Data and Safety Monitoring Board (DSMB) Charter TEMPLATE

How to use this template Charter

This template Charter should be used in accordance with the guidance document "Data and Safety Monitoring Boards"

*Instructions to researchers are in **purple italics** – instructions should be deleted once that section has been completed.*

*Where sample wording is given, it is highlighted in **green italics**.*

Trial title:	*<insert>*
Trial registration number:	*<insert>*
Study protocol version this charter is based on:	*<insert>*
Sponsor-Investigator: & contact information:	*<insert>* *<insert>*

Acknowledgment

The members of the DSMB must sign the charter to indicate they have read and understood and will adhere to the charter.

Name and title	**DSMB Role** (*e.g., chair, clinical expert, biostatistician, independent statistician (ex officio DSMB member)>*	**Signature**	**Date**
<insert>	*<insert>*	*Sign*	*Date*

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Instructions are in purple italics – instructions should be deleted once that section has been completed.

Sample wording is in regular black font or green italics.

1. INTRODUCTION

This charter is for the Data and Safety Monitoring Board (DSMB) for the clinical trial titled *< insert trial title>*.

This charter defines the responsibilities of the DSMB, its membership, and the purpose and timing of its meetings. The Charter also provides the procedures for ensuring confidentiality and proper communication, the statistical monitoring procedures to be implemented by the DSMB, and an outline of the content of the reports that will be provided to the DSMB.

See Section 10 for a list of definitions of the terms and abbreviations used in this charter.

2. DSMB MEMBERSHIP

The DSMB consists of the following members who collectively have experience in the clinical area of interest, biostatistics and randomised clinical trials. A quorum will require at least <*insert – must be at least 2*> members.

Insert below the required details for the DSMB members. Note that the Chair should have previous experience of serving on DSMBs and experience in chairing meetings, and must be able to facilitate and summarise discussions.

The DSMB will consist of:

Voting members

DSMB Role	**Name and title**	**Affiliation / Institution**	**Contact details**	**Summary of experience**
DSMB Chair				
DSMB Biostatistician				
DSMB Clinical Investigator				
<insert>				
<insert>				

Non-voting members:

The (Independent) Statistician preparing confidential reports for the Closed Session will be <*insert contact details or delete if not applicable*>*

** In their guidance, the FDA suggest that it is optimal for a statistician independent of the sponsor to perform the unblinded interim analysis. Although this is ideal, this is often not practical due to financial or time constraints, and instead the trial statistician prepares the report. If the trial statistician does perform the analysis, any working procedures should clearly describe the measures that will be taken to prevent dissemination (directly or indirectly) of unblinded study information to individuals responsible for the further conduct of the study or future analyses.*

Trial investigators will not be members of the DSMB.

2.1 Exclusion of conflicts of interest

The DSMB membership will be restricted to individuals free of any conflicts of interest. Even the appearance of conflict of interest among DSMB members must be avoided. Any DSMB member who has, or develops, a significant conflict of interest should resign from the DSMB.

The DSMB members must disclose conflicts of interest to fellow members. Declaration of a conflict of interest is an ongoing process; it will be completed at the time of joining the DSMB and prior to each DSMB meeting and will be recorded in the meeting minutes.

Conflicts of interest can include:

- Stock ownership in any commercial companies involved.
- Stock transaction in any commercial company involved (if previously holding stock).
- Consulting arrangements with the sponsor.
- Frequent speaking engagements on behalf of the intervention.
- Career tied up in a product or technique assessed by the trial.
- Hands-on participation in the trial.
- Involvement in the running of the trial.
- Emotional involvement in the trial.
- Intellectual conflict (e.g. strong prior belief in the trial's experimental arm).
- Involvement in regulatory issues relevant to the trial procedures.
- Investment (financial or intellectual) in competing products.
- Involvement in the publication.

The DSMB will function independently of all other individuals and bodies associated with the conduct of the trial.

2.2 Resignation/termination of DMC member and replacement

DSMB membership is for the duration of the clinical trial. If any members leave the DSMB during the trial, the Sponsor-Investigator will promptly appoint their replacement with agreement from the remaining members of the DSMB. Further appointments may be made to the DSMB if members believe additional expertise is required. DSMB members can decide to terminate the membership of a DSMB member based on a simple vote in case of non-performance or other significant reasons as determined by a majority of the DSMB.

3. RESPONSIBILITIES OF THE DSMB

3.1 Stewardship of the trial

The DSMB is responsible for the stewardship of the trial for all participating sites and/or institutions. The stewardship includes continuous review of participant recruitment, accrual, retention, and withdrawal. It further involves oversight of participant management, adherence to protocol-specified regimens, and procedures for data management and quality control.

The DSMB will be responsible for safeguarding the interests of trial participants by assessing the safety of the interventions during the trial, and the general progress of the trial.

Specifically, the role of the DSMB will be to:

- Monitor and review participant safety in the trial (including evidence for treatment harm [e.g. toxicity data, safety events])
- Review participant recruitment, accrual, retention, treatment discontinuation, trial withdrawal, serious breaches, and protocol deviations that require exclusion of the participant from the per-protocol analyses
- Monitor efficacy based on pre-planned interim data analyses (*delete if not appropriate*)

Where there are additional DSMB responsibilities, list them here (examples are given below).

- *Advise on protocol modifications suggested by investigator or sponsor (e.g. to inclusion criteria, trial outcomes or sample size)*
- *Monitor planned sample size assumptions*
- *Suggest additional data analyses*
- *Assess data quality, including completeness (and by doing so encourage collection of high-quality data)*
- *Monitor compliance with the protocol by participants and investigators*
- *Evaluate emerging literature which may have an impact on the scientific plausibility or need for the trial / assess the impact and relevance of external evidence*
- *Monitor continuing appropriateness of participant information*
- *Monitor compliance with previous DSMB recommendations*

This responsibility will be exercised by providing recommendations about continuing, modifying or stopping the trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the selection/recruitment/retention of participants, participant management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control.

The DSMB will be advisory to the Sponsor-Investigator and through them to the *Trial Steering Committee (TSC)* / Trial Management Group (TMG)**

** All trials should have a TMG – but not all trials will have a TSC. Delete whichever is not applicable.*

The Sponsor-Investigator holds ultimate responsibility for decisions regarding the trial.

3.2 Safety monitoring

The DSMB is responsible for safeguarding the interests of trial participants by assessing the safety of the interventions during the trial. *The DSMB members should review the plan for the collection of safety data before the first patient is enrolled. Given this, it is desirable to list considered safety variables being collected as part of the study at the end of the charter. All safety outcomes described in the study protocol should be*

included in that list. For laboratory data, critical thresholds to be considered in the analysis should also be included in the charter.

At least one DSMB member will be an expert in the potential safety outcomes of the trial. If important safety items are not considered in the reporting of safety data, the DSMB may request to change or add items to be included.

The DSMB will use the accumulating clinical data to differentiate reported safety events (i.e. serious adverse events, suspected unexpected serious adverse reactions, urgent safety measures) associated with the trial interventions from those with other etiologies. It is therefore important that, where possible, reported safety data indicate the likelihood of the relationship to the study interventions (i.e. causality).

The Melbourne Children's guidance on operating procedures for DSMBs advise refers to available catalogues for the classification of serious adverse events.

The reporting of safety events for this study follows *<insert dictionary here, for example, "MedDRA version XX.0", if not applicable delete>.*

3.3 Monitoring of efficacy data - interim analyses

The DSMB are also responsible for assessment of the efficacy of the interventions during the trial i.e. interim analyses of efficacy endpoints. *The current approved study protocol pre-specifies the following interim analyses <and where applicable stopping rules>. [insert relevant paragraph from the protocol including stopping rules to be applied.]*
Delete the above wording where it is not applicable and state: <No interim analyses are pre-specified for this trial.>

Note that even if the trial protocol does not specify an interim analysis to assess efficacy, the DSMB may need to access efficacy information to perform a risk/benefit assessment in order to weigh possible safety disadvantages against a possible gain in efficacy. The DSMB may therefore request to receive efficacy data additional to the available safety data.

4. FREQUENCY AND FORMAT OF MEETINGS

4.1 Initial Meeting

It is recommended that, where possible, the DSMB meets before the trial starts (i.e. first participant enrolled) or early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the Sponsor-Investigator.

An initial meeting of the DSMB will review the role and functioning of the DSMB, discuss the format and content of the DSMB reports and review scientific and ethical issues relating to the design and conduct of the trial. This initial meeting will occur prior to the start of the study (i.e. first participant enrolled) <*amend timing where required*>.

4.2 First Review Meeting

The first full review by the DSMB should occur within one year of recruitment commencing. Note that the protocol and charter should indicate the expected timing of the initial DSMB review. This may be triggered by specific trial events for example "after X# of subjects are enrolled".

The first full review by the DSMB will occur *<insert timing>*

At this meeting, the following will be reviewed:

- Data related to safety
- Data related to efficacy <*delete where not applicable*>
- Data relating to trial conduct.

4.3 Subsequent Review Meetings

Subsequent DSMB meetings will occur <*insert timing*>. At the meetings, the following will be reviewed:

- Data related to safety <*specify timing*>
- Data related to efficacy <*specify timing, delete where not applicable***>**
- Data relating to trial conduct.

Note that where formal stopping rules are detailed in the trial protocol, meetings should be scheduled to take place around the timepoint(s) of the planned interim analyses.

Where interim analyses will be conducted, provide details. <Select from>
< *No interim analysis is detailed in the trial protocol*>.
OR <*An interim analysis will be undertaken at the following time points* <*insert full details*>>.

<*Select from***>**
< No formal stopping rules are detailed in the trial protocol>.
OR <*Formal stopping rules are detailed in the trial protocol and will be applied at the following time points* <*insert details*>. *The stopping rule should be used for guidance rather than as an absolute rule; the DSMB should take into account the safety data from the trial as well as external evidence from other studies in deciding whether a recommendation is made to stop the trial or not. Reasons should be recorded if the stopping guideline is disregarded by the DSMB.*

Where formal stopping rules are detailed in the trial protocol, meetings should be scheduled to take place around the timepoint(s) of the planned interim analyses.

4.4 Ad Hoc Meetings

Additional ad hoc meetings of the DSMB may be scheduled if requested by either the Sponsor-Investigator/TMG/TSC or the DSMB.

5. CONDUCT OF MEETINGS

Meetings will consist of an open session and, usually, a closed session.

5.1 Open Session

Members of the <*insert whichever applicable TSC/TMG*>, which includes the Sponsor-Investigator, will meet with the DSMB and the statistician who prepared the DSMB report at the commencement of each meeting. This "*Open Session"* provides the DSMB an opportunity to query the < *insert whichever applicable TSC/TMG*>members about issues that have arisen during the review of the data. Once the DSMB members are satisfied that all their queries have been addressed, the < *insert whichever applicable TSC/TMG* >members will then leave the meeting to enable the confidential *Closed Session* of the DSMB to commence. The Sponsor-Investigator will remain available to return, if required, to assist with any questions.

5.2 Closed Session

The statistician who prepared the DSMB report will remain for the first part of the closed session in order to take the DSMB through the report and answer questions if required. The statistician who prepared the DSMB report will then leave the closed session. The remainder of the closed session will involve only DSMB members to allow discussion of confidential data from the clinical trial.

5.3 Meeting attendance and quorum

The minimum number of members in attendance for the DSMB to be quorate for decision-making is *<insert details>*.

If the report is circulated before the meeting, DSMB members who will not be able to attend the meeting may pass comments to the DSMB Chair for consideration during the discussions.

Consider also including:
"If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DSMB. If a member des not attend a third meeting, they should be replaced."

5.4 Meeting deliberations

Include an outline of how deliberations will proceed.

The Chair will facilitate and summarise discussions and will encourage consensus.
Following its review of the data, the DSMB will reach consensus on its list of recommendations.
<Consensus will be determined through informal or, where required, formal voting>.

5.5 DSMB Recommendations

The recommendations provided by the DSMB may include: continuing the trial unchanged; continuing the trial with modifications; or terminating the trial. The DSMB may also make recommendations about other aspects of the trial such as the recruitment of participants and the conduct of the trial. All recommendations will be sent to the Sponsor-Investigator promptly, within *<insert time frame (e.g. 3 weeks)>,* and through the Sponsor-Investigator to the *TMG and/or TSC (delete wording that does not apply*). The <*insert whichever is applicable <TSC/TMG>* will advise on whether to continue or terminate the trial, and whether amendments to the protocol or changes in trial conduct are required based on the DSMB recommendations.

In the event that the DSMB recommends the early termination of the trial, the final decision to stop the trial early or modify the trial protocol will be made by the Sponsor-Investigator following advice from the < *insert whichever applicable TSC/TMG*>. If this situation arises at any time, the decision of the Sponsor-Investigator will be discussed with the DSMB immediately.

The DSMB will be advisory to the Sponsor-Investigator and through him/her to the <*insert whichever applicable TSC/TMG*>. The Sponsor-Investigator holds ultimate responsibility for decisions regarding the trial.

The Sponsor-Investigator will be responsible for promptly presenting the recommendations of the DSMB to the <*TSC/TMG*>for ready review. The <*TSC/TMG*> will advise on whether to continue or terminate the trial, and whether amendments to the protocol or changes in trial conduct are required based on the DSMB recommendations.

Response to the DSMB's recommendations:

- If the Sponsor-Investigator/*<TSC/TMG>* does not agree with the DSMB recommendations, a memo justifying the reasons for not complying with the recommendations of the DSMB will be promptly *<insert XX days> (e.g. 30 days),* forwarded to the DSMB and to the Sponsor.
- If the DSMB is not satisfied with the Sponsor-Investigator/*<TSC/TMG>* response to their recommendations, the DSMB will promptly *<insert XX days> (e.g. 30 days)* notify the Sponsor.

Note that in the event that the Sponsor-Investigator/*<TSC/TMG>* wishes to remove one or more DSMB members, a memo justifying the reasons for this will be promptly, *<insert XX days> (e.g. 30 days)* forwarded to the DSMB and to the HREC.

5.6 Meeting Minutes

The DSMB will have minutes taken for both the Open and Closed meetings. Meeting minutes should be signed by the DSMB Chair and distributed as soon as possible after the DSMB meeting. The <*insert whichever applicable TSC/TMG*>will provide staff to assist with minute-taking. The person taking minutes for the closed meeting will be independent of the trial team and will ensure the minutes of the closed meeting remain confidential until the completion of the trial.

5.7 Trial publications

The DSMB may be sent copies of accepted papers for their information.

DSMB members should be named and their affiliations listed in the main report/publication. A brief summary of the timings and conclusions of the DSMB meetings should be included in the body of the main trial paper.

6. STATISTICAL MONITORING AND REPORTS

6.1 Data analysis and DSMB reporting

In their guidance, the FDA suggest that it is optimal for a statistician independent of the sponsor to perform the unblinded interim analysis. Although this would be ideal, this is often not practical due to financial or time constraints, and instead the trial statistician prepares the report. If the trial statistician does perform the analysis, any working procedures should clearly describe the measures that will be taken to prevent dissemination (directly or indirectly) of unblinded study information to individuals responsible for the further conduct of the study or future analyses.

6.1.1 Open and Closed Reports

The statistician <*provide details as outlined above – will the statistician preparing the closed reports be independent? If not independent, indicate whether working procedures describe the measures to prevent dissemination of unblinded study information to individuals responsible for the further conduct of the study or future analyses* > will undertake the data analysis and the creation of the DSMB reports. The statistician preparing the information for the DSMB will prepare two reports, an "open" and a "closed" report (see sections 6.1.1 and 6.1.2 below). Both the open report and the confidential closed report will be sent to the DSMB members for review <*insert #*> days prior to the scheduled meeting.

The open report will also be circulated to the <*insert whichever applicable TSC/TMG*>which will meet shortly after the DSMB to discuss any recommendations made by the DSMB along with any other trial related issues.

6.1.1.1 Open Reports *(see the template open report provided on the CRDO website>*

Open reports will contain the following information:

- Trial number and title.
- Brief summary of the trial design and progress.
- Details of any protocol amendments since the previous report
- Status of accrual (actual vs target recruitment)
    - If accrual is slower than expected include a plan for increasing enrollment.
    - Report all sites by name, target recruitment and current recruitment <*delete for single site trials>*
- Summary of baseline characteristics
- Summary of adverse events*
- Summary of serious adverse events*
- Summary of suspected unexpected serious adverse reactions*
- Summary of urgent safety measures
- Summary of significant safety issues
- Details of serious breaches
- Number of protocol deviations requiring exclusion from the per-protocol analysis (such as study treatment discontinuations and, where applicable, withdrawals from study procedures and follow up)
- *<Summary of the primary efficacy endpoint> (where applicable)*

** For trials involving investigational medical devices (IMD), replace these terms with those appropriate for IMDs. Refer to the NHMRC Guidance: "Safety monitoring and reporting in clinical trials involving therapeutic goods" (EH59, November 2016) – see CRDO website for the link.*

Data in this report will be presented across all participants with NO reference to treatment arm or group.

6.1.1.2 Closed Reports

Closed reports will contain the following information:

- Trial number and title.
- Brief summary of the trial design and progress.
- Details of any protocol amendments
- Status of accrual (actual vs target recruitment)
    - If accrual is slower than expected include a plan for increasing enrollment.
    - Report all sites by name, target recruitment and current recruitment <*delete for single site trials>*
- Summary of baseline characteristics
- Summary of adverse events*
- Summary of serious adverse events*
- Summary of suspected unexpected serious adverse reactions*
- Summary of urgent safety measures
- Summary of significant safety issues
- Details of any serious breaches
- Number of protocol deviations requiring exclusion from the per-protocol analysis (such as study treatment discontinuations and, where applicable, withdrawals from study procedures and follow up)

- *(And where the study protocol specifies a formal interim analysis and/or if evaluation of overall risk-benefit balance requires assessment of the primary study outcome)* Summary of the primary efficacy endpoint by treatment arm, and statistical comparison of the primary outcome by treatment group.

** For trials involving investigational medical devices (IMD), replace these terms with those appropriate for IMDs. Refer to the NHMRC Guidance: "Safety monitoring and reporting in clinical trials involving therapeutic goods" (EH59, November 2016) – see CRDO website for the link.*

The format of these reports will be determined by the DSMB in consultation with the statistician preparing the report. (*For most trials) Information will be presented by pseudo-labelled treatment arm (e.g. "A" and "B"). In some circumstances, unintended unblinding may occur if certain reported parameter values are expected to be associated with the interventions. In such circumstances, the need for presenting data by treatment arm should be carefully considered among members of the DSMB.*

The key to identify the treatment regimens may be supplied by the statistician if requested by the DSMB.

Additional information may be presented in subsequent reports if specifically requested by the DSMB.

7. CONFIDENTIALITY

Information relating to, or arising from, the trial, disclosed in the course of DSMB meetings or discussions and other communications, or in DSMB draft and final reports is confidential and can only be used and disclosed in accordance with the terms of this charter and the confidentiality agreement between MCRI and each DSMB member's institution/company. DSMB members hereby acknowledge and agree that they have read, understood and accepted the terms of the confidentiality agreement between MCRI and their institution/company.

After each meeting, the DSMB members should *(select from the following options)*:

- *Destroy their reports after each meeting. Fresh copies of previous reports will be circulated with the new report before each meeting if requested.*
- *Store the papers safety after each meeting so that they may check the next report against them. After the trial is reported the DSMB members should destroy all interim reports.*

8. COMMUNICATIONS

At any time during the trial, regulatory authorities, the Human Research Ethics Committee, the TSC <*delete if not applicable*>, TMG or any other body or individual involved with the conduct of the trial may seek the advice of the DSMB about any concern that they may have about the conduct, outcome or continuation of the trial. Any such requests should be forwarded in writing to the DSMB Chairperson at the address provided above.

If any suspected unexpected serious adverse events occur, which are thought to relate to the experimental treatment, the Chair of the DSMB will be notified within 72 hours. The Chair will then decide whether an additional meeting of the DSMB should be held.

9. KEY TERMS

DSMB: A Data Safety Monitoring Board is an independent data-monitoring group that may be established by those responsible for trial conduct to monitor the progress of a clinical trial with particular focus on potentially arising safety issues.

MCRI: Murdoch Children's Research Institute

SERIOUS BREACH: A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: the safety or rights of a trial participant, or the reliability and robustness of the data generated in the clinical trial. Note: this guidance's definition of serious breach differs from the definition in the Australian Code for the Responsible Conduct of Research and is about deviations from the requirements of Good Clinical Practice or the clinical trials protocol.

SPONSOR-INVESTIGATOR: When acting as the Sponsor for MCRI investigator-initiated clinical trials (i.e. those without an external sponsor), MCRI takes on the liability for harm caused by the trial design, the liability for not working to Australian regulation, and the reputational risk associated with the potential discovery of poor quality or unsafe research audit or regulatory inspection. To mitigate these risks, the MCRI (as Sponsor) must ensure that the trial is conducted in accordance with the National Statement, the Australian Code, GCP and relevant regulatory requirements. MCRI delegates some Sponsor responsibilities to the Coordinating Principal Investigator leading the trial. The term "Sponsor-Investigator" has been adopted by MCRI for this role.

Each study site also has a Principal Investigator (PI) who is responsible for the trial at their study site. The Sponsor-Investigator may be the PI for the trial at his/her study site.

TMG: The TMG is a group of people at the coordinating or principal site, who oversee the day-to-day conduct of a clinical trial, including safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. This group should be small and include the key individuals responsible for the everyday management of the clinical trial, such as the Site Principal Investigator, trial coordinator, research nurse, data manager, statistician etc. The group should closely review all aspects of the conduct and progress of the clinical trial and should meet regularly (informally or formally) to ensure that there is a forum for identifying and addressing issues. Particular attention should be paid to: progress towards clinical trial milestones (recruitment accrual, timelines etc.); adherence to the protocol; and adherence to good research practices. For many investigator-initiated trials, the TMG performs the role of a TSC (see below) and/or the DSMB.

<*delete if not applicable*> **TSC:** Trials may or may not have a TSC. The aim of this committee is to provide independent oversight for trials, including responsibility for the scientific integrity of the protocol and the assessment of study quality and conduct. The TSC usually includes the Sponsor-Investigator, some principal investigators from study sites and possibly other key members of the TMG. The TSC also often includes external members who are independent of the trial conduct and may have an independent chair. Such a committee is often only used for trials that are large, complex or potentially controversial, or where there is a need to include a range of key stakeholders in the oversight of the trial.