 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, if approved by the local Ethics Board.

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 in the database, confirming full eligibility of the participant.

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 is accomplished.

1. Notify the bedside ICU nurse that RRT will be started imminently. Even though there is a 12-hour window to start RRT, the aim should be to start RRT as soon as possible.

2. Contact the ICU and nephrology attendings (or respective fellows) 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.

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, 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. PaO₂/FiO₂ ≤ 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.**

By the same token, patients in the standard arm may be started on RRT at anytime 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.

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 score (SOFA_{CV}) 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 viewed as a reasonable option.

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

<table>
<thead>
<tr>
<th>Score</th>
<th>Clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Mean arterial pressure ≥ 70 mmHg</td>
</tr>
<tr>
<td>1</td>
<td>Mean arterial pressure &lt; 70 mmHg</td>
</tr>
<tr>
<td>2</td>
<td>Dopamine ≤ 5 µg/kg/min or any dose of dobutamine or milrinone</td>
</tr>
</tbody>
</table>
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 vasoppressors and/or inotropes for the preceding 12 hours (i.e., SOFA<sub>CV</sub> 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<sub>CV</sub> 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:

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

- **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

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: Data Collection
The following section will provide guidance on how to complete each element of the case report forms. For additional information regarding data entry and the Medidata RAVE™ platform, please refer to the STARRT-AKI Data Entry Guidelines.

Form 1: Eligibility
Inclusion and Exclusion Criteria. As confirmation that the participant has met eligibility, record whether or not they met each of the study inclusion and exclusion criteria (see Clarification of Eligibility Criteria in Part 2 of this document) and confirm overall study eligibility.

Date and Time of Study Eligibility. Record the date and time (local time) at which the participant met FULL study eligibility (dd/mmm/yyyy). This is a crucial time point as consent needs to be secured within 12 hours of this time.
Form 2: Consent

1a. Indicate whether consent of any approved type was obtained within 12 hours of patient meeting full study eligibility and, if not, indicate the reason(s) for not obtaining consent in 1b.

2. Provide the date (2a) and time (2b) of the initial consent for study entry (i.e., the initial consent prior to randomization), regardless of whether it was provided by the patient, a SDM, or documented as a deferred/waived consent, if applicable.

3. Indicate the type of consent model that was used for study entry on the date and time specified in question 2. Select ONE response only.

4. This question applies in cases where initial consent was obtained from an SDM, either by telephone, email or in person. Indicate whether consent to continue participation was ultimately obtained from the patient post-randomization.

   • If yes, indicate the date and time that the patient provided consent.
   • If no, indicate the reason why patient consent was not obtained.

5. This question only applies in cases where initial consent could not be obtained from either the patient or an SDM and a deferred/waiver of consent model was used. Indicate whether consent to continue participation was ultimately obtained from the patient, a SDM, or another individual authorized to act on the patient’s behalf post-randomization.

   • If yes, indicate ALL methods by which consent was obtained to continue participation. For example, if it became possible to reach an SDM by telephone and consent was obtained, and then two days later the patient regained capacity and also provided consent to continue, you would indicate BOTH i) SDM consent and ii) patient consent.
   • If no, indicate the method by which consent to continue participation was either declined or not obtained. Select the ONE best response.

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

THIS FORM WILL BE SUBMITTED ON A DEDICATED MS Excel SPREADSHEET (NOT on MEDIDATA RAVE).

This form is only completed for non-enrolled patients whose 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 completely eligible but consent could not be secured.

• Bloodwork parameters: These should reflect the last available value at the time eligibility was being assessed.
- **Intervention**: The receipt of mechanical ventilation, inotropes and vasopressors should reflect what was happening at the time of screening.

- **SOFA score**: A SOFA score incorporating multiple clinical domains from the preceding 24 hours should be completed as well (see Form 7 below). The most extreme score for each organ system in the preceding 24 hours should be selected.

- **Outcomes**: 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.

**Form 4: Randomization**

Only randomize a patient *after* initial consent has been obtained by the patient themselves, a SDM, another individual authorized to act on the patient’s behalf, or by documented deferral/waiver of consent.

- **Date and time of randomization**: Record the date and time that the participant’s randomization was completed in the eCRF.

- **Group/Treatment Arm to which patient is randomized**: Record the randomization assignment revealed in the study database.

**Form 5: Demographics and Details of Hospitalization**

- **Date of Birth**: Record the participant’s full date of birth at the time of randomization (dd/mmm/yyyy). If you research ethics board does not permit collection of a full date of birth, consider entering the day of the month as 1, 15, or 30 as per your site requirements.

- **Sex**: Record the participant’s biological sex.

- **Race**: Record the patient’s race based on self-report or best judgement.

- **Ethnicity**: Record if patient is Hispanic or not.

- **Earliest available weight since admission**: Record the participant’s weight in kilograms (kg) or in pounds (lbs). This information will be sought from the flow sheet from the patient’s first day in hospital, at the research 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 record the patient’s weight based on the average weight estimated by the bedside ICU nurse and attending physician. The same weight as recorded for assessment of oliguria in the screening phase should be recorded here.

- **Was the patient transferred to your research site from another acute care hospital?**: Please indicate either “Yes” or “No”.
  - If yes, please indicate the date of the original hospital admission (i.e., at the other acute care hospital) as well as the date and time of the ICU admission at the other acute care hospital, if known. In addition, please indicate the date of transfer to the current hospital / research site as well as the date and time of ICU admission at the research site.
If no (i.e., the patient’s hospitalization commenced at the study hospital site), please indicate the date of admission to the current hospital/study site as well as the date and time of ICU admission at the research site.

- **Diagnostic Category**: Check one category which is most responsible for admission. If there are multiple concurrent conditions driving the patient’s hospitalization, chose the system most responsible for the patient’s AKI.

**Form 6: Risk Factors**

**Pre-hospitalization Risk Factors for AKI**

- **Baseline serum creatinine**: 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 sCr obtained on the present hospitalization is the baseline. This value is the same baseline sCr collected during the screening process.

- **Baseline estimated GFR based on CKD-EPI formula**: Using the baseline sCr (see above), 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](http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr)

- **Pre-hospitalization urine albumin concentration**: 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, enter this instead. If unavailable, please indicate this.

- **Pre-hospitalization urine protein concentration (if urine albumin concentration 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, enter this instead. If unavailable, please indicate this.

- **Pre-hospitalization urine creatinine concentration**: Use the closest outpatient value prior to the current hospitalization but no more than 365 days prior to the current hospitalization. Enter the value and the units being used. If value exceeds the upper limit of the local assay, enter this instead. If unavailable, please indicate this.

- **Pre-hospitalization urinalysis (if neither urine albumin:creatinine ratio nor urine protein:creatinine ratio are available)**: Use the closest outpatient value prior to the present hospitalization but no more than 365 days prior to the current hospitalization. If unavailable, please indicate this.

**Pre-existing comorbidities**

**NOTE**: All of the following comorbidities are recorded based on their presence or absence on the ICU medical record:

- **Hypertension**: Indicate “Yes” if the patient is reported as having a past history of “hypertension” on the ICU admission note.
Diabetes mellitus. Indicate “Yes” if the patient is reported as having a past history of “diabetes”, “diabetes mellitus” or “DM” on the ICU admission note.

Heart Failure. Indicate “Yes” if the patient is reported as having a past history of “congestive heart failure”, “CHF”, or “HF” on the ICU admission note.

Coronary artery disease. Indicate “Yes” if the patient is reported as having a past history of “Coronary Artery Disease” on the ICU admission note.

Liver Disease: Indicate “Yes” if the patient is reported as having a past history of “Liver Disease” on the ICU admission note.

Hospital-Acquired Risk Factors for AKI

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 hospital, the date of admission is the date patient admitted at the initial (transferring) hospital.

Cardiopulmonary bypass in preceding 7 days: 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.

Aortic aneurysm repair in preceding 7 days: Defined as repair of an abdominal aortic aneurysm using open surgery or endovascular repair during the 7 days prior to trial randomization.

Other vascular surgery in preceding 7 days: 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.

Trauma in preceding 7 days: Defined as major trauma in the 7 days prior to randomization that is playing a major role in the patient’s current critical illness.

IV contrast exposure in preceding 7 days: Please review the medical record (at the study hospital only) to identify the administration of intravenous 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 as a form of IV contrast.

Receipt of aminoglycoside in preceding 7 days: Please scan the medication records (at the study hospital only) to identify the receipt of 1 or more doses of gentamicin, tobramycin or amikacin during the 7 days prior to randomization.

Receipt of amphotericin B in preceding 7 days: Please scan the medication records (at the study hospital only) to identify the receipt of 1 or more doses of amphotericin B during the 7 days prior to randomization.

Obstetric complications in the preceding 7 days: If patient has delivered in the preceding 7 days, check as “yes”.

Version 2.0: July 05 2016
Sepsis

- Has the patient met criteria for diagnosis of Sepsis in preceding 72 hours? 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 rise of at least 2 points. (Note: As per the SEPSIS-3 consensus definition guidelines released in 2016, the presence of a change total SOFA score of ≥ 2 will enable the designation of “sepsis” in the presence of suspected infection. Sepsis will be further classified as “septic shock” if there is concomitant administration of vasopressors.)

Form 7: Pre-Randomization SOFA

NOTE: Use the most extreme result for each component in the 24 hours preceding randomization.

Respiratory

Select all arterial partial pressure of oxygen (PaO₂) values obtained from blood gas samples and the fractional inspired oxygen (FiO₂) that was being administered at the same time. Calculate the quotient PaO₂/FiO₂ for each set of values; the lowest PaO₂/FiO₂ is used to determine the SOFA-Respiratory score.

- 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 PaO₂/FiO₂ is 150 but he/she is not receiving mechanical ventilation, the score is 3 and NOT 2.
- In some cases, PaO₂ may not have been obtained as part of routine clinical care; in that case, choose the lowest oxygen saturation (SaO₂) for the day and use the chart below to "translate" SaO₂ into PaO₂.
- In some cases, FiO₂ may not have been recorded; as an alternative, use Appendix 1 to "translate" O₂ flow rates through face mask or nasal cannula into an FiO₂ value.
Coagulation

Select the LOWEST platelet count during the 24 hour prior to randomization.

Liver

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.

**Cardiovascular**

- 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 just on phenylephrine?
  - Automatic score of 3.
- Was patient on just dobutamine or milrinone?
  - 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 0.
  - If MAP < 70 mmHg, then assign a score of 1.

**CNS-Glasgow Coma Scale (GCS)**

Identify the lowest calculated GCS score during the 24 hours prior to randomization.

- If patient intubated, assign a “1” for verbal.
- DO NOT ACCOUNT FOR WHETHER PATIENT IS SEDATED OR RECEIVING PARALYTIC AGENTS. Patient’s score should be based on actual abilities.

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

<table>
<thead>
<tr>
<th>Category</th>
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<td>Verbal</td>
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<td>5</td>
</tr>
<tr>
<td></td>
<td>confused</td>
<td>4</td>
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<tr>
<td></td>
<td>inappropriate</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>incomprehensible</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>none</td>
<td>1</td>
</tr>
<tr>
<td>Motor</td>
<td>obeys commands</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>localizes pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>withdraws to pain</td>
<td>4</td>
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<td>flexion to pain</td>
<td>3</td>
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<td>2</td>
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<td></td>
<td>none</td>
<td>1</td>
</tr>
<tr>
<td>Eye opening</td>
<td>spontaneous</td>
<td>4</td>
</tr>
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<td>3</td>
</tr>
<tr>
<td></td>
<td>to pain</td>
<td>2</td>
</tr>
</tbody>
</table>
Renal

Use the highest sCr value during the 24 hour prior to randomization to determine the 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 sCr concentration. If urine output is 200-500 mL/day, crosscheck with highest sCr value and assign the score based on whether the urine output or sCr places the patient in a higher (i.e., sicker) category.

Form 8: Pre-Randomization Severity of Illness (Simplified Acute Physiology Score (SAPS) II)
For the below fields, use the worst value during 24 hours preceding randomization. If data is not available, select the Not Available option.

- **Heart rate**: This would be the highest recorded heart rate in the 24 hours preceding randomization.
- **Systolic blood pressure**: This is the lowest recorded systolic blood pressure in the 24 hours preceding randomization.
- **Temperature**: Record the highest temperature in the 24 hours preceding randomization in degrees Celcius or Farenheit.
- **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).
- **Mechanical ventilation or CPAP**: Indicate Yes or No. If yes, record PaO₂/FiO₂ ratio
- **Urine Output in ICU over preceding 24 hours**: If patient has been in ICU for under 24 hours, record urine output and specify the duration of collection.
- **Blood urea nitrogen**: Record the highest value in the 24 hours preceding randomization.
- **Serum sodium**: Record the lowest value in the 24 hours preceding randomization.
- **Serum potassium**: Record the highest value in the 24 hours preceding randomization.
- **Serum bicarbonate**: Record the lowest value in the 24 hours preceding randomization.
- **Billirubin**: Record the highest value in the 24 hours preceding randomization.
- **WBC count**: Record the highest value in the 24 hours preceding randomization.
- **Metastatic cancer**: Record as Yes/No based on ICU admission note.
- **Hematologic malignancy**: Record as Yes/No based on ICU admission note.
- **AIDS**: Record as Yes/No based on ICU admission note.
- **Type of admission**: Specify if admission type is Scheduled, Unscheduled, or Medical.

Form 9: Pre-Randomization Data

**Physiologic Parameters (last available values prior to randomization):**

- **Respiratory rate**: Choose the value recorded closest to but preceding randomization.
- **Aterial pH**: Choose the value recorded closest to but preceding randomization.
- **Cumulative fluid balance (since current ICU admission)**: 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 2000 hrs, record the cumulative balance as of the preceding midnight.

**Laboratory Data (last available values prior to randomization):**

- **Serum creatinine**: Choose the value recorded closest to but preceding randomization.
- **Hemoglobin**: Choose the value recorded closest to but preceding randomization.
- **Platelet count**: Choose the value recorded closest to but preceding randomization.

**Interventions at time of randomization:**

- **If receiving mechanical ventilation or CPAP:**
  - **PEEP**: as recorded closest to but preceding randomization.
  - **Mean Airway Pressure**: as recorded closest to but preceding randomization.
- **Maximum dose of norepinephrine**: Based on values recorded in the 24 hours preceding randomization.
- **Maximum dose of epinephrine**: Based on values recorded in the 24 hours preceding randomization.
- **Maximum dose of vasopressin**: Based on values recorded in the 24 hours preceding randomization.
- **Maximum dose of phentolamine**: Based on values recorded in the 24 hours preceding randomization.
- **Maximum dose of dopamine**: Based on values recorded in the 24 hours preceding randomization.
- **Maximum dose of dobutamine**: Based on values recorded in the 24 hours preceding randomization.
- **Maximum dose of levosimendan**: Based on values recorded in the 24 hours preceding randomization.
- **Maximum dose of milrinone**: Based on values recorded in the 24 hours preceding randomization.
- **Receipt of diuretic during the ICU day?**: Indicate Yes or No based on whether patient received furosemide, bumetanide, ethacrynic acid (or any loop diuretic) or metalozoneat ANY dose or ANY frequency during the 24 hours preceding randomization.
- **Receipt of total parenteral nutrition (TPN)?**: Indicate Yes or No based on whether patient received any TPN during the 24 hours preceding randomization.
- **Receipt of enteral nutrition?**: Indicate Yes or No based on whether patient received any enteral nutrition during the 24 hours preceding randomization.

**Quality of Life Assessment at Baseline:**

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).
Clinical Frailty Scale (CFS) Score:

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 lead to the current hospitalization. Assignment of score is based on information gleaned from patient, family members and clinical notes.

For more information on the CFS score, see:

- [https://www.youtube.com/watch?v=brlcorfx9Ts](https://www.youtube.com/watch?v=brlcorfx9Ts)
- [https://www.youtube.com/watch?v=_3QKcuf-Mhs](https://www.youtube.com/watch?v=_3QKcuf-Mhs)

Form 10: Daily Data

This information is collected for 14 days following randomization, constituting Day 0 to 14. Almost always, Day 0 is a partial day namely the time from randomization to the end of that “ICU day”. The daily data is collected only while patients are in the ICU. Please complete the form even if patient 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 in the midst of and “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 the ICU?*

  This should coincide with the usual data collection in the ICU. Some ICUs will define the “day” as the calendar day (00:00-23:59) while others may consider a “day” as running from 08:00-7:59. To facilitate data collection, the “days” associated with data collection in the STARRT-AKI trial will correspond to the cutoffs for “days” used in the study 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 0800 on April 20 to 07:59 on April 19 etc.

**LABORATORY AND PHYSIOLOGIC PARAMETERS:**

- **Urine Output on study Day:** Provide the actual urine output in mL without “adjustment” for time even if a day lasts less than 24 hours.
- **Hours of urine collection:** Indicate the duration of time for which urine collection is documented. For example on Day 0 (i.e., day of randomization), a patient randomized at 2200, and the “ICU Day” ends at 0759, record hours as 10.
- **Total fluid balance:** 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. Complete this even if patient was not in ICU for a full 24 hours.
- **Serum potassium:** Record the value documented as part of the routine morning ICU bloodwork for that ICU day. 
  *NOTE: If serum potassium was below 3.0 mmol/L at any time during the study day, then please complete the adverse event form.*
- **Serum phosphate:** Record the value documented as part of the routine morning ICU bloodwork for that ICU day. 
  *NOTE: If serum phosphate was below 0.5 mmol/L at any time during the study day, then please complete the adverse event form.*
- **Serum bicarbonate:** Record the value recorded as part of the routine morning ICU bloodwork for that ICU day. The bicarbonate value may also be recorded from point of care or blood gas machines if it is local practice to draw routine blood tests from those devices.
- **Arterial pH:** Record the value recorded as part of the routine morning ICU bloodwork for that ICU day.
- **Ionized Calcium:** Record the value documented as part of the routine morning ICU bloodwork for that ICU day.
- **PaO₂/FiO₂:** Record the value documented as part of the routine morning ICU bloodwork for that ICU day.
- **Hemoglobin**: Record the value recorded as part of the routine morning ICU bloodwork for that ICU day.

**RENAL REPLACEMENT THERAPY:**

- **Receiving RRT on Study Day?**:
  - The first question is whether any RRT was received during that study day. This simply asks you to indicate whether a patient got ANY RRT for part of that study day, irrespective of their treatment arm. Response to this question will then trigger other questions, as appropriate.

  IF RESPONSE IS NO....there will be a trigger asking the user to comment on the circumstances for not administering RRT on that if participant is in the standard arm and whether new vascular access was inserted:

  IF RESPONSE IS “YES,” several additional questions will be triggered:

  Indicate whether RRT was initiated *for the first time in the trial* on the study day (Day 0-14).
  - If yes, was RRT initiated on study date?: Indicate Yes and you will also be asked to specify the time at which the patient started their first RRT session.
  - *Answer N/A* if RRT initiated on previous day but patient still got 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, anticoagulation and ultrafiltration that were prescribed. We recognize that delivered therapy may differ from prescribed therapy but you are only asked to record that which was prescribed.

    If RRT was administered, further indicate:

    - The duration it was prescribed for the study day in question; if CRRT was started, default duration is 24 hours. If SLED or IHD started, state duration prescribed in hours.
    - Anticoagulation; Specify type of anticoagulation used (IV heparin, regional citrate). If anticoagulation was not used, select None.
    - Ultrafiltration achieved during the RRT session, in mL.

**Vascular Access:**

- **Vascular access inserted on study day?**: Indicate Yes or No.
  - If yes, specify the Site and Side

**Form 11: RRT Initiation Data**

**Severity of Illness: SOFA Score 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.**

**Respiratory**

Select the *arterial* partial pressure of oxygen (PaO2) value that was last recorded prior to RRT initiation obtained from blood gas samples and the fractional inspired oxygen (FiO2) that was being administered at the same time. Calculate the quotient PaO2/FiO2 and select the appropriate category.

- In order to assign 3 or 4, the patient must be receiving invasive or non-invasive mechanical ventilation;
- If a patient’s PaO2/FiO2 is ≤ 200 but he/she is *not* receiving mechanical ventilation, the score is 2;
- In some cases, PaO2 may not have been obtained; in that case, choose the lowest oxygen saturation (SaO2) for the day and use the chart below to "translate" oxygen saturation (SaO2) into PaO2;
- in some cases, FiO2 may not have been recorded; as an alternative, use Appendix 1 to "translate" O2 flow rates through face mask or nasal cannula into an FiO2 value.

**Coagulation**

- The last platelet count prior to RRT initiation

**Liver**

- The last bilirubin 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

**Cardiovascular**

- Was patient on any norepinephrine or vasopressin at the time of RRT initiation?
  - If yes, determine dose at that time and patient will get a 3 or 4
  - Was patient just on phenylephrine? AUTOMATIC SCORE OF 3.
- Was patient just on dobutamine or milrinone and no other pressors or inotropes? AUTOMATIC SCORE of 2
- If no pressor or inotrope, look for MAP at the time of RRT initiation;
  - if MAP < 70 mmHg, then assign a score of 1;
  - if MAP ≥ 70 mmHg, then assign a score of 0

**CNS- Glasgow Coma Scale**

- If patient intubated, assign a “1” for verbal.
• DO NOT ACCOUNT FOR WHETHER PATIENT IS SEDATED OR RECEIVING PARALYTIC AGENTS. Patient’s score should be based on actual abilities.

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

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<td>None</td>
<td>1</td>
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<tr>
<td>Total</td>
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</tr>
</tbody>
</table>

**Renal**

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 based on whether the urine output or sCr places the patient in a higher (i.e., sicker) category.

**Physiologic Parameters at RRT Initiation:**

Please record the last available heart rate, systolic blood pressure, temperature, respiratory rate, and PaO₂/FiO₂ using the last available data prior to actual initiation of RRT.

- **Urine output in preceeding 24 hours:** 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.

- **Fluid balance up to time of RRT initiation:** Please record the cumulative fluid balance (if available) that is recorded on the ICU flow sheet for the day preceding the day RRT was initiated. For example,
if RRT initiation took place at 20:00 on March 8, record the cumulative balance value for the ICU run sheet that concluded on the morning of March 8.

**Laboratory Data at RRT Initiation:**

Please record results obtained closest to the time of RRT initiation.

**RRT initiation in the standard arm:**

- **For a subject in the Standard arm, was criteria for initiating RRT met?** For patients in the standard arm, this question aims to characterize the conditions under which RRT was 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 one of the conditions above being present. 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.

**Form 12: Adverse Event Data**

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 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 not study-related if they are related primarily to the underlying disease or to AKI and its sequelae.

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 either 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. Please see the protocol for more details on the definition of AEs and SAEs in STARRT-AKI.

AEs/SAEs will only be systematically collected for the first 14 days after randomization. Follow-up for outcomes of AEs/SAEs will take place until Day 90 following randomization.

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 (Fax: 416-864-3016; email: ChavdaN@smh.ca). 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.

The site research coordinator will notify the local ethics board (according to local requirements) about each local SAE. For participating sites using a central ethics board, sites will report as per the central ethics board requirements.

For each reported adverse event you will be asked to indicate the following:

- **AE type** (select ONE):
  - *RRT-associated hypotension*: defined as a drop in blood pressure requiring one of: initiation of a vasopressor during RRT session or need to escalate dose of a vasopressor during the RRT session or premature discontinuation of RRT session due to blood pressure drop.
  - *Severe hypophosphatemia*: defined as serum phosphorus < 0.5 mmol/L on routine morning ICU blood work.
  - *Severe hypokalemia*: defined as serum potassium < 3.0 mmol/L on routine morning ICU blood work.
- **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 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 CVC:** defined as any confirmed occlusive or non-occlusive thrombus in the vein in which a CVC was placed (or remains in place) or in the venous system drained by the vein in which the CVC was placed; further qualified by embolism as a result of thrombus.

- **Pneumothorax following 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 CVC insertion; further qualified by requirement for chest tube placement.
Hemothorax following 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.

Inadvertent arterial puncture at time of CVC insertion

Other, specify

- Event onset date
- Event stop date (or indicate if AE is still ongoing at 90 days post-randomization)
- Was event possibly or probably related to study procedures? The answer to this question should always be “Yes”, otherwise the AE/SAE should not be reported.
- Was event classified as a serious adverse event (SAE)? If yes, indicate the category of SAE and check all that apply.
- Describe the AE or SAE - include and relevant tests/lab data, actions taken, and resolution of the event.
- SAE Resolution: Specify if the event Recovered, Recovered to previous baseline, Significant impairment, Death, or Other.

Form 13: Protocol Violations

THE ONLY PROTOCOL VIOLATIONS COLLECTED IN THE eCRF FOR THIS STUDY ARE WITH REGARD TO THE INITIATION OF RRT OUTSIDE OF THE SPECIFIED TIME INTERVALS MANDATED BY THE STARRT-AKI PROTOCOL. All other protocol deviations and violations will be captured in the Protocol Deviation Log.

For patients randomized to the accelerated RRT initiation arm, indicate why RRT was not started within 12 hours of fulfilling full eligibility.

For patients randomized to the standard RRT initiation arm, indicate why RRT was started within 12 hours of fulfilling full eligibility.

Form 14: ICU and Hospital Discharge Data

ICU DISCHARGE/DEATH:

- Alive at ICU Discharge: 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 (i.e., 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 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”.

- Disposition at time of ICU discharge. 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 admissions and discharges are not considered.

- **RRT administered (≥ 1 session) in 7 days following ICU Discharge?** If alive at ICU discharge, indicate if patient received additional RRT in the 7 days following ICU discharge.
- **ICU readmission during the index hospitalization.** 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 hospital.

**HOSPITAL DISCHARGE/DEATH:**

- **Date of last RRT in hospital:** Indicate the date of the last RRT session prior to hospital discharge but within the 90-day follow-up window OR indicate that no RRT was administered.
- **Last serum creatinine recorded in the hospital:** Indicate the last available sCr prior to hospital discharge but within the 90-day follow-up window.
- **Date of last serum creatinine recorded in the hospital:** 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.
- **Alive at Hospital Discharge:** If patient is 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 (i.e., by 90 days) then indicate ‘N/A still in hospital at Day 90.’
- **Plan for further RRT at the time of hospital discharge?** Indicate Yes or No.

**Form 15: Resource Utilization Through Day 28**

Data on this form includes all resource utilization, even if these took place during multiple ICU stays or multiple hospitalizations.

- **Total number 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.
- **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.
- **Number of days of mechanical ventilation:** An “mechanical ventilation day” is defined as any day on which the participant received ≥ 2 hours of invasive mechanical ventilation; time on CPAP and BiPAP not considered.
- **Number of days of vasoactive therapy:** An “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.
- **Was patient re-admitted to hospital following discharge from their index hospitalization?** If yes, record all hospital re-admissions from the date of index hospitalization discharge through Day 28.
patient is still in the hospital (i.e., not discharged from index hospitalization), indicate ‘N/A, not discharged from index hospitalization by Day 28’.

Form 16: Day 90 Outcomes Data

Vital Status Data at 90 Days:

- **How was 90 day vital status obtained?** Indicate the source of information. If not obtained, provide an explanation.

- **Vital status at 90 days following randomization:** Indicate if patient is Alive or Deceased. If patient is alive, provide disposition at day 90. If deceased, complete the Death form (Form 17).

Kidney Function at 90 Days:

- **Requirement for RRT at 90 days following randomization?** Indicate “Yes” if patient is receiving RRT at 90 days, regardless of whether or not it was withdrawn for some portion of the 90 day follow-up period. Indicate “No” if the patient is not receiving RRT at 90 days, even if RRT was never initiated (i.e., for patients in the standard arm who recover kidney function prior to receiving any therapy). Indicate “Not available/unknown” if patient is deceased at 90 days following randomization or this information is not known. Indicate Not Applicable, if RRT was never initiated.

- **Date of last RRT session prior to or on Day 90.** Indicate the date of the last dialysis session during the 90 days following randomization. Indicate ‘N/A, no RRT’ if RRT was never initiated.

- **Date blood sample collected:** Ask for blood sample collection as close as possible to day 90 but there is a flexible window for this. Blood 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.

- **Day 90 serum creatinine:** Indicate the serum creatinine result obtained between 76 days and 132 days from randomization. Indicate N/A if data is not available.

- **Day 90 urine sample collected:** 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.

- **Day 90 eGFR:** Indicate eGFR result obtained within the window (see above).

- **Day 90 albumin:creatinine ratio**

Hospital Re-Admissions (Day 29 to Day 90):

- **Was patient re-admitted to hospital between Day 29 and Day 90?** Indicate ‘Yes’ if patient was hospitalized between Days 29 to 90 following randomization and record all hospital re-admissions from Day 29-Day 90. If patient was not discharged from prior hospitalization, indicate ‘N/A, not discharged from prior hospitalization by day 90’. If this information is not known, indicate ‘Not available/Unknown.’

Health-related Quality of Life Assessment (HRQoL):

Indicate whether it was possible to administer the EQ-5D (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).
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.

**Chronic Frailty Scale (CFS) Score:**
Select the most appropriate option.

**Form 17: Death**
- **Death of Death:** Indicate the date of death.
- **Cause of Death:** Select one category and one cause only.

**Form 18: Retrospective Amendment of Eligibility**
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.

- **Date site 1st became aware of change in eligibility:** Indicate the date site became aware of the change in patient’s eligibility criteria.
- **Inclusion Criteria:** Check all that apply.
- **Exclusion Criteria:** Check all that apply.

**Form 19: Study Termination/Early Discontinuation**
- **Did the patient complete the full study to 90 days?** If yes, indicate the date of Study Completion (day 90 date or date of death). If No, indicate the date of Early Discontinuation and specify reason patient did not complete the study (Day 90 or Death).
- 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? Indicate ‘Yes’, ‘No’ or ‘Not Applicable’ if site is not participating in optional sub-study.

Form 20: Day 365 Outcomes Data
This is an optional sub-study. Data may be collected by calling the patients or by linking to government (i.e., provincial or state) registries. For data linkages, collection of a unique personal health number information will be required.
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

<table>
<thead>
<tr>
<th>Total urine output over 2 hours</th>
<th>Sensitivity</th>
<th>Combined cohort</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100 ml</td>
<td>90.2%</td>
<td></td>
<td>60.0%</td>
</tr>
<tr>
<td>&lt;200 ml</td>
<td>87.1%</td>
<td></td>
<td>84.1%</td>
</tr>
<tr>
<td>&lt;300 ml</td>
<td>85.3%</td>
<td></td>
<td>88.0%</td>
</tr>
<tr>
<td>&lt;400 ml</td>
<td>66.7%</td>
<td></td>
<td>88.0%</td>
</tr>
<tr>
<td>&lt;500 ml</td>
<td>50.5%</td>
<td></td>
<td>88.0%</td>
</tr>
</tbody>
</table>

### References

B: Aid To Capacity Evaluation (ACE)

PATIENT Modified Aid to Capacity Evaluation Screening Tool

Is the patient able to communicate?  

Yes □ 

No □ 

Does the patient understand his/her current medical condition?  

Why are you in hospital?  
What problem are you having right now?  

No □ 

Yes □ 

Does the patient understand the purpose of the research study?  

What is the research for?  
Why are you being asked to participate?  

No □ 

Yes □ 

Does the patient understand the option of declining to participate (with no impact on medical care)?  

Could you refuse to participate?  
Would this affect your medical care?  

No □ 

Yes □ 

Does the patient understand the risks of participating?  

What could happen to you if you participate?  
Could the research cause side effects?  

No □ 

Yes □ 

Does the patient have the ability to make a decision that is not substantially based upon hallucinations, delusions, or cognitive signs of depression?  

Why have you decided to accept/refuse to participate?  
Do you think we are trying to harm you?  

No □ 

Yes □ 

Patient demonstrates capacity (do not proceed to consent process)  

Patient does NOT demonstrate capacity (proceed to consent process)
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 reponse 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 eligibilie 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. Pleaes refer to Data Entry Guideliens 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 prescipriton and contact information for the Coordinating Centre as well as the Principal Investigaotrs.