Data and Safety Monitoring Board (DSMB) Charter

Protocol	Strategy for Patient Orientation Research (SPOR) Innovative Clinical Trials Multi-Year Grant
Nominated Principal Investigator:	Dr. Terry Klassen
Protocol title:	Innovation in Pediatric Trials (iPCT) Initiative
Sponsor:	CIHR - SPOR
DSMB Charter version:	3.5
DSMB Charter date:	January 18, 2019

1. Introduction

The purpose of this charter is to define the responsibilities of the SPOR Innovation in Pediatric Clinical Trials (iPCT) initiative's Data Safety Monitoring Board (DSMB), detail membership requirements, describe the data to be reviewed, delineate the meeting process, and outline the considerations and policies of the DSMB. The DSMB will act in an independent expert advisory capacity to monitor participant safety. The DSMB may wish to review this Charter at regular intervals to determine whether any changes are needed.

2. Organization and interactions

a. Membership of the DSMB

The DSMB consists of a Chair and 4-6 members with expertise in relevant (clinical) specialties for the study, including members who are knowledgeable about statistical methods for clinical research and analysis of research data. Other members should bring expertise in the clinical specialty the studies are conducted in (pediatric emergency medicine).

The DSMB Chair must be willing to make firm commitment to participate as Chair for the duration of the project.

The DSMB members are appointed by the Network Coordination Centre (NCC) Lead in consultation with the DSMB Chair and must meet the following requirements:

- Be willing to serve as a DSMB member for the duration of the project;
- Comply with the conflict of interest policy specified in this charter;

Although DSMB members are expected to serve for the full duration, in the unlikely event that a member is unable to continue participation, the reason will be documented, and a replacement member will be selected by the DSMB Chair. The new member must have comparable expertise and qualifications to the DSMB member she/he is replacing.

A list of members are mentioned in Appendix A.

b. Conflict of Interest

The DSMB must consist of individuals who are impartial, independent of the investigator(s) and who have no financial or scientific interest in the study that could impair the members' ability to objectively review study data as outlined below:

- DSMB members must not have any real or perceived scientific, financial, professional, personal, proprietary, or another conflict of interest related to the conduct, outcome, or impact of the study. DSMB members should preferably not be working at any of the participating sites.
- DSMB members must not be engaged in any simultaneously occurring competitive studies in any role that could pose a conflict of interest. DSMB members must also identify and disclose any concurrent service on other DSMBs of the same, related, or competing products;
- DSMB members must be independent of the sponsor, regulatory agencies, principal investigators, clinical care of the study participants, or any other capacity related to study operations. All DMSB members must disclose all possible conflicts of interest in writing before beginning service as a DSMB member.

c. Confidentiality

All materials, discussions, and proceedings of the DSMB are privileged and confidential. DSMB members agree to use this information exclusively to accomplish the responsibilities of the DSMB. No communication of the deliberations or recommendations of the DSMB, either written or oral, may occur except as required for the DSMB to fulfill its responsibilities. Individual DSMB members are expected to maintain confidentiality regarding the study outside the DSMB (including, but not limited to the investigators, REB, regulatory agencies, or sponsor) except as authorized by the DSMB.

If requested, this charter and accompanying list of Board members may be sent to a Research Ethics Board (REB). In the case, this charter will be marked as not for dissemination, and be sent by the Study Principal Investigator or the Network Manager to the REB Chair, with a cover letter. The SPOR - iPCT iniative does not release Board members' names in response to media inquiries until after publication of the main results of the study.

3. DSMB Responsibilities

The DSMB is responsible for safeguarding the interests of individuals participating in iPCT and approved related trials.

This responsibility will be implemented by providing recommendations for continuation or early termination of iPCT trials based on an 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.

The DSMB is advisory to the Study Principal Investigators and ultimately the iPCT Steering Committee. The DSMB is an independent board appointed by the NCC Lead and approved by the SPOR - iPCT Executive team.

The DSMB's responsibilities are to regularly monitor iPCT clinical trials, review and assess the performance of its operations, and make recommendations, as appropriate, to the Study Principal Investigator and, through the NCC lead, to the iPCT Steering Committee concerning:

- Protection of the safety and interests of the study participants;
- Review of the research protocol, informed consent documents, and plans for data safety and monitoring before initiation of study, - if needed - periodically during the study, and at the conclusion of the study;
- Conduct interim and final evaluation of the study, including safety data, participant recruitment, accrual and retention, risk versus benefit, and other factors that can affect study outcome, including aggregate and individual participant data related to safety.
- Review and evaluation of *ad hoc* safety issues concerning the study at the request of the Study Principal Investigator.
- Continuation, termination, or other modifications of the study based on the performance and observed beneficial or adverse effects of the study; and
- Amendments to the study protocol and consent forms, including whether any new data from other sources affect the equipoise of the study being monitored
- Operation according to the procedures described in this charter and all procedures of the DSMB.

4. DSMB Tasks

a. Before study opening

The DSMB will review completed protocols to assess that the monitoring plan ensures patient safety and research integrity. Consent and assent forms will be reviewed.

b. During the study

Once a study is open the protocol monitoring shall be facilitated at least semiannually (generally by conference calls) by submission of data summaries from the Data Coordinating Centre regarding each study to the Network Manager who sends these data summaries and available site monitoring reports to the DSMB Chair for preparation of the DSMB Report.

The primary responsibility of the DSMB is to monitor the study for participant safety. The DSMB will review the following safety and related data:

- Participant recruitment, accrual, retention, and withdrawal information;
- Adverse events (AEs) and serious adverse events (SAEs);
  - Tabulated by body system, intensity, seriousness, duration, treatment given, and the relationship to the study drug and study procedure
  - Comparison of events that occur between treatment arms
  - Individual events of particular concern
- Site monitoring reports;
- Any other safety-supporting data requested by the DSMB.

The DSMB will make a recommendation regarding the study continuation, termination, or modifications based on the review. Studies that are accruing poorly may be recommended to be placed into probationary status or closed.

Serious adverse events (SAEs) will be monitored by the DSMB Chair and must be reported by the Sponsor to the DSMB Chair via email **within seven working days** of learning of the event.

All participant withdrawals will be monitored by the DSMB Chair and must be reported by the Sponsor to the DSMB Chair via email **within two weeks** of learning of the withdrawal.

The DSMB may consider data from other studies or external sources during its deliberations, if available, as these results may have a profound impact on the status of the participants and design of the current study.

5. Meetings

a. Projected Schedule of Meetings

An initial meeting of the DSMB will be held before the start of the studies or as soon after that as possible for the members to:

- review the charter;
- receive an overview of study network activities;
- form an understanding of the protocol and definitions being used;
- establish a distribution and meeting schedule;
- review the study modification and termination guidelines; and

Subsequent DSMB meetings will be held to review and discuss study data according to the schedule as described in the table below.

Timeline	***Data Review by***
Biannually	Entire DSMB
Ad hoc (SAE)	Entire DSMB

b. *Ad Hoc* Meetings

An *ad hoc* meeting of the DSMB may be called at any time by the DSMB Chair or Study Principle Investigator if imminent participant safety issues arise. If a significant safety concern arises during the study, the DSMB Chair may convene a meeting to review safety and any other aspect of the study. Significant safety events may include, but are not limited to, the following:

- A death or life-threatening condition sustained by a participant, regardless of causality;
- An unexpected serious safety issue newly identified during the development program that could expose participants to unnecessary risks;
- Any other concern regarding participant safety raised by any DSMB member.

Proposed study amendments that significantly alter the treatment plan and deal with participant safety concerns will prompt an ad hoc meeting of the DSMB for review before implementation of changes. This may require suspension of enrollment pending DSMB review.

c. Meeting Format

DSMB meetings will be conducted by teleconference and facilitated by the DSMB Chair, consisting of an open session and a closed session. A quorum, defined as **four members of the DSMB including the DSMB Chair must be present to hold a DSMB meeting**.

Open Session

The open session may be attended by the investigator(s) and representatives of the Sponsor. Investigator and sponsor representatives may attend the open session with DSMB members. The Data Coordinating Centre provides a report for each study, containing: recruitment updates, compliance, withdrawals and other blinded data and non-confidential information regarding operational/logistical issues. This session gives the DSMB an opportunity to query an investigator about issues that have arisen during the review of safety data. Unblinded information will not be discussed in the open session.

Closed Session (if needed)

The closed session will be restricted to attendance by the DSMB members, and a recorder (NCC administrator) for the review of an interim analysis, prepared by the Methods Core.

At the closed session, study blinding may be broken. Closed sessions also consist of a review of the recommendations the DSMB wishes to make to the investigator and a formal vote.

d. Voting

DSMB recommendations will be agreed upon by formal majority vote. In the event of a split vote, the DSMB Chair will cast the deciding vote.

6. DSMB Considerations and policies

a. Stopping Rules

After considering the information in the open and closed session DSMB report, the DSMB will determine whether the study should continue as planned, proceed with modifications, or be terminated. The justification to terminate the study may be due to the DSMB's analysis that there are overwhelming safety issues. If the DSMB votes to terminate the study, the Network Manager will prepare a final study report for the DSMB, and a final DSMB meeting will be held. The DSMB's recommendations at the final DSMB meeting may include continuing action items to the investigator based on the final review.

b. Meeting Minutes

Minutes of DSMB meetings will be kept in two parts: open session and closed session.

Open Session

Open session meeting minutes include (at a minimum):

- Protocol number, study title, version;
- DSMB meeting date;
- Copy of the open session agenda;
- A list of attendees, including DSMB members and any others present, listing their professional title and role at the meeting;
- A list of attendees who have been unblinded to any data;
- Information reviewed and related discussion during the open session, including rationale for recommendations provided by voting DSMB members;
- A copy of the DSMB recommendation letter.

The DSMB Recorder is responsible for recording and generating meeting minutes of both open and closed sessions.

Draft minutes of open sessions will be sent to the DSMB Chair for review and approval within three working days of the meeting. The draft minutes will be reviewed by the DSMB Chair within seven working days, and final minutes of the open session will be distributed to the DSMB

members and the investigator within ten working days of the DSMB meeting. Final minutes will be distributed to DSMB members by PDF version sent by secure email.

Closed Session

Draft minutes of closed sessions will be sent to the DSMB Chair for review and approval within one working day of the DSMB meeting. The draft minutes will be reviewed by the DSMB Chair within three working days, and final minutes of the closed session will be distributed only to the DSMB members within five working days of the DSMB meeting. Final minutes will be distributed to DSMB members by PDF version sent by secure email.

Closed session meeting minutes will not be divulged beyond the DSMB until after the study is closed unless either:

- The DSMB voting members approve the release to preserve the integrity of the study and the safety of participants; or
- Health Canada –Therapeutic Product Directorate requires disclosure.

The investigator, Network Manager and sponsor will receive a complete copy of the open and closed session meeting minutes at the completion of the study.

7. Report to DSMB

a. Responsibility for Preparing DSMB Data Reports (open session)

The report is prepared by the DCC, and sent to the DSMB Chair three weeks before the planned meeting.

b. Responsibility for Preparing DSMB Interim analysis (closed session)

The report is prepared by the Methods Core, and sent to the DSMB Chair three weeks before the meeting.

a. Content of the Reports to the DSMB

The DSMB chair will prepare the report to include two DSMB parts – open session and (if available) closed session.

- *Open Session Report*: The open session report presents data only in aggregate and focuses on study conduct issues, like accrual and withdrawal rates, eligibility rates, reasons for ineligibility and discussion of blinded materials. To protect the blind participant-specific data and treatment group data are not presented in the open session report.
- *Closed Session Report*: In the event of serious adverse events or significant protocol violations, the DSMB may bequest closed session reports that include unblinded comparative statistical outputs.The closed session reports include unblinded comparative

statistical outputs. The closed session report is considered confidential and must be destroyed at the conclusion of the meeting.

b. Distribution of the Report to the DSMB

Reports to the DSMB are distributed to DSMB members two weeks before a scheduled meeting. The report is dated and provided to individual DSMB members in PDF format sent by secure email.

c. DSMB Reports to Investigator

Following each meeting, the DSMB will issue a confidential report separate from the minutes of the open and closed sessions that will be sent to the investigator. The report includes a summary of the open session discussion, does not include unblinded data or discussion of the unblinded data, and provides the DSMB's recommendations accompanied by clear, concise rationale for them. The report should contain sufficient information to explain the rationale for any specific actions by the DSMB without jeopardizing conduct or scientific integrity of the study (unblinding). If no recommendations are made, the report may simply state, "The DSMB recommends that the study continues as planned."

The report should be presented to the investigator both in writing and orally. The DSMB Chair communicates directly with the investigator to allow them the opportunity to ask questions and discuss any recommendations. If the report does include DSMB recommendations for changes or termination of the study, the report must include a minimum amount of data such that the investigator can make a reasoned decision in response to the recommendation.

If the investigator accepts the recommendations of the DSMB, the investigator will be responsible for implementing the actions in response. In the event the study must be amended, the investigator will prepare and submit the amendment to the DSMB and REB for approval before implementing amendment changes.

If the investigator rejects the DSMB's recommendations, the investigator must provide the DSMB with a written explanation of their decision and supporting rationale within one working day. If the DSMB has recommended that the study is stopped, but the investigator decides to continue the study, the investigator will inform all concerned regulatory authorities of its decision to continue the study despite the DSMB's recommendation. Public disclosure of the decision to stop the study is at the discretion of the investigator. The DSMB will not make any public announcements.

8. Other

a. Amendments to the DSMB Charter

This DSMB charter can be amended as needed during the study. All amendments will be documented with sequential version numbers and revision dates and will be recorded in the open session DSMB meeting minutes. Each revision will be reviewed and agreed upon by the DSMB.

b. Archiving

All DSMB documentation and records will be retained in sealed envelopes in the Sponsor Study File by the National Coordinating Centre for 25 years after completion of the study. Access to archived data will be controlled by the sponsor, which will release the information only as specified in this charter or as required by law.

Appendix A – DSMB members

Voting members

Member name	*Conflicts of interest*
Garth Meckler (chair)	
Mark Roback	
Anupam Kharbanda	
Eyal Cohen	
Lise Nigrovic	

Ex-officio (non-voting)

NCC Lead: Dr. Geert W. 't Jong

Network Manager: Tannis Erickson

Appendix B – Definitions

Study Principal Investigator: The investigator who is primarily responsible for a trial.

SPOR Principal Investigator: The investigator designated as Primary Investigator on the SPOR application (Dr. Klassen).

iPCT Steering Committee: Executive committee consisting of the study leads (PIs) and the leads within each core (Network Coordinating Centre; Data Coordinating Centre; Methods Core)