



Canadian Cancer Trials Group (CCTG)

Policies for the Data Safety Monitoring Committee

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1 Policy Description

The Canadian Cancer Trials Group (CCTG) has a single Data Safety Monitoring Committee (DSMC) that is advisory to the CCTG Director. Every clinical trial conducted by the CCTG must include a plan for data and safety monitoring as part of the protocol:

1. All phase III trials led by CCTG are overseen by the DSMC.
2. Phase II trials meeting the following criteria are overseen by the DSMC:
 - Single arm trials with a sample size of 100 patients or more
 - Randomized trials with sample size of 80 patients or more
 - Trials that include blinded therapy
3. Intergroup trials in which the CCTG participates, but are led by another cooperative group, are expected to include a DSMC. In the unusual circumstance in which another cooperative group conducts a trial that is not overseen by a DSMC, a role of the CCTG DSMC is considered.
4. IND Program trials that do not meet criteria for DSMC review are reviewed by a process outlined in SOP: TMG-SOP-0158. The IND Program may request DSMC review for IND trials that do not meet criteria for DSMC review and that have unique trial-related issues requiring independent DSMC review.

The DSMC's procedures are in accordance with the US National Institutes of Health (NIH) and the National Cancer Institute (NCI) as the Canadian Collaborating Clinical Trials Network (CCCTN) within the National Clinical Trials Network (NCTN) in addition to national regulations and guidelines in Canada.

2 Introduction and Scope

The importance and complexity of safely and rigorously conducting randomized controlled trials necessitates the need for independent Data and Safety Monitoring Committees. The concept for these committees, known by a variety of names that account for their roles and membership, was first developed in the 1960s¹. Since that time, considerable literature about their purpose, function and accountability has been generated^{2,5}. In general, accepted broad mandates include ensuring that the safety of patients / subjects enrolled onto trials is protected, that integrity of trial data and analysis is preserved given the potential importance of trial results to future patients, and that trial feasibility issues are appropriately monitored given the scarcity of research funding and the opportunity cost involved with every trial²⁻⁵. The purpose of this document is to provide a description of CCTG's DSMC, including its scope, accountability, and operational components. This document takes into account principles gleaned from DSMC literature, including a comprehensive document developed by the Data Monitoring Committees: Lessons, Ethics and Statistics Study Group (DAMOCLES)^{2,5}

The content of this document is also compliant with Health Canada's principles and requirements of International Conference on Harmonization Good Clinical Practice guidelines⁶, and the requirements of the NCI US^{7,8} and Cancer Therapy Evaluation Program (CTEP)⁹ that apply across cancer cooperative groups in the United States and Canada funded by the NCI US.

The broad responsibilities of CCTG's DSMC are to assist in protecting the safety of trial participants and to facilitate meeting CCTG's mission which is "to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer with the ultimate goal of reducing morbidity and mortality from this disease". To meet this mission, the DSMC must assist in ensuring that the results of trials are valid and credible and that the continued conduct of a given trial is consistent with this mission.

3 Definitions

3.1 Terms

Data Safety Monitoring Committee

CCTG has a single DSMC that is advisory to the Director. The DSMC is responsible for assessing, at intervals, the progress of a clinical trial, safety data, and critical efficacy endpoints, and to recommend to the Director whether to continue, modify, or stop a trial. The DSMC is comprised of individuals who are both members and non-members of the CCTG; these individuals are to be independent from those CCTG members responsible for carrying out the trials under consideration, including the faculty and staff of the CCTG Operations and Statistical Centre (OSC) in Kingston.

Clinical Trials Committee

The Clinical Trials Committee (CTC) is responsible for advising the Director on all substantial issues related to CCTG's scientific agenda, including its policies and clinical trials, and is responsible for approving and prioritizing the initiation of individual trials. In this capacity, the CTC may be responsible for receiving the written DSMC summary minutes and deliberating on the recommendations of the DSMC and advising the Director about the implications of these recommendations for the CCTG.

Operations and Statistical Centre Safety Processes

CCTG has standard processes for ongoing safety evaluation of a trial under evaluation. These are outlined in a series of Standard Operating Procedures and Work Instructions. These processes are designed to ensure patient safety on trials is reviewed regularly by comparing the trial experience to what was expected from existing and new sources of information, such as adverse event reporting, Investigator Brochures, scientific literature, etc. The review also ensures information that should go to patients, investigators, Research Ethics Boards (REBs) and regulatory authorities is provided. This internal review process includes oversight by the Safety Desk of the Compliance and Oversight Office and the Trial Team.

Study Chair and Trial Committee

The Study Chair of a CCTG trial is the CCTG member, external to the OSC, who is responsible for leading the trial. The Trial Committee includes the Study Chair, co- investigators chosen to assist in leading the trial, and members of the CCTG OSC responsible for leading the trial, including the Senior Investigator (SI), Senior Biostatistician, and Study Coordinator. The names and roles of these individuals are recorded on the face sheet of every trial protocol.

3.2 Acronyms

CCTG	Canadian Cancer Trials Group
CTC	Clinical Trials Committee
CTEP	Cancer Therapy Evaluation Program
CTSU	Clinical Trials Support Unit
DSMC	Data Safety Monitoring Committee
IND	Investigational New Drug
NCI US	National Cancer Institute (United States)
REB	Research Ethics Board
SI	Senior Investigator

4 Terms of Reference

4.1 Accountabilities

The DSMC's responsibilities are to advise on all matters related to the safety of subjects enrolled in CCTG trials, on selected matters related to the integrity and potential conclusions of study data, and the appropriateness of continued trial conduct. The DSMC is advisory to the CCTG Director. The DSMC's recommendations and resulting actions are communicated throughout the CCTG, including to the CTC, Disease Site Chairs, IND Program, Trial Study Chairs and Committees and membership. Where the Director and the Chair of the DSMC disagree, a specific presentation of a given item by the DSMC Chair to the CTC can be arranged (either at a CTC meeting or through a conference call).

For trials involving NCI US and CTEP through the NCTN, the DSMC's recommendations and CCTG responses to these recommendations are communicated according to NCI US and CTEP policies. As the DSMC is advisory to the CCTG Director, in the unlikely situation where the Director does not concur with the DSMC, specific communication by the CCTG Director with the NCI Program Director or CTEP Associate Director is required. The DSMC Chair is included in these discussions.

For trials not involving NCI US and CTEP for which the Director and the DSMC disagree, the Director, in conjunction with the DSMC Chair convenes an ad hoc committee of 1-3 CTC members who have no potential conflict of interest with the item in question to review the issue and provide additional advice to the Director.

For trials in which the CCTG Director has direct scientific involvement, (i.e. is the SI), the DSMC makes its recommendations to the CCTG Deputy Director. Identical processes ensue with the Deputy Director assuming those Director roles described above.

The DSMC's recommendations and CCTG responses to these recommendations are available for local REBs of centres participating in CCTG trials, and, where applicable, to industry and other regulatory collaborators.

4.2 Scope by Trial Type

4.2.1 Phase III Trials

All phase III CCTG-led trials include DSMC oversight.

4.2.2 Phase II Trials

Phase II trials meeting the following criteria include DSMC oversight:

- Single arm trials with a sample size of 100 patients or more
- Randomized trials with sample size of 80 patients or more
- Trials that include blinded therapy

IND Program trials that do not meet criteria for DSMC review are reviewed according to SOP internal to that program (TMG-SOP-0158). The IND Program may request DSMC review for IND trials not meeting criteria for independent DSMC review for trials with unique issues.

4.2.3 Intergroup Trials

The DSMC's terms of reference and composition are set to meet requirements of the NIH, NCI US, and NCTN program guidelines. CCTG's DSMC is responsible for all trials led by the CCTG, including intergroup trials led by the CCTG. Intergroup trials in which the CCTG participates, but are led by another cooperative group, are expected to include a DSMC. In this case, the responsibility for DSMC oversight is with the lead group responsible for the trial. In the unusual

circumstance in which another cooperative group conducts a trial that is not overseen by a DSMC, oversight by the CCTG DSMC may be considered.

When the CCTG is the coordinating group of an NCI US-sponsored NCTN trial, processes including but not limited to membership, meetings, recommendations, and decisions are consistent with the NCTN Program Guidelines. This includes participation of NCI program and statistical staff as non-voting NCI representatives to the DSMC to ensure the NCI stewardship responsibility for NCTN program trials.

As the DSMC is advisory to the CCTG Director, as indicated in section 4.1.1, in the unusual situation where the CCTG Director does not agree with the advice of the DSMC, a specific consultation process between the Director and the CTEP Associate Director is required. The DSMC Chair is included in such discussions.

4.2.4 Investigational New Drug Program (IND) Trials

Phase II trials conducted within the IND Program that meet criteria described in 4.2.2 are overseen by the DSMC. Phase I trials and Phase II that do not meet criteria described in 4.2.2 are reviewed by a process that is internal to the IND Program and are included in the mandate of the DSMC. These processes are detailed in SOP: TMG-SOP-0158. The IND Program may request DSMC oversight for IND trials that are not otherwise mandated to have DSMC review should these trials have specific issues that the IND Program Director and/or CCTG Director deem would benefit from independent review.

4.3 Responsibilities within Trials Oversight

4.3.1 Safety of Trial Participants

The DSMC is responsible for reviewing safety and adverse event data. Sources of data for review include adverse event tables as are normally provided in CCTG Meeting Books, including specific updating for each DSMC meeting and, where applicable, pharmaceutical company and regulatory agency communications. These review materials are collated and / or prepared for the DSMC by the OSC in accordance with its Standard Operating Procedures. When necessary, the DSMC makes recommendations for corrective action which may include early termination, suspension or modification of a trial, or changes in consent processes.

4.3.2 Integrity of the Trial Data and Conclusions

The DSMC reviews all planned interim analyses, major proposed amendments that affect trial outcome measures or accrual targets, and any requests for unplanned analyses or release of trial results prior to the protocol-defined primary analysis. The DSMC advises whether, and to whom, outcome results be released when analyses are performed prior to the protocol-defined primary analysis.

4.3.3 Trial Feasibility and Relevancy

As part of the review of CCTG trials, the DSMC regularly assesses accrual rates of all studies to ensure that their completion remains feasible. When judged not feasible, the DSMC recommend closures to the CCTG Director. As a broad guideline, the DSMC may apply the criteria developed by NCI US and CTEP which state that closure of trials should be recommended if the accrual rate of the trial during the fifth to sixth annual quarter following trial activation is less than 20% of the projected accrual for that quarter. Similarly, if the accrual rate during the fifth to sixth quarter is greater than 20% but less than 50% of projected, the DSMC may recommend that specific measures to improve accrual or alter study design be provided.

New data from studies external to the CCTG might influence the design, safety or relevance of a CCTG trial. The Trial Committee Study Chair of a CCTG trial provides the results of such studies

to the DSMC as part of the Trial Summary Form and on request. The DSMC may recommend continuing, amending or closing a study based on such new evidence.

4.3.4 Evaluation of Trial Risk and Complexity Level

CCTG evaluates trial risk and complexity level at trial initiation in accordance with CTG-POL-0011 CCTG Policy for Investigator Credentialing. For each DSMC meeting and for each trial under DSMC oversight, the Trial Committee provides a The Trial Summary Form which includes the assigned risk level, indicates whether the risk has changed, and if changed, the proposed plan to address the change in risk for DSMC review and input.

4.3.5 Duration of Oversight

Trials remain under DSMC oversight until analysis of the primary outcome has been completed. For trials that are closed to accrual, all patients have completed protocol therapy and the analysis of the primary outcome is pending, the DSMC is required to review late toxicity tables only.

5 Membership

5.1 Chair of the DSMC

The DSMC is chaired by an external member of the CCTG. The CCTG Director is responsible for the appointment of the DSMC Chair, with input from the CTC. Prior DSMC experience is a criterion used in selecting the Chair and any additional training required is structured according to that experience in collaboration with the DSMC Chair and Group Director. The Chair is expected to provide leadership on administrative and scientific issues, have medical and trial methodology expertise, and be able to facilitate discussion, integrate differing points of view, and ensure that processes to reach consensus are implemented.

The term of appointment for the DSMC Chair is 3 years, renewable once. The term of the Chair may be extended at the recommendation of the CCTG Director and following consultation with the DSMC Chair.

5.2 DSMC Voting Membership

Voting Members of the DSMC include CCTG and non-CCTG members external to the CCTG OSC. Members are identified and selected through a consultative process that includes the DSMC Chair and the CCTG Director.

Voting members of the DSMC include 9-14 individuals that ideally ensure representation of the following required skills and experiences:

- i. systemic therapy of cancer (at least 2);
- ii. radiation oncology (at least 2);
- iii. surgical oncology (at least 1);
- iv. biostatistics (at least 1);
- v. clinical trials methodology (at least 1);
- vi. ethics (at least 1);
- vii. patient representative (at least 1);
- viii. non NCI US / CTEP cooperative group member external to CCTG (1); and,
- ix. NCI US / CTEP representative (1) – non-voting for NCI US/CTEP trials per NCTN Program Guidelines.

DSMC members may have roles, including that of Study Chair, of studies monitored by the DSMC. In such situations, the DSMC member should indicate a conflict of interest and be absent when any discussions or voting of that specific trial are conducted.

The terms of appointment for DSMC members are normally 3 years, renewable once. In special circumstances, and after a consultation process between the DSMC Chair and the CCTG Director, a member may be asked to participate for a longer term. Members may be appointed on an ad hoc basis through a consultation process involving the DSMC Chair and the CCTG Director should additional expertise be required in the review of certain studies.

Onboarding and training of new DSMC members is led by the DSMC Chair and the CCTG OSC Member. This includes online training on the DSMC Policy and requirements via the Site Training Utility (effective for new members 2021June), as well as in-person or remote orientation and training.

5.3 CCTG OSC Membership on the DSMC

The DSMC includes a designated CCTG OSC staff who is a non-voting member responsible for providing administrative assistance to the DSMC.

5.4 Compensation, Confidentiality and Conflict of Interest

5.4.1 Compensation

No payment or rewards is given to DSMC members for their participation on the committee. Members of the DSMC is reimbursed according to CCTG Group Policy for travel costs and hotel accommodations.

5.4.2 Confidentiality

Neither written nor oral communication of the deliberations or recommendations of the DSMC should be made outside of the Committee except as indicated in section 6.4. Knowledge of interim data and analyses is restricted to DSMC members during the course of a trial, including any follow-up period, until the trial is completed and the results are released. This information is securely protected from inadvertent or inappropriate access by non-DSMC members.

As per CCTG Group Policy, a “Statement of Confidentiality” must be provided by all DSMC members before each DSMC meeting. Members of the DSMC have confidential access to a DSMC file on the CCTG website. Access to this website includes confidentiality policies that pertain to all DSMC materials.

5.4.3 Conflict of Interest

The CCTG Group Policy on conflicts of interest related to potential financial activities apply to the DSMC. Individuals with a potential conflict of interest should inform the DSMC Chair to determine whether the individual should be absent during any discussions or voting on specific trial issues.

In addition, DSMC members may also be investigators who have participating roles on specific trials and may therefore also have potential conflicts of interest; for example, their knowledge of interim results could influence their conduct during the trials. Members with such conflicts should inform the DSMC Chair to determine whether the individual should be absent during any discussions or voting on specific trial issues.

The CCTG Director reviews possible conflicts of interest and determine whether there is sufficient basis to exclude the individual from serving on the DSMC.

6 Meetings

6.1 Schedule and Scope

The DSMC reviews all Phase III trials at six-month intervals (i.e. twice/year). One meeting is face-to-face, generally at the CCTG Spring Meeting, and the second is held virtually (e.g. Webex, Zoom) in the Fall. In addition, ad hoc teleconferences may be necessary to address urgent trial-specific issues that may arise between meetings (i.e. to review planned interim analysis data or review emerging safety data).

All trials the DSMC oversees are reviewed at each meeting. The review always includes assessment of safety (as per section 4.3.1) and accrual (as per section 4.3.3). Additional aspects for review include interim analyses which occur based on the schedule and statistical approach to described in the study protocol. Also, the Study Chair / Trial Committee may communicate specific requests for analyses or provide external data for review.

All DSMC members are expected to be familiar with materials provided for each trial for each meeting. The DSMC Chair delegates responsibility for leading the discussion of each trial under review to specific DSMC members so that this leadership role is shared appropriately.

6.2 Materials

At the time of the Spring and Fall Meetings, the DSMC is provided with the following (as applicable):

- i. Copy of the DSMC's internal minutes from its most recent previous meeting;
- ii. List of trials to be reviewed at that meeting (i.e. the agenda);
- iii. Trial Summary Form provided by the CCTG Trial Committee;
- iv. CCTG Meeting Book Tables: This web- based document includes a one-page trial summary and trial schema, accrual and eligibility data, baseline characteristics of entered patients, toxicity data, and in selected instances, reporting of other outcome data;
- v. Additional SAS Meeting Book Tables for all open and closed blinded trials. Event data are presented by 'masked' treatment arm. The treatment arm is not identified unless required by the DSMC;
- vi. Any trial-specific communications from the Study Chair or Trial Committee (in addition to the Trial Summary Form), as appropriate;
- vii. Any data/information requested by the DSMC resulting from its previous meeting(s);
- viii. When an interim analysis is reviewed, the DSMC receives a report from the trial biostatistician that provides the background to the trial, the parameters of the interim analysis, and the results. Statistician responsibilities include preparing all analyses, including interim analyses, of trials where treatment received is blinded and preparation of unblinded results is required.

After meetings, DSMC members should shred any paper copies and delete from personal computers and / or electronic memory apparatus' all DSMC meeting materials. The CCTG OSC member responsible to the DSMC ensures web-based materials are properly coded and maintained according to the CCTG document management procedures.

6.3 Meeting Format

The meeting is divided into open and closed sessions, as determined by the DSMC Chair. Presence of a majority (50% + 1) of DSMC voting members constitute a quorum.

6.3.1 Open Session

When required, the DSMC reviews trial material in an open session that includes members of a Trial Committee as invited guests. Trial Committee members (e.g. Trial Statistician, Study Chair, Senior Investigator) present interim analyses, or other specific issues such as accrual, consideration of new external data etc. The Trial statistician should be present at the open session when an interim analysis is reviewed, if requested by the DSMC. When any analysis involving blinded data is presented, only the trial statistician may be present at the DSMC meeting. Guests may be present for the open session for only the agenda items that deal with their specific trial.

6.3.2 Closed Session

The closed session is restricted to DSMC members. Each trial is reviewed as described in Section 4.3. The DSMC attempts to reach a unanimous consensus with respect to the recommendations required for each trial. When a unanimous consensus cannot be reached, a vote is taken and the resulting recommendation is based on the majority of voting members present. DSMC minutes reflect the numbers voting for and against a given issue. No further details about the vote should be included in the minutes.

6.4 Recommendations

The DSMC makes recommendations regarding the continuation of a study (with or without major or modifications), the temporary suspension of enrolment and/or study intervention, or closure of a study and / or release of trial outcome information.

Recommendations and any additional commentary deemed appropriate by the DSMC are communicated in writing to the CCTG Director. When the DSMC recommends a substantive alteration of trial conduct (e.g. study closure, release of trial results prior to a planned final analysis), the documents that the DSMC evaluated for the decision are made available to the Director. Any clarifications of the recommendations required by the CCTG Director are obtained through communication with the DSMC Chair.

Following clarification (if required), the DSMC Chair completes a “DSMC Recommendation Report”. This report includes only the DSMC’s recommendations. Following review, the CCTG Director provides a response to each DSMC recommendation indicating agreement (or not) and the nature of any required action.

For trials in which the CCTG Director has direct scientific involvement, (i.e. is the SI), the DSMC recommendations are reviewed by the CCTG Deputy Director. Identical processes then ensue with the Deputy Director assuming those Director roles described above.

The resulting document with the DSMC and CCTG Director recommendations and any resulting actions is the “DSMC Summary Report”. The report is posted on the CCTG website for CCTG members and communicated to relevant stakeholders including intergroup collaborators, NCI US and CTEP. This report is available for investigators to circulate to their local REBs. For CCTG-led trials that are on the Clinical Trial Support Unit (CTSU) menu, the CTSU is sent an excerpt of the DSMC Summary Report that includes only the relevant trials for posting to its members’ websites. For CCTG trials that include collaboration with an industry partner, the trial-specific DSMC Summary Report is forwarded to the partner.

When necessary, the OSC DSMC staff member assists with administrative matters related to preparing these documents.

7 Records

Detailed minutes of all DSMC meetings are written by the DSMC Chair and reviewed by the OSC staff member responsible to the DSMC. Once finalized, these minutes are posted to the DSMC private web page where they may be accessed by DSMC members. The DSMC Chair and OSC staff member responsible to the DSMC ensures these minutes are consistent with the recommendations recorded in the DSMC Summary Report (described in section 6.4). The reason for any discrepancy between the detailed DSMC minutes and the DSMC Summary Report should be described in an annotation provided by the DSMC Chair.

8 Roles and Responsibilities

Role	Responsibility
DSMC	<ul style="list-style-type: none"> Responsibilities per CTG-POL-0005 to oversee data safety as described.
DSMC Chair	<ul style="list-style-type: none"> External Chair appointed by CCTG Director. Provide leadership on administrative and scientific issues, provide medical and trial methodological expertise, and facilitate discussion.

9 Appendix

None.

10 References

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10. National Cancer Institute National Clinical Trial Network Program Guidelines, NCI, NIH, December 15, 2012. Version 1.1

11 Revision History

Version Number	Version Date	Brief Description of Revision(s)
V001	November 28, 2006	Initial Release
V002	January 8, 2013	Full review. Update to address Safety Conference Committee and to harmonize with TMG-SOP-0158 Safety Monitoring for IND Program Trials.
V003	December 4, 2017	Full review. Updated to current CCTG Policy Template, Administrative update to Reference Section – broken links; Administrative up to terms (Senior Investigator); Clarification of NCTN non-voting member for CCTG Led NCTN trials
V004	May 26 th , 2021	Full review. Removal of obsolete safety conference references (s. 4.3.1); Addition of confirmation of review for trial risk and complexity (s 4.3.4); Incorporation of training processes for DSMC Chair and Members including Site Training Utility addition (effective for new members June 2021; s 5.0); Update to materials (s 6.2).

12 Signature

Signature of Responsible Group Leader:	Dr. Janet Dancey	On file	2021Jul13
	Name	Signature	Date