



1. Purpose

The purpose of this SOP is to outline the role and composition of the independent Data Monitoring Committee (DMC) during the conduct of a clinical trial.

2. Responsibilities

Principal Investigator: The Principal Investigator (PI) is responsible for ensuring the DMC receives the necessary information to facilitate their responsibilities.

DMC: The DMC is responsible for adhering to and documenting the following procedures.

3. Procedures

- 3.1 An independent DMC may be established by the Principal Investigator of a research study to assess the progress of a clinical trial, safety data, critical efficacy variables and/or any other items as outlined in the DMC operating procedures for the study.
- 3.2 DMC independence is intended to protect the integrity of the clinical trial through the control of sharing of important trial data and information.
- 3.3 The DMC should be comprised of clinical trial scientists and other experts knowledgeable in the appropriate disciplines including statistics.
- 3.4 The DMC should have written operating procedures (see Appendix 4.1) which include membership, frequency of meetings and objectives.
- 3.5 If the Principal Investigator or Methods Centre representatives are on the DMC, their role should be clearly defined (i.e. whether or not they can vote on key issues).
- 3.6 If the Principal Investigator or Methods Centre representatives are on the DMC, procedures should clearly address the control of dissemination of unblinded study information.
- 3.7 The DMC will make recommendations to the Principal Investigator based on the outcome of their assessments.
- 3.8 The DMC should document all meetings and discussions.

4. Appendix

- 4.1 Sample – DMC Operating Procedures

5. References

- 5.1 ICH Topic E9: Statistical Principles for Clinical Trials

SAMPLE

Data Monitoring Committee Operating Procedures

Protocol Title:	
Protocol No./Trial Registry No.:	
Study Sponsor:	
Date of Document:	



**Clinical Evaluation
Research Unit**

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1. Introduction

This operating procedure defines the primary responsibilities of the DMC and guides the activities of the DMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Operating Procedure provides the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMC, and an outline of the content of the Open and Closed Reports that will be provided to the DMC.

Definition and terms and abbreviations to be used in the Operating Procedure:

DMC = Data Monitoring Committee

SC = Steering Committee

PI = Principal Investigator

<<Study Acronym>> = <<Study>>

2. Primary Responsibilities of the DMC

The DMC is primarily responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMC will provide recommendations for stopping or continuing the trial.

Additionally, the DMC may also make recommendations relating to the selection/recruitment/retention of participants, patient management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMC is advisory to the clinical trial leadership group, hereafter referred to as the Steering Committee (SC). The DMC normally reports to the SC through the PI. The SC will be responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

3. Organizational Diagram

The following diagram shows the relationships between the DMC and other committees/individuals involved in the trial.

<<Diagram>>

4. Membership of the DMC

4.1 Members

The DMC is an independent multidisciplinary group that collectively, has experience in the management of critically ill patients and in the conduct and monitoring of randomized clinical trials.

The DMC membership is for the duration of the trial. If any members leave the DMC during the course of the trial, the PI in consultation with the SC will promptly appoint replacements.

The members of the DMC are:

DMC Chair:

DMC Member:

DMC Member:

Etc...

4.2 Responsibilities of the Chair of the DMC

The Chair of the DMC is appointed on the recommendation of the SC. Specific responsibilities of the Chair include, but are not limited to:

- a) Organization and scheduling of meetings of the DMC (facilitated through the study Methods Centre)
- b) Producing and archiving the minutes of DMC meetings
- c) Discussing recommendations arising for the meetings of the DMC with the PI

4.3 Conflicts of Interest

DMC members will have no major apparent financial or intellectual conflict of interest that could prevent them from objectively reviewing the study protocol, interim and final data and giving advice to the SC.

DMC members will disclose to the Chair of the DMC any other conflicts they consider relevant.

The DMC members will be responsible for advising the Chair of the DMC of any changes in consulting agreements or financial interests that occur during the course of the trial. Any DMC member who develops significant conflicts of interest during the course of the trial should resign from the DMC.

4.4 Expenses of the DMC

All expenses of the DMC will be paid for by the study budget. Members of the DMC will be reimbursed for costs after providing receipts for expenses. Members of the DMC will not receive honoraria or other direct or indirect financial compensation for the activities related to this DMC.

5. Frequency and Purpose of the DMC Meetings

5.1 Format of Meetings

The initial meeting of the DMC will be a face-to-face meeting. Subsequent meetings will be held either face-to-face or using teleconference technology. A decision on the format for the meeting will be reached by consensus of the DMC with the PI and SC. Each meeting will normally have four different components. The initial part of the meeting is for members of the DMC only. The next component will involve the DMC with the PI and members of the SC with other participants invited as necessary. The third component of the meeting is also closed for members of the DMC only. The final part of the meeting is the DMC meeting with the PI to relay the results and recommendations of the meeting.

5.2 Organizational Meeting

The initial meeting of the DMC will be an organizational meeting. This will be a face-to-face meeting. The DMC will review, revise and finalize the operating procedures for the DMC. The DMC will review the scientific and ethical issues related to the study design and conduct and discuss the operating procedures and relationships with other stake holders in the study. The organizational meeting will be attended by the DMC and representatives of the SC including the PI. The DMC will be provided in advance with drafts of the clinical trial protocol including statistical analysis plan and the DMC operating procedures. Members of the DMC will receive copies of the current version of the case report forms for reference and outline of the initial draft of the open and closed reports. The reports reviewed at this meeting will be the results of the pilot study.

5.3 Early Safety/Trial Integrity Reviews

Following initiation of the trial, the DMC will normally meet three times annually. These meetings will normally be held by teleconference around the same time as the SC Meetings prior to the Canadian Critical Care Trials Group Meetings. During the early phases of protocol enrollment, the DMC will review safety information, factors relating to quality of trial conduct and ensure proper implementation of procedures to assess the sample sizes. The DMC will be provided with documentation from the SC to carry out these reviews.

5.4 Formal Interim Efficacy Analyses

The DMC will meet for the purpose of formal interim analysis when finalized data is available on <number> enrolled subjects and subsequently for <number> enrolled subjects. This meeting will be to review data relating to treatment efficacy, patient safety and quality of trial conduct. These meetings will normally be held by teleconference.

6. Procedures to Ensure Confidentiality & Proper Communication

These procedures are to ensure confidentiality for all parties and to enhance the integrity and credibility of the trial. The procedures implemented will ensure appropriate communication without unduly restricting transfer of information and decision making by the DMC. They will also facilitate exchange of information without compromising the blinding of the trial and the subsequent successful conduct of the trial. The following principles guide the functions and communication of the DMC:

- a. The DMC is independent of the PI and SC, but supportive of the aims and methods of the study.
- b. The DMC serves in an advisory role to the PI and SC.
- c. The PI and SC receive DMC recommendations under advisement.
- d. The DMC and PI with the SC work collaboratively to ensure rigorous and timely conduct of the study.

6.1 Closed Sessions

The closed sessions of the DMC involve only members of the committee. The DMC may invite the study statistician from some or the entire component of the meeting. It is only during the closed sessions that the DMC will review safety and efficacy data by the group (blinded).

6.2 Open Sessions

Open sessions of the DMC allow for adequate access to information provided by the study investigators, SC, sponsors and funding partners. The open sessions will normally involve the members of the DMC, the PI and members of the SC. Other participants will be invited as necessary. Data reviewed in open sessions remains blinded and is presented as aggregated data.

6.3 Open and Closed Reports

Reports are provided to the DMC by the PI and SC for each meeting. The primary trial statistician is responsible for preparation of the open reports. Open reports are available to all who attend the open session of the DMC. These data will include, but are not limited to, information on the treatment other than the investigational product,

baseline characteristics, pooled data on eligibility violations, completeness of follow-up and compliance. This data is presented in an aggregated format.

Closed reports are made available only to those attending closed sessions of the DMC. Closed reports for the closed sessions of the DMC are prepared by the primary trial statistician. These reports will include, but are not limited to, analysis of primary and secondary efficacy end points, subgroup and adjusted analysis and analysis of adverse events and serious adverse events. The data will be presented by study arm, with the study groups masked and identified as “A, B, C and D.” Reports will be provided to members of the DMC a minimum of a week prior to the meeting.

6.4 Minutes of the DMC Meeting

The Chair of the DMC will prepare minutes of the meetings. Two sets of minutes will be prepared: open minutes and closed minutes.

The open minutes will describe the proceedings of the open session of the DMC meeting and present all recommendations by the DMC. It is critical that these minutes do not unblind the efficacy and safety data if the DMC is not recommending early termination.

Closed minutes will describe the proceedings from all sessions of the DMC meeting including a list of all recommendations by the committee. These minutes are available only to the members of the DMC during the course of conduct of the trial. Copies of the closed session minutes will be archived by the DMC Chair and the primary trial statistician.

All copies of the open and closed DMC minutes will be available to the PI and SC after closure of the recruitment phase of the trial.

6.5 Recommendations to the Steering Committee (SC)

At each meeting of the DMC during the conduct of the trial, the DMC will make a recommendation to the SC to continue or prematurely termination the trial. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines according to this operating procedure. The recommendation to suspend enrollment will either be for permanent enrollment suspension or enrollment pending protocol modification.

Recommendations by the DMC regarding the study protocol will be made to the PI and the SC. The DMC will be notified about changes to the protocol or to study conduct. DMC agreement will be sought in all substantive recommendations or changes to protocol or to study conduct prior to implementation.

7. Statistical Monitoring Guidelines

The primary endpoint of this study is <primary endpoint>. Our primary analysis will <analysis plan>.

Interim analysis will be performed after finalized data are available for <number> and <umber> subjects. The results of interim analyses will be reviewed by a DMC who will not disclose any of the efficacy results unless an early stopping decision is made. <Statistical plan/details>.

8. Content of DMC's Open and Closed Reports

8.1 Open Statistical Report: An outline

Open statistical reports should contain the following:

- One-page outline of the study design
- Statistical commentary explaining issues presented in Open Report figures and tables
- DMC monitoring plan and summary of Open Report data presented at prior DMC meetings
- Major protocol changes
- Information on patient screening
- Study accrual by month by institution
- Eligibility violations
- Quality control variables as developed by the SC
- Baseline characteristics
 - Demographics
 - Laboratory values and other measurements
- Hours between randomization and initiation of treatment
- Adherence to study medication schedule
- Length of follow-up data available
- Participant treatment and study status
- Primary and secondary efficacy endpoints

8.2 Closed Statistical Report

The entire trial team including the study statistician will remain unaware of which treatment combination is referred to by the masked arm codes until the final primary analysis is completed. Should the DMC request uncoding of the treatment arms, they may make this request directly and confidentially to the designated database designer who will not inform anyone outside of the DMC that this request was made.

8.2.1 An Outline for Safety Analysis

- Detailed statistical commentary explaining issues raised by Closed Report figures and tables (by coded treatment group)
- DMC monitoring plan and summary of Closed Report data presented at prior DMC meetings
- Repeat of the Open Report information, in greater detail by treatment group
- Analysis of serious adverse events and overall safety data
- Analysis of lab values, including basic summaries and longitudinal analyses
- Discontinuation of study medications

8.2.2 An Outline for Interim Analysis

- Detailed statistical commentary explaining issues raised by Closed Report figures and tables (by coded treatment group)
- DMC monitoring plan and summary of Closed Report data presented at prior DMC meetings
- Repeat of the Open Report information, in greater detail by treatment group
- Analysis of primary and secondary efficacy endpoints
- Analysis of serious adverse events and overall safety data
- Analysis of lab values, including basic summaries and longitudinal analyses
- Discontinuation of study medications

9. Role of DMC in Publications

9.1 Publication of Study Results

Manuscripts that arise from the trial will be shared with the DMC. The DMC will be given the opportunity to comment on sections that relate to their input in the trial for accuracy. The DMC will also be offered the opportunity to comment on the entire draft or manuscripts for their opinion. The DMC members and their affiliations will be listed in reports of the trial.

9.2 Publication of the DMC Activities

Members of the DMC may publish material relevant to their participation from this trial following publication of the initial manuscript reporting results of the trial. Members of the DMC will not publish primary or secondary outcome results of data arising from the trial. Any manuscripts planned for presentation or publication by the DMC in regards to this trial will be shared with the PI and SC for comment on accuracy prior to publication.

10. References

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3. Ellenberg SS, Fleming TR, DeMets DL. *Data Monitoring Committees in Clinical Trials: A practical perspective*. John Wiley and Sons Ltd.; 2003.
4. Sydes MR, Spiegelhalter DJ, Altman DG, Babiker AB, Parmar MK, DAMOCLES Group., et al. Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. *Clinical Trials* 2004 Feb;1(1):60-79.