Australian Clinical Trials Alliance

Trial Safety Oversight: Guidance for CTNs

Version 1.0

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ABBREVIATIONS

ACTA	Australian Clinical Trials Alliance
AE	Adverse Event
CEC	Clinical Event Committee
CRF	Case Report Form
CTN	Clinical Trial Network
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
MeDRA	Medical dictionary for regulatory activities
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
SAE	Serious Adverse Event
SDMC	Safety Data Monitoring Committee
STInG	Statistics in Trials Interest Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
TSC	Trial Steering Committee

PURPOSE OF DOCUMENT

This document is intended to assist clinical trial networks (CTNs) in establishing a data safety monitoring board (DSMB) for safety oversight of a trial, or multiple trials, conducted by the network.

ROLE OF ACTA IN DEVELOPING TERMS OF REFERENCE

The Australian Clinical Trials Alliance (ACTA) is providing options to assist CTNs with their responsibilities for trial safety oversight. This generic advice, provided by ACTA, should be considered and applied by each CTN taking into account the individual nature of each CTN, specific trial and region regulatory requirements, including those specified in the HREC approval, and the responsibilities of the sponsor and principal investigator to monitor and report adverse events and other safety issues.

There are a number of excellent guidance documents published by the National Health and Medical Research Council (NHMRC) and the Therapeutic Goods Administration (TGA) that outlines responsibilities of those involved in clinical trials to monitor and report adverse events and safety issues as well as documents provided from other sources.

Therefore, this document is intended to be used alongside published documents:

- *Data Safety Monitoring Boards* (DSMBs)[1]
- *Risk-based Management and Monitoring of Clinical Trials involving Therapeutic Goods*[2]
- *Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods*[3]
- *Australian Code for the Responsible Conduct of Research*[4]
- *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods*[5]
- *Guide to Managing and Investigating Potential Breaches of the Code for the Responsible Conduct of Research*[6]
- *Australian Clinical Trial Handbook*[7]
- *National Statement on Ethical Conduct in Human Research*[8].

ACKNOWLEDGEMENTS

We acknowledge the contributions of ACTA CTN members and members of ACTA's Efficient and Effective CTNs Reference Group and ACTA Statistics in Trials Interest Group (STInG) in the preparation, development and review of this document. ACTA gratefully acknowledges the Australian and New Zealand College of Anaesthetists and Murdoch Childrens Research Institute Clinical Research Development office for the use of the following document – Murdoch Children's Research Institute guidance document titled *Data and Safety Monitoring Boards*[9].

USE OF THIS DOCUMENT

ACTA requests that the following acknowledgement is included in any CTN trial safety oversight committee or DSMB that are developed and documented using knowledge gained from this document. This will assist ACTA in identifying the usefulness and impact of this document in creating trial safety oversight committees for CTNs.

> '[Name of CTN] acknowledges the contribution of ACTA to the development of trial safety oversight processes within our network (reference: *Trial Safety Oversight: Guidance for CTNs*).'

DISCLAIMER

The information in this document is for general guidance only. ACTA does not make any representations or warranties (expressed or implied) as to the accuracy, currency or authenticity of the information provided.

INTRODUCTION

Trial safety oversight helps to safeguard trial participants while allowing independent evaluation of the risks and benefits of the research. This guidance document describes different structures for networks when considering trial safety oversight. This document is intended to help researchers decide whether a DSMB is required for trial safety oversight and the alternative structures that can be used for trial safety oversight when a DSMB is not required. The term DSMB will be used throughout this document, however, the terms Safety Data Monitoring Committee (SDMC) and Data Safety Monitoring Committee (DSMC) are commonly used in the sector.

TRIAL SAFETY OVERSIGHT STRUCTURES FOR CLINICAL TRIALS NETWORKS

There are a number of different trial safety oversight structures which networks have established or may consider establishing. These include:

- One DSMB established by the network to provide trial safety oversight for all trials in the network's portfolio
- A DSMB established for each specific trial
- Alternative committees/structures to DSMB for each specific trial that may include the following:
  - Safety Review/Dose Escalation Committee
  - Medical Monitor
  - Clinical Event Committee (CEC).

Establishing a DSMB requires a lot of resources, coordination and time. A risk assessment should be performed to determine whether a DSMB is required, and if so, what its function and role will be. If a non-DSMB committee or structure is adopted, it will be important to justify to the Human Research Ethics Committee (HREC) why this is the case and the appropriate processes planned for monitoring safety and data integrity throughout the trial.

ASSESSING THE NEED TO ESTABLISH A DSMB

The DSMB provides oversight of trial safety and data integrity during the course of the trial.

The network or investigators should assess whether there is a need to establish a DSMB during the planning phase of the trial. A DSMB is commonly convened in the following scenarios[1]:

- Large later phase trials (IIb to IV) that address major health outcomes (mortality, major disease morbidity or end-points addressing safety and efficacy)
- Trials in which there are unknown and uncertain risks, or there is a significant risk of harm to patients, where these can be assessed during interim analyses of the trial
- Where this is concern about data integrity and credibility
- Where it may be ethically important to stop the trial early if the trial has definitively answered the questions in terms of safety or efficacy or both.

DSMBs may not be required in the following scenarios:

- Early phase clinical trials where the Principal Investigator has access to the safety data
- Non-randomised trials
- Before-after trials
- Cluster cross-over trials in which analysis cannot occur until after the final cross-over
- Trials where there are no major concerns about safety which can be addressed by alternative structures/committees.

The NHMRC guidance document[1] provides an example decision making tree for the establishment of a DSMB, and scenarios and common duties of DSMBs and non-DSMB committees.

GUIDANCE ON DATA SAFETY MONITORING BOARDS BY THE NHMRC

The NHRMC published a document on the use of DSMBs after consultation with the CTNS, regulatory authorities and industry organisations. The current guidelines should be read in conjunction with the NHMRC guidance document on DSMBs[1], which provides further information and recommendations on the following:

- The role of the DSMB
- Assessing the need to establish a DSMB
- Whether the DSMB needs to be independent
- What training and experience should DSMB members have
- How the function of the DSMB is documented
- When a DSMB is most likely to be convened
- Alternative structures/committees to DSMBs
- What the role of the Human Research Ethics Committee (HREC) is in trial safety oversight.

ESTABLISHMENT OF THE DSMB

Members of the DSMB are usually appointed by the sponsor or Trial Steering Committee (TSC) or Trial Management Committee (TMC). Some networks act as the sponsor and are therefore responsible for appointing the members. Sponsors may delegate functions to Contract Research Organisation, Chief Principal Investigator, or coordinating centre (network).

Members of the DSMB usually have combined expertise in clinical trial design, statistics, past experience on DSMB and clinical expertise in the field being investigated. The members' details, roles and responsibilities should be documented in the Charter.

CONFLICT OF INTEREST

Members of the DSMB should be free of apparent conflict of interest. These may be scientific, regulatory or financial. Members of the DSMB should not own stock in the companies with products being evaluated by the trial. Conflict of interests can be declared before the trial commences and at the start of each meeting. Any declared conflict of interest should be kept on record by the trial office. These may include any financial interests or consultancy agreements they have with the sponsor of the trial or with other companies or sponsors with products being evaluated by the trial. It will be at the discretion of the DSMB to decide whether these conflicts of interests will affect the DSMB aims and whether any member with a significant conflict of interest should resign.

The DSMB members will be responsible for advising fellow team members of any consultancy agreements or financial interests that occur during the trial. Any significant conflict of interest that occurs during the trial should be immediately reported to the trial office.

DSMB COMMITTEE DUTIES

Common duties of the DSMB may include:

- Review of protocol and protocol amendments
- Monitor data completeness and integrity
- Evaluate blinded or unblinded analysis of primary +/- secondary end-points as part of a pre-planned interim analysis
- Monitor and review participant safety including evaluation of Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety issues
- Assess recruitment rates (including actual versus target)
- Assess protocol compliance
- Monitor data completeness and integrity including timeliness of data entry, accuracy, and loss to follow-up
- Evaluate occurrence of study withdrawal
- Evaluate information provided from the trial regarding new evidence from other studies, particularly related to continuation of equipoise
- Recommend actions to the TSC/TMC regarding issues outlined above, including continuation or stopping of the trial (based on safety, efficacy or futility).

The DSMB must maintain confidentiality of all interim data to keep trial investigators and sponsors blinded to the data and results of analysis that could influence the scientific integrity of the study.

DOCUMENTING MEMBERSHIP AND FUNCTION OF THE DSMB

The membership and function of the DSMB are documented in the Charter. The Charter is usually drafted on behalf of TSC/TMC and is reviewed by the DSMB at their first meeting. Revision of the Charter may be necessary to take into account feedback from the DSMB. The Charter is usually endorsed by both the TSC/TMC and the DSMB.

ROLES AND FUNCTION OF THE DSMB

MONITORING TRIAL CONDUCT

The DSMB should consider if the trial conduct is of high quality and if it is ethical to continue the trial. In order to do this, the DSMB may consider data quality, protocol adherence, participant withdrawals and trial recruitment. If there is a large number of protocol deviations or breaches, or there is a large number of participant withdrawals, it may signal problems with the efficacy, safety and/or feasibility of the trial. In particular, if there are imbalances in protocol deviations, breaches or withdrawals between the treatment arms, it may introduce bias to the results.

MONITORING SAFETY

The DSMB commonly reviews SAEs and AEs. When assessing the safety data, the DSMB will need to consider the risks of the trial intervention relative to the control group and potentially standard of care and other aetiologies. SAEs and AEs should ideally be presented using a formal coding system (e.g. MedDRA [Medical dictionary for regulatory activities]), which has been endorsed by the International Conference on Harmonisation, and National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) for the coding of adverse and serious events.

MONITORING EFFICACY

The DSMB may also monitor the efficacy data within the trial (e.g. to determine if one treatment arm is far superior than the other such that it is not ethical to continue the trial), however, this should be pre-specified in the study protocol. A judgement of superiority/inferiority may be based on the analysis of the data and pre-defined stopping rules.

MONITORING FUTILITY

The DSMB may monitor the data during interim analysis for futility (to assess whether the data suggests the trial is not going to answer the question of interest such that it is not ethical to continue the trial). The decision by the DSMB to make a recommendation to stop a trial based on futility needs to be seriously considered and should only occur in exceptional circumstances. The decision to stop the trial may be considered on clinical judgement, other safety data and other new evidence.

CONSIDERATIONS OF EXTERNAL DATA

During the course of the trial, new information may become available about the intervention. It is important that the DSMB takes new information into consideration when making recommendations about the conduct of the trial to the TSC/TMC. The TSC/TMC may provide details of publications/external evidence regarding the intervention to the DSMB. The new external data (updated meta-analysis, etc) should be assessed very carefully.

MAKING RECOMMENDATIONS ABOUT TRIAL CONDUCT AND TRIAL CONTINUATION

The DSMB provides recommendations to the Principal Investigator and through the Principal Investigator to the TSC/TMC regarding the trial. Recommendations may include modifications to the trial conduct, continuing the trial or stopping the trial based on futility, net benefit (superiority) or net harm (inferiority).

RECOMMENDATIONS ABOUT STOPPING THE TRIAL EARLY AND PRE-DEFINED STOPPING BOUNDARIES

Some TSCs and TMCs may pre-define stopping boundaries. If used, pre-defined stopping rules should be included in the protocol before the trial commences (or at worst before the first interim analysis) and these should be documented or referred to in the DSMB Charter. It is recommended that the Charter stipulates whether these are 'hard' stopping boundaries for each interim analysis target, and therefore, if the interim data crosses these pre-defined boundaries, the DSMB should recommend to the TSC/TMC to stop the trial. Otherwise, it is common that these boundaries be used at the discretion of the DSMB to make a recommendation to the TSC/TMC to stop the trial based on a combination of clinical judgement, pre-defined 'stopping rules' and other safety data.

The decision to stop a trial early can be difficult and complex and may need to balance risk to participants with learning more about the efficacy and/or safety of the intervention. If the DSMB is considering recommending stopping the trial early, they need to assess the ethical, statistical and clinical implications of that decision and take into consideration both internal and external data. Stopping a trial early should only happen under extraordinary circumstances, and there are excellent references that the DSMB should consider if they are planning to make a recommendation to stop a trial early.[10,11] It is therefore important that the DSMB membership includes experts in trial design, the clinical area of interest, statistics, and has previous experience on DSMBs.

CONFIDENTIALITY

Members of the DSMB and any additional unblinded attendees should not disclose any interim results outside of the meeting. DSMB members should sign a confidentiality agreement before the trial commences to this effect.

NON-DSMB COMMITTEES

If it is decided that a DSMB is not required, an alternative (non-DSMB) Committee may be set up, such as a Trial Safety Committee. Duties performed by non-DSMB Committees will depend on the requirements by the trial sponsor. Common duties of the non-DSMB Committees are outlined in the NHMRC guidance document[1], which includes convening regular meetings to review safety reports, data quality, event rates, protocol adherence and withdrawals.

COMMUNICATIONS TO THE WIDER MEMBERSHIP

Communications to the wider membership about important outcomes or recommendations from the DSMB or Trial Safety Committee can be disseminated via a memo or newsletter to the site investigators. Communications should be approved by the TMC or TSC where recommendations are made about trial conduct.

FREQUENCY AND FORMAT OF MEETINGS

Frequency of meetings for the DSMB (or alternative committee) should be established in the protocol and/or DSMB charter. The format of the meetings should be set out in the Charter.

INTRODUCTORY MEETING/ORGANISATIONAL MEETING

For an individual trial DSMB, it may be appropriate to hold an introductory/organisational meeting familiarising members with Terms of Reference, review of the protocol, review of the proposed DSMB charter, introduction of DSMB members to each other, evaluation of conflict of interest, and establishing principles of confidentiality. The meeting can be used to provide advisory review of scientific and ethical issues relating to study design and conduct, to discuss the Terms of Reference and Charter for the role and functioning of the DSMB, and to discuss the format and content of the open and closed reports that will be used to present trial results at future DSMB meetings.

The meeting may be held during the final stages of protocol development. The introductory/organisational meeting will be attended by the DSMB members, a representative of the TSC/TMC and the study statistician. The DSMB may be provided with the drafts of the clinical trial protocol, trial Case Report Form (CRF), the DSMB Charter and the current versions of the case report forms to review.

FIRST REVIEW/EARLY SAFETY/TRIAL INTEGRITY REVIEW MEETING

One or more 'Early Safety/Trial Integrity Reviews' may be held during the early stage of protocol enrolment to review early safety information, review scientific and ethics issues relating to the quality of trial conduct and to ensure proper implementation of procedures to reassess the sample size where required. The Charter should outline the times that this meeting is likely to be scheduled.

Documents that may be reviewed at these meetings include:

- Conflict of interest form
- Draft minutes from previous meeting/organisational meeting
- DSMB Charter
- Trial protocol including amendments
- Summary of changes to protocol since last meeting
- Trial CRF
- Summary of changes to the protocol since the last meeting
- Shell tables for open DSMB report (to be prepared by TSC/Statistician as with requirements outlined in the Charter)
- Trial shell tables for closed DSMB report (to be prepared by TSC/Statistician as with requirements outlined in the Charter)
- Trial summary
- Recruitment report
- Data quality report from data quality meeting
- Open data safety integrity report.

In addition, for trial integrity reviews:

- Number of active sites, planned number of sites
- Total recruitment, recruitment by site-week per week, and projections
- Qualitative statement regarding site and participant recruitment
- Aggregate data on eligibility violations
- Completeness of follow-up and data collection
- Compliance with intervention delivery
- Any planned or implemented protocol amendments.

In addition, for early safety reviews:

- Explanation for how SAE and other AEs are being reported
- Any specific SAEs that trial staff want to raise
- Aggregate SAE by treatment arm (will need to be in closed session)
- Any Suspected Unexpected Serious Adverse Reactions (SUSARs) should be tabulated.

FORMAL MEETINGS

There will then be a number of meetings during the study. When these will occur should be pre-defined in the protocol and/or Charter. These will often be performed after pre-defined recruitment targets have been reached, for example, 30% and 60% recruitment targets, or pre-defined time points (e.g. annually). Reports for these meetings should be prepared by an independent Statistician and should be tabled to the DSMB for discussion. These reports may include blinded data or non-blinded data for consideration. As part of these meetings, there may or may not be a formal interim analysis of the efficacy data. A decision to perform such an analysis should be made a priori and be outlined in the protocol and/or Charter.

Example of documents that may be tabled to all DSMB members and attendees:

- Minutes of the open session from the previous meeting
- Trial DSMB Charter
- Current version of the Trial Protocol
- Current version of the Trial CRFs
- Letter for TSC from DSMB Chair from previous meetings and response (if applicable)
- Trial update/recruitment report
- Open interim report (see Appendix 2 for a list of summaries to be included in the open report).

Example of additional documents that may be tabled to DSMB members and unblinded attendees only:

- Minutes of the closed session from the previous meeting
- Closed interim report (see Appendix 2 for a list of summaries to be included in the closed report).

AGENDA AND PAPERS

Agendas, papers and data reports for the DSMB meeting should be prepared by an independent Statistician and may be prepared in consultation with the Trial Manager, Trial Statistician and the DSMB Chair. Agendas and papers are to be circulated to DSMB members one week prior to the meeting.

The agenda will usually include the following:

- Meeting location, time and dial in numbers.
- DSMB members (and roles)
- Attendees (and roles, and whether they are blinded or unblinded)
- Apologies
- Conflicts of interest
- Open sessions items and report
- Closed session items and report.

QUORUM PROCESS

Effort should be made to ensure that all DSMB members attend each meeting. The admin officer, who provides administrative support to the DSMB and is appointed by the Chair of the TSC, should make every reasonable effort to schedule meetings accordingly. Members who cannot attend in person at face-to-face meetings can attend by teleconference. It should be pre-specified in the Charter what represents a quorum for the meeting to go ahead.

If, at short notice, any DSMB members cannot attend at all, then the DSMB may still meet for discussion purposes only if the Chair and one other member is present. If the DSMB is considering recommending major actions after such a meeting, then the Chair should communicate with the absent member(s) as soon after the meeting as possible to confirm their agreement with such actions. If a meeting does not concur, then a further teleconference should be arranged with the full DSMB in attendance.

PROCEDURES FOR PROVIDING RECOMMENDATIONS

Recommendations about the conduct of the trial/trials from the DSMB Chair on behalf of the DSMB should be made to the TSC Chair following the meeting. This recommendation should be made in the format of a letter addressed to the Principal Investigator from the DSMB Chair. This recommendation should be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this Charter/Statistical Plan. The recommendation may also be based on any new external data. It is ultimately the Principal Investigator, on behalf on behalf of the TSC, who accepts or rejects the decisions made by the DSMB. If there is a disagreement between the TSC and DSMB, then a joint meeting should be convened to discuss the reasoning. However, the TSC will have the final decision about the conduct of the trial.

MEETING MINUTES

Minutes for all DSMB meetings should be drafted by the admin officer and reviewed by the DSMB Chair before circulating to members. Two sets of minutes should be prepared for the open and closed sessions, respectively. Open minutes should be circulated to all members of the DSMB and attendees within 1–2 weeks of meeting for comment/edits. Closed minutes should be circulated to DSMB members only within 1–2 weeks of meeting for comment/edits. Closed session minutes can be password protected before distribution to DSMB members and any unblinded statisticians who were involved in the analysis.

APPROVAL OF MINUTES

Approval of the DSMB minutes should be done at the next DSMB meeting.

STATISTICAL MONITORING GUIDELINES

Statistical monitoring plan, which includes tables and listings to be reviewed during the DSMB meetings, should be attached to the Charter.

REFERENCES

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APPENDIX 1: CHARTER TEMPLATE

1. HOW TO USE THE CHARTER TEMPLATE

This template contains sections which are either optional or can be developed at several levels of detail depending upon individual need.

Several different text styles have been used within the template, as follows:

- Text in {curly brackets} are instructions or advice and should be deleted from the final document
- Text in normal black font is intended as examples and can be deleted or edited
- Text enclosed in [square brackets] is intended to be replaced by whatever it is describing.

Once complete, the charter should be submitted for acceptance by the DSMB.

This document can be provided in Microsoft Word format by contacting acta@clinicaltrialsalliance.org.au

[Insert logo]	**DATA AND SAFETY MONITORING BOARD CHARTER**	Version number: [Insert version number]
		Date of issue: [Insert date of issue]

Title: [Insert title of trial]

Protocol date: [Insert protocol date and version number]

Registration: [Insert registration identifier]

Study sponsor: [Insert study sponsor]

Sources of funding: [Insert funder and identifier]

CHANGE CONTROL REGISTER

Version number	Author	Reviewed by	Approved by	Changes date	Date approved
[Insert]	[Insert]	[Insert, i.e. DSMB]	[Insert, i.e. steering committee]	[Insert]	[Insert]

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1. INTRODUCTION

This Charter is for the Data and Safety Monitoring Board (DSMB) for the [insert title of trial].

1.1 TRIAL SUMMARY

[Provide synopsis of the trial]

1.2 SCOPE OF THE CHARTER

This Charter defines the role and responsibilities of the DSMB, the operational procedures, including the membership of the DSMB, type and frequency of meetings, procedures for confidentiality, ensuring proper communication, documenting and dealing with conflicts of interests, the minimum numbers of members present at DSMB meetings before there is a quorate for decision meeting, and the recommendations that are permissible from the DSMB to the Principal Investigator and the Trial Steering Committee (TSC) or Trial Management Committee (TMC). This Charter also outlines the content of data reports and reporting requirements provided to the DSMB for its meetings to monitor the progress of the trial and provide advice on safety issues and conduct of the trial.

2. MEMBERSHIP OF THE DSMB

{The NHRMC Guidance document on DSMBs written in 2018 provides guidance on how to select suitable members of the DSMB. It is the responsibility of the Principal Investigator to invite members to a form a DSMB on behalf of the TSC/TMC.}

The DSMB will consist of the following members with clinical and biostatistics expertise. A quorum will require at least [insert number] members present during each meeting.

Voting DSMB members

DSMB Chair: [Insert name]
[Insert contact details]

DSMB Biostatistician: [Insert name]
[Insert contact details]

DSMB Clinical Investigators: [Insert names]
[Insert contact details]

Non-voting members

Unblinded Independent Statistician: [Insert names]
[Insert contact details]

{The closed report should be prepared by an independent Statistician who should liaise directly with the data centre/ Database Manager to obtain the study data and randomisation schedule for the study. The unblinded independent Statistician can be an attendee of both the open and closed sessions of the meeting. The roles and responsibilities of the independent Statistician should be defined in separate terms of reference. This may include whether they can be a member of the CTN and/or whether they can be involved in protocol development/trial design.}

Blinded Statistician: [Insert names]
[Insert contact details]

{The open report (and shell of the closed report) can be prepared by the blinded Statistician or a member of the Trial Management Team, if the latter the roles and responsibilities of this person should be outlined in the terms of reference. If the report is prepared by a member of the trial team, they can only be an attendee of the open session of the DSMB meeting.}

Administrative support (unblinded, minutes): [Insert names]
[Insert contact details]

{Cannot be directly involved in the management of the trial.}

Members of the trial team (attendees)

Trial Manager
Principal Investigator
Trial Coordinator

{Members of the trial team, for example, the Trial Manager, Principal Investigator and the Trial Coordinator can attend the open session of the DSMB meeting only.}

3. CONFLICTS OF INTEREST

{People selected to the DSMB should be free of conflict of interest. It is the responsibility of the Principal Investigator to ensure that conflicts of interests are declared at the start of the trial and during each meeting as a standing agenda item. ACTA has developed a conflict of interest template which members can complete prior to their involvement on the DSMB and frequently renewed.}

Members of the [insert name of trial] DSMB should be free of apparent conflict of interest. These may be scientific, regulatory or financial. Members of the DSMB should not own stock in the companies with products being evaluated by the trial. Conflict of interests should be declared before the trial commences and at that start of the meeting and should be disclosed and held by the trial office. These include any financial interests or consultancy agreements they have with the sponsor of the trial or with other companies or sponsors with products being evaluated by the trial. It will be at the discretion of the DSMB to decide whether these conflicts of interests will affect the DSMB aims and whether any member with a significant conflict of interest should resign.

The DSMB members will be responsible for advising fellow team members of any consultancy agreements or financial interests that occur during the trial. Any significant conflict of interest that occurs during the trial should be immediately reported to the trial office. Members of the DSMB should not disclose any interim results outside of the DSMB.

4. CONFIDENTIALITY

Members of the DSMB and any additional unblinded attendees should not disclose any interim results outside of the DSMB. Members will sign a confidentiality agreement before the trial commences.

5. RESIGNATION/TERMINATION OF THE DSMB MEMBER AND REPLACEMENT

Membership of the DSMB will be for the course of the trial. If it becomes apparent that a member develops a significant conflict of interest, they will be asked to resign from the DSMB. The DSMB may request through the Principal Investigator to the TSC/TMC that an additional member may be required, for example, if additional clinical or statistical expertise is required. The DSMB may decide to terminate a member from the DSMB based on a majority vote by the DSMB. If a member resigns, the TSC/TMC will promptly appoint a suitable replacement.

6. PRIMARY RESPONSIBILITIES OF THE DSMB

{The 2018 NHRMC Guidance document on DSMBs[1] provides guidance on the roles and responsibilities of the DSMB}.

The role of the DSMB is to assess the safety [and efficacy] of the interventions during the trial, and to monitor the conduct of the trial. Specifically, the role of the DSMB includes:

- Monitor and review of participant safety during the trial
- [Monitor the efficacy based on pre-planned interim analyses (if required)]
- [Review recruitment rates actual versus target]
- [Review protocol adherence/breaches and provide recommendations to improve protocol adherence]
- [Review serious adverse events and other safety issues (SAEs, AEs, SUSARS, etc)]
- [Provide recommendations to the TSC/TMC for continuing or stopping the trial (based on safety, efficacy or futility – see NHRMC report on DSMBs)]
- [Contribute to enhancing the integrity of the trial by making recommendations to the TSC/TMC on selection criteria, recruitment and retention].

The DSMB will be advisory to the Principal Investigator and through the Principal Investigator to the [insert acronym of the trial] TSC/TMC, which comprises the trial leadership group.

The Principal Investigator will be responsible for promptly reviewing the DSMB recommendations and responding to the DSMB Chair. The TSC/TMC will advise on whether to continue or terminate the trial and determine whether amendments to the protocol or changes in study conduct are required based on the DSMB's recommendations. If the TSC/TMC does not agree on the DSMBs recommendations, a memo outlining the reasons will be forwarded to the DSMB to the reviewing HREC within [x] days.

The Principal Investigator holds the ultimate responsibility for the decisions regarding the trial.

7. FREQUENCY AND SCHEDULING OF MEETINGS

The DSMB will meet in person or by teleconference prior to the start of recruitment, and at scheduled intervals during the trial. {It should be outlined in the charter how often the DSMB will meet, for example, yearly or at recruitment targets for example, 25%, 50% or 75%.}

The Trial Manager or Principal Investigator will advise the DSMB via the Administration Officer when to schedule a meeting as outlined in the DSMB Charter. Alternatively, the DSMB at their discretion may schedule ad hoc meetings that fall outside of the pre-planned meetings in the Charter.

{The TSC/TMC is responsible for coordinating the meeting date, time and venue for the DSMB meetings.}

8. FORMAT AND PURPOSE OF MEETINGS

8.1 INTRODUCTORY MEETING/ORGANISATIONAL MEETING

{For an individual trial DSMB it may be appropriate to hold an introductory meeting familiarising members with terms of reference, role of the DSMB members and trial documentation, conflict of interest and confidentiality forms, election of Chair.}

The initial meeting of the DSMB will be an 'organisational meeting'. It will be held during the final stages of protocol development, to provide advisory review of scientific and ethical issues relating to study design and conduct, to discuss the Terms of Reference and Charter for the role and functioning of the DSMB, and to discuss the format and content of the open and closed reports that will be used to present trial results at future DSMB meetings. The organisational meeting will be attended by the DSMB members, a clinician representative of the TSC/TMC and the study Statistician. The DSMB will be provided with the drafts of the clinical trial protocol, trial Case Report Form (CRF), the DSMB Charter, and the current versions of the case report forms.

[Insert the time/date when the meeting is likely to be scheduled.]

8.2 FIRST REVIEW/EARLY SAFETY/TRIAL INTEGRITY REVIEW MEETING

One or more 'Early Safety/Trial Integrity Reviews' is usually held during the early stage of protocol enrolment to review early safety information, review scientific and ethics issues relating to the quality of trial conduct and to ensure proper implementation of procedures to reassess the sample size.

The Early Safety/Trial integrity review meeting will be held [insert the time/date when the meeting is likely to be scheduled.]

At this meeting, the following will be reviewed: [List documents that could be reviewed here.]

{Example of documents that could be tabled:

- Conflict of interest form
- Draft minutes from previous meeting/organisational meeting
- DSMB Charter
- Trial protocol
- Summary of changes to protocol since the last meeting
- Trial CRFs
- Summary of changes to CRFs since the last meeting
- Trial shell tables for open DSMB report (to be prepared by TSC/Statistician as with requirements outlined in the Charter)
- Trial shell tables for closed DSMB reports (to be prepared by TSC/Statistician as with requirements outlined in the Charter)
- Trial summary
- Recruitment report
- Data quality report from data quality committee meeting
- Open data safety integrity report (circulated to all DSMB members and attendees).

For a trial integrity meeting, the following will also be included:

- Number of active sites, planned number of sites
- Total recruitment, recruitment by site-week per week, and projections
- Qualitative statement regarding site and participant recruitment
- Aggregate data on eligibility violations
- Completeness of follow-up and data collection
- Compliance with intervention delivery
- Any planned or implemented protocol amendments.

For an early safety meeting, the following will also be included:

- Explanation for how SAEs and other AEs are being reported
- Any specific SAEs that trial staff want to raise
- Aggregate SAE by treatment arm (will need to be in closed session)
- Any SUSARs should be tabulated.}

8.3 INTERIM SAFETY REPORT MEETING

[Insert number of planned interim analyses meeting] safety reports are planned for the [insert trial name] trial. These will be performed after [1st recruitment target/time point] and [2nd recruitment target/time point] patients have completed [specify] follow-up {add/delete schedule if required}. The independent Statistician [insert name] will perform the interim analyses, results of which will be tabled with the DSMB for discussion. The details of the interim analysis should be pre-defined in the protocol. Any proposed modification to the protocol or the trial advised by either the DSMB or TSC will be communicated to the respective Chairs.

{Example of documents that could be tabled for an interim analysis DSMB meetings:

Tabled documents at open meetings (circulated to all DSMB members and other attendees)

- Minutes of the open session from the previous meeting
- Trial DSMB Charter
- Trial protocol version
- Trial CRF version
- Letter for TSC Chair from DSMB Chair from previous meeting(s) (if applicable)
- Trial summary
- Trial update/recruitment report
- Open interim analysis report (see Appendix 2 for a list of summaries to be included in the open report).

Tabled documents at closed members (circulated to DSMB members and unblinded attendees) – [list people receiving these documents]

- Minutes of the closed session from the previous meeting
- Closed interim analysis report (see Appendix 2 for a list of summaries to be included in the closed report).}

8.4 QUORUM PROCESS

Effort should be made to ensure that all DSMB members attend the meetings. The Admin Officer, who provides administrative support to the DSMB, will make every reasonable effort to schedule meetings accordingly. Members who cannot attend in person at face-to-face meetings can attend by teleconference. A quorum is reached for the meeting if [specify number] members of DSMB are present.

If, at short notice, any DSMB members cannot attend at all then the committee may still meet for discussion purposes only if the Chair and one other member are present. If the DSMB is considering recommending major actions after such a meeting, then the Chair should communicate with the absent member(s) as soon after the meeting as possible to confirm their agreement with such actions. If they do not concur, then a further teleconference should be arranged with the full DSMB in attendance.

8.5 AGENDA AND PAPERS

{Notification and preparation of reports for submission to the DSMB should be done in consultation with the Trial Statistician. The process begins at least a few months in advance to prepare for the meeting. This will allow for sites to enter in end-point data, data cleaning by the project team, statistical analysis, data report preparation, preparing agendas and papers, and scheduling of meetings.}

Agendas, papers and data reports for the DSMB meetings will be prepared in consultation with the Trial Manager, Trial Statistician and the DSMB chair. Agendas and papers are to be circulated to members one week prior to the meeting.

The agenda will usually include the following:

- Meeting location, time and dial-in numbers
- DSMB members (and roles)
- Attendees (and roles, and whether they are blinded or unblinded)
- Apologies
- Conflicts of interest
- Open sessions items and reports
- Closed sessions items and reports.

8.6 OPEN SESSIONS

DSMB members, unblinded Statistician, Trial Manager, Trial Coordinator and Principal Investigator will attend the open session of the DSMB meeting. This will be a joint session between members of the trial management team and the DSMB. This gives the DSMB an opportunity to query trial team members about the conduct of the trial.

8.7 CLOSED SESSIONS

DSMB members, the unblinded Statistician and [Admin Officer] will then remain for a closed session.

{The documents for the closed session can be password protected and files should be stored securely on protected servers which doesn't compromise the integrity of the trial and expose results to the project team.}

8.8 PROCEDURES FOR PROVIDING RECOMMENDATIONS

Recommendations about conduct of the trial from the DSMB Chair on behalf of the DSMB will be made to the TSC Chair following the meeting. This recommendation will be made in the format of a letter addressed to the Principal Investigator from the DSMB Chair. This recommendation will be based primarily on safety [and efficacy] considerations and will be guided by statistical monitoring guidelines defined in this Charter/statistical plan. It is ultimately the Principal Investigator on behalf on behalf of the TSC who accepts or rejects the decisions made by the DSMB. If there is a disagreement between the TSC and DSMB, then a joint meeting should be convened to discuss the reasoning. However, the TSC will have final decision about the conduct of the trial.

8.9 MEETING MINUTES

{Meeting minutes should be circulated as soon as possible after the meeting for members and attendees to comment. Two sets of minutes should be prepared for the open and closed sessions, respectively. Closed session minutes can be password protected before distribution to DSMB members and to other unblinded attendees (including the unblinded Statistician)}.

Minutes will be drafted by the [list person responsible] and reviewed by the DSMB Chair before circulating to members. Open minutes will be circulated to all members within 1–2 weeks of meeting for comment/edits. Closed minutes will be circulated to DSMB members only and unblinded Statistician within 1–2 weeks of meeting for comment/edits. [List all the names of people who have received closed minutes.]

8.10 APPROVAL OF MINUTES

Approval of the draft DSMB minutes will be done at the next DSMB meeting.

9. STATISTICAL MONITORING GUIDELINES

{A statistical monitoring plan, which includes tables and listings to be reviewed during the DSMB meetings, should be attached to the Charter.}

APPENDIX 2: EXAMPLE CONTENTS OF DSMB'S OPEN AND CLOSED REPORTS

OPEN STATISTICAL REPORT: AN OUTLINE

Note: all of the following should be presented pooled across treatment arms:

- Summary of the study and Trial Protocol
- Statistical commentary explaining issues presented in Open Report figures and table
- DSMB monitoring plan and summary of Open Report data presented at prior DSMB meetings
- Major protocol changes
- Information on patient screening (screening log).
- Study accrual (by month and since last meeting), overall and by institution
- Baseline characteristics
  - demographics
  - laboratory values and other measurements
  - previous health status and other similar information
- Adherence to treatment schedule (pooled by treatment regimen)
- Completion of scheduled visits (pooled by treatment regimen)
- Reporting delays for key events (pooled by treatment regimen)
- Length of follow-up data available (pooled by treatment regimen)
- Participant treatment and study status (pooled by treatment regimen)
- (Serious) adverse events (pooled by treatment regimen)
- Primary efficacy outcome (un-adjudicated and adjudicated) and secondary efficacy outcomes (pooled by treatment regimen) (if pre-specified)
- Completeness and query status of data, in particular the adjudication status of the primary outcome (pooled by treatment regimen).

CLOSED STATISTICAL REPORT: AN OUTLINE

Note: this report is generally presented by treatment arm, although the treatment arms may be masked, but available upon request by the DSMB members.

- Detailed statistical commentary explaining issues raised by Closed Report figures and tables
- DSMB monitoring plan and summary of Closed Report data presented at prior DSMB meetings
- Repeat of the Open Report information presented by treatment group.

APPENDIX 3: EXAMPLE AGENDA

Name, date, time and place of meeting

Dial-in numbers

DSMB Members

Chair
DSMB Statistician
Members

Attendees

Blinded Statistician
Admin Officer (minutes)
Unblinded independent Statistician
Trial Manager
Principal Investigator
Trial Coordinator

Apologies

Tabled documents

1. Trial summary
2. Trial DSMB Charter
3. Trial protocol
4. Trial CRF
5. Recruitment report
6. Shell data reports (open and closed)
7. Conflict of interest form.

AGENDA

1. Opening

1.1 Welcome
1.2 Apologies
1.3 Confidentiality and conflict of interest

Combined open and closed sessions (all members and attendees present)

2. Review of documents

2.1 Trial Charter version
2.2 Trial protocol version
2.3 Trial CRF version

3. Progress of the trial

3.1 Update (Trial Manager)
3.2 Recruitment and follow-up issues

4. Early safety/trial integrity reviews

4.2 Discuss format and requirements for early safety/trial integrity reviews

Formal interim analysis meetings

5. Open reports

5.1 Review and discuss format for open reports

6. Closed reports

6.1 Review and discuss format for closed reports

7. Other business

8. Next meeting

TBA

APPENDIX 4: CONFIDENTIALITY AGREEMENT

I, _____ (name),

_____ (position) of,

_____ (organisation)

_____ (address),

acknowledge the confidential nature of all activities of the Committee, including all discussions, whether by verbal, written or electronic and all associated documents.

I agree that I will not supply details or copies of documents to any third party outside the Committee except as outlined in the Committee Terms of Reference or agreed to in writing by the Committee.

I understand that my obligations under this agreement continue to have full force and effect when I am no longer a member of the Committee.

Signature: _____ Date: / /

Signed on behalf of the [*administering CTN*] by:

Position: _____

Signature: _____ Date: / /

APPENDIX 5: CONFLICT DECLARATION

Name (please print):

Committee name:

Period covered by declaration:

Once each year, all members of the Committee must provide signed declaration forms describing any arrangements that have been entered into, or have been active, over the previous 12-month period that may give rise to a conflict, including, but not limited to, any financial benefits. These declarations will be recorded in the minutes of the appropriate Committee meeting. It is understood that information provided by the relevant members is for the purposes of disclosing potential conflicts of interest within the group, will not be put to any other purpose, and will be viewed only by the relevant Committee. Where in the opinion of the Committee, members are required to lodge a conflict of interest statement and fail to do so within a reasonable period of time, such members will become ineligible to hold any office within the group.

Description of interest	Actions taken by the individual to address the conflict	Steps taken by the Committee for dealing with the conflict

I certify that I have disclosed all interests relevant to my role and will disclose any further interest arising during the year at Committee meetings.

Signature: Date: / /

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