The Canadian **DONATION** and **TRANSPLANTATION** Research Program
Programme de recherche en **DON** et **TRANSPLANTATION** du Canada

CDTRP Data and Safety Monitoring Board (DSMB) Terms of Reference

Version 4
November 1rst 2022

1.0 Background:

1.1 The DSMB is responsible for the safeguarding the interests of individuals participating in CDTRP and approved related trials. This responsibility will be implemented by providing recommendations for continuation or early termination of CDTRP supported trials based on assessment of safety. The DSMB may also make recommendations related to the selection, recruitment or retention of participants, their management and adherence to protocol-specific regimens, and the procedures for data management and quality control.

1.2 The DSMB is an independent board appointed by the CDTRP Research Services platform Lead and approved by the CDTRP Executive. It meets semi-annually (June & October) or more often if necessary.

1.3 The principal role of the DSMB is to regularly monitor CDTRP supported clinical trials, review and assess the performance of its operations, and make recommendations, as appropriate, to the study sponsor or sponsor/principal investigator with respect to:

- Benefits/risks ratio of procedures and the burden under which the study participants are placed
- Completeness, quality, and analysis of measurements that are made
- Performance of individual centers participating on a trial (including possible recommendations on actions to be taken regarding any center that performs unsatisfactorily)
- Interim results of the study for evidence of efficacy or adverse effects
- Possible early termination of the study because of:
  - early attainment of study objectives,
  - safety concerns (if applicable), or
  - inadequate performance
- Desirability of proceeding to the full-scale trial at the completion of the feasibility phase, when applicable
- Possible modifications/amendments to the study protocol
- Forwarding DSMB recommendations to other parties

2.0 Membership of the DSMB:

The DSMB is composed of a Chair and members with expertise in biostatistics, clinical trials, bioethics, and the specific research area(s). It is expected that consultants or ad-hoc members may be added to the DSMB for any given trial to provide greater representation of expertise in the relevant scientific field specific to that trial. All standing members of a DSMB may vote. Consultants for a given protocol have the same voting rights as an official DSMB member when reviewing the specific protocol.

2.1 DSMB will be chaired by the DSMB Chair, and will include at least 5 members, appointed by the CDTRP Executive Committee.

2.2 The membership of the DSMB will meet the following criteria:

a. have a minimum membership, including an independent statistician, solid organ transplant physician, hematopoietic stem cell transplant physician, ethicist, patient advocate (layperson), and a pediatric representative.
b. additional members will be appointed for a specific study monitoring as needed.

Members of the DSMB will include the following individuals listed in Appendix A:

3.0 DSMB Meetings

3.1 The DSMB will meet at least twice a year – either in person or through video-assisted conference call – organized by the DSMB Coordinator.

3.2 CDTRP Research Services Platform Lead and the Study Investigators may participate to the meetings for information purposes but will be recused from DSMB discussions and decisions.

3.2.1 Any unmasking of data for safety monitoring will be done in a fashion to ensure that the investigators do not see the interim data.

3.3 CDTRP Program coordinator serves as the Coordinator for the CDTRP DSMB and is responsible for scheduling calls and meetings and maintaining meeting minutes.

4.0 DSMB activities and responsibilities

4.1 Prior to study opening: The DSMB will review completed protocols to assess that the monitoring plan ensures patient safety and research integrity. It will assess the ease of protocol comprehension in a multi-institutional setting, ability to proceed through institutional IRBs as written, and the data collection methodology including quality control measurements for ability to answer the primary objectives and to avoid overburden to institution's data managers, as applicable. Consent and assent forms will be reviewed

4.2 Once a study is open the protocol monitoring shall be facilitated at least twice annually (generally by conference calls) by submission of data summaries from the study Principal Investigator to the CDTRP DSMB coordinator. It is the study Principal Investigator's responsibility to assure submission of updated and accurate data. Failure to submit data on time may result in temporary suspension of active DSMB support of the study, with a notification letter sent to the sponsor REB advising of withdrawal of services. This data summary will be reviewed by the DSMB to ensure that the protocol does not have undue toxicity and poor outcomes. These will be adjudicated in great part by the stopping rules present in all studies. Accrual to the protocol will also be reviewed. Studies that are accruing poorly may be recommended to be placed into probationary status or closed.

4.3 Ad hoc safety reviews: The Chair of the DSMB may call ad hoc meetings of the DSMB, as needed.

4.4 Serious Adverse Events (SAEs) that are both related to the study and unexpected (i.e. not mentioned in the Investigator Brochure, product label or consent document) will be reported in a timely fashion to the CDTRP DSMB Coordinator by the study Principal Investigator, as outlined in the protocol and generally within 7 days of receipt of notification. Those will be forwarded to the DMSB Chair.

Note: SAEs that are both related to the study and unexpected (i.e. not mentioned in the Investigator Brochure, product label or consent document) must also be communicated in an expedited fashion to all sites and respective REBs, the study sponsor and relevant regulatory authorities – in compliance with Health Canada Division 5 regulation (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_68_tc-tm-eng.php). These entities have the authority to close of suspend trial enrolment. These entities may also terminate trial interventions for previously enrolled patients.

4.5 The DSMB may make recommendations to protect the safety of study participants at anytime.

4.6 The DSMB may also recommend termination of the trial if it appears that the trial cannot be concluded successfully.

4.7 Any closure of the protocol by the REB/IRB in any of the institutions must be reported to the CDTRP DSMB coordinator who will share with the DSMB Chair.

5.0 Process of study monitoring

5.1 The DSMB coordinator will ensure the preparation of open and closed reports, minutes, and recommendations at least one week before each regularly scheduled DSMB meeting.

- 5.1.1 Open reports will include overall study progress and safety data. Open reports will be made available to DSMB members, the clinical trial Investigators and project coordinators for the studies.
- 5.1.2 Closed reports will include study progress and safety data as described below in Section 6, aggregated by coded study arm. Closed reports may include other safety-related information requested by DSMB members. Closed reports will be made available only to DSMB members. In closed reports, data coded by study arm will be reviewed initially without disclosing the study drug/treatment assignment for the two arms. By majority vote of DSMB members participating in any given meeting, the study statistician may disclose the study drug assignments for the two arms as needed for monitoring the integrity and safety of the trial. Minutes will be circulated only to DSMB members.

5.2 DSMB members must be independent from the sponsor, members of the study team, REB, regulatory agencies, steering committee, and advisory board, and may not participate in the clinical care of participants in any capacity related to study operations. DSMB members must recuse themselves from receiving study progress reports and discussion related to any study in which they have a real or perceived scientific, financial, professional, personal, proprietary, or other conflict of interest related to the conduct, outcome, or impact.

5.3 At the conclusion of each DSMB meeting, the members will determine whether any changes in conduct of a trial are recommended. The DSMB chair will forward these recommendations to the study principal investigator.

5.4 Study progress reports are to include:

Study progress

a. Study Accrual (by centre)
   i. Number of patients registered (eligible and ineligible)
   ii. Total discontinuations of study participation because of patient or physician preference
b. Study data submission compliance
c. Proposal for study amendment if necessary

Safety data

a. Number of deaths, listed by cause
b. Survival presented as a Kaplan-Meier survival curve for studies that have enrolled at least 10 patients
c. SAE (summary table) based on predefined categories, peak severity
d. Number of cases where administration or use of the investigational product was permanently discontinued because of toxicity
e. Suspected unexpected serious adverse reactions (SUSAR):

Brief narrative for each new SUSAR that was not discussed at the previous DSMB meeting with the PI and local investigator adjudication of causality (related/unrelated)

A SUSAR is any unexpected adverse reaction (UAR) that at any dose:

I. results in death;
II. is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
III. requires hospitalisation or prolongation of existing hospitalisation;
IV. results in persistent or significant disability or incapacity;

f. Other safety data, as required by the protocol

5.5 Statistical monitoring guidelines

Monitoring plan will be part of all statistical plans for trials and the DSMB will review protocols at these time points.

5.6 Intent of the formal monitoring procedure is to provide an objective, pre-specified point of reference for the DSMB in its evaluation of trial safety. The DSMB can and should use all available evidence and its expert judgment in deciding whether to recommend continuation of the study.

References:
Jay Herson. Data and Safety Monitoring Committees in Clinical Trials. Chapman and Hall/CRC Biostatistics Series. Francis &Taylor Group LLC, 2009.
Pediatric Blood and Marrow Transplant Consortium Data and Safety Monitoring Committee (DSMC) Charter, December 2015

6.0 Evaluation of new studies

6.1 When a request for a new study to enter the DSMB is received, the DSMB coordinator will send the request form and the study protocol to all DSMB members for comments and concerns. A minimum of 3 yes from the members is needed to accept the new study.

Appendix A

DSMB Members (Voting)

Chair, BMT	Paul Martin, MD - Chair Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North Seattle, WA 98109 Ph: (206) 667-5000 pmartin@fhcrc.org
Vice-chair, Solid Organ Transplant	Anthony Jevnikar, MD London Health Sciences Centre University Hospital 339 Windermere Rd, London, ON N6A 5A5 Ph: (519) 661-2111, Ext 33688 jevnikar@uwo.ca
Heart transplant/interventional cardiology	Simon Urschel, MD University of Alberta / Stollery 4C2.32, Walter McKenzie Center 8440 - 112 Street Edmonton, AB, T6G 2B7 Ph: (780) 407-8361 urschel@ualberta.ca
Pediatrics, Solid Organ, Ethics	Aviva Goldberg, MD Pediatric Nephrololgy University of Manitoba Ph: (204) 787-4947 agoldberg@hsc.mb.ca
Legal expert	Blake Murdoch, JD, MBA CDTRP Core 1 466 Law Centre (111 St. and 89 Ave.) Faculty of Law, University of Alberta Edmonton, AB, T6G 2H5, Ph: 780-264-3786 bmurdoch@ualberta.ca
Adult, Nephrology, Ethics	Ramesh Prasad, MD St. Michael's Hospital 30 Bond Street Toronto, ON, M5B 1W8 Ph: (416) 867-3722

	prasadr@smh.ca
Biostatistician	Tony Panzarella, MSc, PStat Program Director, MSc in Biostatistics, Dalla Lana School of Public Health, University of Toronto Ph: 416-978-8979 tony.panzarella@utoronto.ca
Patient representative	Vacant

Ex Officio (Non-Voting)
Patricia Gongal, Ph.D.
CDTRP Executive Director
University of Alberta
6-002 Li Ka Shing Centre for Health Research
Edmonton, Alberta
Canada T6G 2E1
pgongal@cdtrp.ca

DSMB Coordinator
Julie Turgeon, Ph.D.
CDTRP Program Coordinator
CRCHUM, Tour Viger- R12.414
900 rue St-Denis
H2X 0A9, Montréal (Qc)
Ph : (514) 890-8000 ext. 31627
julie.turgeon.chum@ssss.gouv.qc.ca