Data Safety Monitoring Board (DSMB) Charter

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

Principal Investigators (PIs):

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

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

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

DSMB Members Signature Page

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

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

DSMB Members:

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

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

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

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

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

Principal Investigators:

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

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

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Introduction

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

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

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

Protocol Overview

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

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

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

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

Interventions

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

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

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

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

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

Outcomes

Primary outcome:

1- All-cause mortality at 90 days.

Secondary outcomes:

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

Implications:

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

DSMB Aims and Roles

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

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

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

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

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

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

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

Serious Adverse Events

1. Definition

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

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

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

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

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

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

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

2. Procedures for Reporting a SAE

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

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

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

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

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

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

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

Membership

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

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

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

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

Quorum

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

Meeting Format

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

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

After each meeting, the DSMB will recommend whether to:

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

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

The DSMB will follow these guidelines in formulating a recommendation:

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

Stopping Rules

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

Payments

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

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

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

Reports

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

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

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

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

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

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

Confidentiality

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

Archiving of DSMB Activities and Related Documents

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