Guidance document title: **Data and Safety Monitoring Boards**

Version: 3.0

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Author Signature:  **Date:** 28 November 2018

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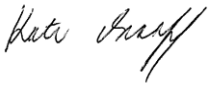
Responsibility:  **Date:** 8 July 2021

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These signatures confirm the reviewers agree with the technical content of the document and that this document is approved for implementation at the RCH Campus.

This document is effective from the date of the last approval signature and will be reviewed in two years.

Document History

Version	Author	Description of Change
1.0	CRDO - F. Williams	New Issue
2.0	CRDO - F. Williams	Inclusion of wording from the NHMRC Guidance: Data Safety Monitoring Boards (DSMBs) (EH59, November 2018) https://www.nhmrc.gov.au/guidelines-publications/eh59NHMRC Appendix 1 from the above document was also incorporated into this MCTC Guidance (refer to Appendix 2).
3.0	CRDO	**New**: 3.3.1.2.1: Confidential Disclosure Agreements (CDA) applicable to external DSMB members. APPENDIX 2: Template DSMB CDA with fee APPENDIX 3: Template DSMB CDA without fee **Updated:** Section 7 in Appendix 1: CRDO Data and Safety Monitoring Board Charter Template.

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1. PURPOSE

A Data and Safety Monitoring Board (DSMB)* is one of a range of monitoring mechanisms available to mitigate the risks inherent in a clinical trial. Every trial must identify the most appropriate mix of trial and safety monitoring activities.

DSMBs are an important component of many monitoring plans but are not required for all clinical trials. This document describes the typical role and function of a DSMB so that researchers can use this information to determine whether a DSMB should be convened as part of a trial's overall monitoring strategy. It also describes alternative monitoring structures that may be utilised when a DSMB is not warranted.

This document also provides procedures for establishing and operating a DSMB; note that **these procedures should be read in conjunction with the DSMB Charter template** referenced throughout this guidance document (see Appendices for the link).

Note that this document is intended for use in investigator-initiated clinical trials.

**For the purpose of this document, the term DSMB will be used and is intended to describe an independent committee who monitor the safety of a trial. Note that other terms for such a committee exist, including Data Monitoring Committee (DMC) and Data and Safety Monitoring Committee (DSMC).*

2. RESPONSIBILITY AND SCOPE

It is the responsibility of the **Sponsor-Investigator*** of the study together with the Trial Steering Committee (TSC)** or (where there is no TSC), the Trial Management Group (TMG)** to:

- make the final decision regarding whether a DSMB is required;
- and where a DSMB is required, to appoint the members and ensure a charter which details the roles and responsibilities of the DSMB members is developed and followed..

Establishing a DSMB may also be requested as a pre-requisite for ethical approval.

** Sponsor-Investigator: For MCRI investigator-initiated clinical trials without an external sponsor, the sponsor is MCRI. Taking on the role of Sponsor means taking 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 through 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.*

*** See Glossary*

APPLICABILITY

This standard operating procedure (SOP) applies to all Melbourne Children's campus employees (including visiting medical officers, visiting health professionals, contractors, consultants and volunteers) who propose to undertake, review and/or govern (clinical) trials involving Melbourne Children's patients and staff.

3. PROCEDURE

3.1. WHAT IS A DSMB AND WHAT IS ITS ROLE?

Risks associated with clinical trials include: the risks to participant safety, the risk to data validity and, where real or perceived conflicts of interest exist, the risk to trial credibility. A DSMB is one of a range of mechanisms available to Sponsor-Investigators to mitigate these risks.

A DSMB is a multi-disciplinary group established to review the accumulating trial data at regular intervals in order to monitor the progress of a clinical trial for safety, trial conduct and/or efficacy issues. Based on these findings, the DSMB will then make recommendations to the Sponsor-Investigator or the TSC as to whether the trial should continue, be modified, or stopped for safety or ethical reasons. While investigators and sponsors monitor the day-to-day conduct of the trial, DSMBs make recommendations concerning the overall conduct of the trial. The DSMB's access to comparative data (sometimes unblinded) enables it to undertake a more comprehensive, integrated and unbiased review. DSMBs play an important role in:

- Safeguarding the interests of study participants;
- Ensuring that definitive and valid results are produced which will reliably inform the future treatment of patients;
- Enhancing the credibility of the trial.

Every trial must identify the most appropriate mix of (i) general trial monitoring activities to be undertaken by the Sponsor-Investigator and team and (ii) the data and safety monitoring activities undertaken by the DSMB. The TSC/TMG in collaboration with the DSMB should decide the nature of monitoring by the DSMB that is required for the trial. This can include any or all of the following:

- The progress of the trial, in terms of recruitment and issues arising during the trial;
- The accumulating safety data from the trial;
- The critical efficacy endpoint(s) of the trial (N.B. if the DSMB is required to monitor efficacy, the interim analyses of this data should be pre-specified in the study protocol).

It is important to ensure that there remains genuine uncertainty about the most beneficial treatment (equipoise) and, of course, that there is no unavoidable or increased risk of harm for trial participants. However, it is also important to ensure that a clinical trial continues for sufficient duration to answer its primary scientific question. Remaining objective can be difficult for those with a vested interest in the trial, so monitoring conducted by a group independent of the trial (i.e. a DSMB) helps to protect the integrity of trial monitoring and the credibility of trial results. Independence can be summarised as having no involvement with the trial other than as a member of the board, having little or no involvement with the members of the TMG responsible for the trial, and having no direct interest in the outcome or ongoing running of the trial.

The roles and responsibilities of the DSMB members along with the operating procedures of the DSMB should be outlined upfront and agreed on by all parties in the form of a charter (see section 3.5).

3.2. ASSESSING THE NEED FOR A DSMB

Not all clinical trials require monitoring by an **independent board**. DSMBs add administrative complexity to a clinical trial and require resources to set up the committee, coordinate

meetings and prepare reports for meetings. Although there is no single rule for what types of study require a DSMB:

- They are used most in later phase (IIb to IV) trials that address major health outcomes such as mortality or progression of a serious disease and that are designed to definitively address efficacy and safety issues.

- They may also be convened when there is a significant risk of harm, or unknown or uncertain risks, where regular interim, comparative analyses of the accumulating safety data would be beneficial.

DSMBs are **recommended in** the following scenarios:

- Large trials, long-term trials and trials involving particularly vulnerable patients;
- Trials where there are little safety data and/or there are safety concerns in at least one trial arm;

- Trials of any size primarily comparing rates of mortality, major disease morbidity or other significant endpoints concerning patient safety;
- Trials where it may be ethically important for the trial to stop early if the primary question addressed has been definitively answered prior to the completion of the trial.

DSMBs are **not usually required** in the following scenarios:

- Single-centre open-label Phase I and II clinical trials, as the Sponsor-Investigator will have access to all relevant safety data;
- A multicentre, Phase I clinical trial where there are very clear rules for stopping the trial. For example, a classic open-label dose escalation trial with clear and objective criteria for halting the dose escalation when unacceptable side effects are observed.

The TSC/TMG should assess the need for a DSMB during the planning phase of a clinical trial. When making the decision on whether a DSMB should be established or not, aspects such as clinical indication, trial endpoint(s), trial duration and trial population should be considered. Furthermore, the available knowledge in the literature may alert the trial team to the need for a DSMB. The main decision regarding the DSMB should be made based on safety but should also take aspects of practicability and assurance of scientific validity into consideration. These latter criteria are discussed in the following sections.

3.2.1. IS DSMB REVIEW PRACTICAL?

Setting up a DSMB is non-trivial and takes time, as it involves sourcing appropriate members (see section 4.3) including a statistician (ideally one who is independent of the study conduct) who will conduct relevant analyses to be included in the DSMB report. It also involves setting out a charter, arranging meetings and preparing reports for the DSMB which can take up to a few weeks to produce for each review. This means that in a clinical trial with a short time frame there may not be enough time for appropriate preparation of reports for a DSMB. In this case the use of a DSMB might not be beneficial for the trial and might even delay the end of the trial. Similarly if a trial recruits participants over a short period of time and has a short intervention, the DSMB may not have an opportunity to have a meaningful impact.

3.2.2. WILL A DSMB HELP ASSURE THE SCIENTIFIC VALIDITY OF THE CLINICAL TRIAL?

Over time, there may be changes in understanding of disease and standard of care. In addition, sometimes accumulating data from within the clinical trial (e.g. overall event rates) may suggest the need for changes to the trial protocol, such as modifications to the inclusion criteria and/or the endpoints. Recommendations to modify the trial protocol based on accumulating data and/or external evidence are best made by an independent party such as the DSMB who can provide an objective opinion on what would be best for the trial. If, and how this is done should be outlined in the charter.

3.2.3. WHAT ARE THE ALTERNATIVES TO DSMBS?

As outlined in the NHMRC Guidance (EH59, November 2018):

- "In any trials where a DSMB is not convened, a trial group or committee, often with multi-disciplinary representation, may be convened to provide some level of structured oversight. The algorithms for determining the type and nature of data and safety monitoring will vary substantially depending on the trial sponsor, as will the terminology to describe the individuals, groups or committees utilised. The type of oversight provided by 'non-DSMB committees' may include regular meetings to review individual safety reports, aggregate event rates, data relating to the quality, protocol adherence and patient retention rates." It is important to remember that the investigators, TMG, and TSC should not review any outcome data unmasked, or data that are still masked but grouped per treatment arm.

- "Non-DSMB committees may be entirely internal to the study team or, depending on the outcome of the Sponsor-Investigator's risk assessment, may include one or more expert members that are external to the Sponsor-Investigator or study team. The following are examples of individuals, groups or committees that are utilised to provide monitoring and/or oversight for clinical trials. These examples are not intended to be exhaustive of the types of entities that may be utilised for trial monitoring and/or oversight.

    - ***Medical Monitor*** An independent medical monitor may perform a variety of roles related to safety oversight, such as the ongoing monitoring of reports of serious adverse events (SAEs) submitted by investigational sites to identify safety concerns and make recommendations for continuing or stopping a trial.

    - ***Safety Monitoring Committee (SMC)*** This should include one or more individuals with expertise in the study field plus a statistician. The committee's role is to provide independent and timely review of any trial-related safety issues. The SMC members may be recruited from within the institution or externally. The statistician should, ideally, be independent to avoid unblinding of study data, but may be the trial statistician where this is impractical. The SMC can be an alternative for trials that are not of sufficient size, complexity or risk to warrant a fully assembled DSMB, but which, by virtue of potentially increased risk compared to smaller or simpler trials, should have an independent or more robust review.

    - ***Dose Escalation Committee*** These types of non-DSMB committee are commonly utilised in **early phase trials** to perform assessments of safety and pharmacokinetic data prior to dose escalation. Commercial trial safety review

committees often include a medical monitor, sponsor staff and the trial investigator and, where indicated by the risk assessment, one or more external members. In a non-commercial trial, these activities may be conducted by the Trial Management Group."

- ***Clinical Event Committee (CEC)*** A CEC is a panel of independent experts that conduct a central review of trial outcomes (also known as 'endpoints') in a blinded and unbiased manner, ascertaining whether they meet protocol definitions. Although such outcome adjudication committees are not strictly trial oversight committees, they contribute to the quality of the clinical trial by providing a central review of trial outcomes. They are particularly useful when outcomes are complex to assess, include subjective components, or the study cannot be blinded.

  Also note the contributions of the Trial Management Group and, where one is established, the Trial Steering Committee.

- The **Trial Management Group** (see Glossary) at the coordinating or principal study site, oversees all aspects of the conduct of the trial including performing safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. The Trial Management Group remains blinded.
- The **Trial Steering Committee** is an executive decision-making group providing additional independent trial oversight. This group remains blinded.

Sponsors are encouraged to adopt a systematic, risk-based approach when developing a monitoring plan for the ongoing safety of their trials and a variety of practices may be employed. In some trials, more than one type of committee performing a range of complementary roles may be utilised to provide an appropriate level of oversight. In others, much simpler structures and practices may be adequate to provide oversight.

For trials that are in progress, the HREC is responsible for considering information arising from the trial that may bear on the continued ethical acceptability of the trial at the study site(s) it oversees. Although HRECs conduct periodic reviews of ongoing trials, they do not review interim results. Instead, they rely on information provided by the sponsor. As such, the HREC should ensure that the sponsor has appropriate arrangements in place to monitor the safety of participants during the trial by reviewing the sponsor's plans for safety monitoring described in the protocol or ethics application. Information could include details of what interim results will be monitored and when analyses will be completed, who will review interim results, and what guidelines will be followed for modification or termination of a study. As part of their review, the HREC should be given information to assess how trial risks will be mitigated and managed. For randomised controlled trials, the protocol or ethics application should enable the HREC to determine the following:

- If a DSMB is to be convened, what its main role and function will be;
- If a DSMB is not to be convened, whether this is justified given the nature of the trial;

- That appropriate (risk‑based) processes for monitoring trial safety and data integrity are planned.

As the trial progresses, the HREC should be provided with information in annual reports that enable an assessment of whether ongoing safety monitoring is being conducted appropriately, that the trial's safety monitoring plans are being followed and, where necessary, that the plans are being adapted to take into account new findings.

3.3. ESTABLISHING A DSMB

In the event that the TSC/TMG decide that the trial should be monitored by a DSMB, the DSMB should be established prior to finalising the trial protocol to ensure that the DSMB members have no major objections with the design of the protocol and/or the monitoring plan for the trial. In particular, the DSMB should be operational (i.e. ready to commence reviewing data) before enrolment into the trial starts to enable it to respond early should any potential concerns arise regarding participant safety.

DSMB members should be selected by the TSC/TMG and should be approached by the Sponsor-Investigator or their delegate. The selection of DSMB members is extremely important given the importance of the DSMB's role in assuring participant safety during the trial. There are three aspects with respect to membership to be considered when establishing a DSMB: composition of the DSMB, qualifications needed by DSMB members and independence of DSMB members. These are discussed in the following sections.

3.3.1. COMPOSITION OF THE DSMB

Relevant qualifications and experience are essential for DSMB members to ensure that they perform their tasks effectively. Collectively, potential DSMB members should have scientific expertise relevant to the indication being studied, practical experience with conducting clinical trials, a good understanding of the problems and limitations of trials, and statistical expertise. The DSMB's role is multidisciplinary and it is important that the DSMB consists of expertise from different scientific areas.

For practical reasons, the number of members of a DSMB should be limited (minimum of 3, maximum of 10) and an odd number may simplify decision making. The optimal size needs to balance the advantages of larger groups (full range of skills, wide range of opinions, low risk of dominance) with the advantages of smaller groups (availability of members, convenience and cost of meetings, less reluctance to express views, less risk of conflict, less potential for bias towards riskier decisions).

A quorum for each meeting should be decided upon and detailed in the DSMB's Charter.

3.3.1.1. QUALIFICATIONS OF THE DSMB

The minimum requirements for a DSMB are as follows (a member may fulfil more than one of these requirements):

- At least one qualified expert to assess the clinical aspects of efficacy monitoring in the relevant field (if required);
- At least one qualified expert to assess the clinical aspects of safety monitoring in the relevant field;
- At least one qualified member with biostatistical expertise;

- At least one member with experience in clinical trials;
- At least one member with prior experience in serving on a DSMB.

One member of the DSMB should be selected as chair of the DSMB. This decision should be made by the Sponsor-Investigator in conjunction with the TSC/TMG. It is strongly recommended that the DSMB Chair has served on a DSMB previously. The DSMB Chair should understand biostatistical and clinical issues associated with trials; and be capable of facilitating discussion, integrating different points of view and moving toward consensus on recommendations.

DSMB membership should ideally be for the duration of the clinical trial. If any members leave the DSMB during the trial, the TSC/TMG should promptly appoint their replacement in agreement with the remaining members of the DSMB. Further appointments may be made to the DSMB if members of the DSMB or the TSC/TMG believe additional expertise is required.

3.3.1.2. INDEPENDENCE OF THE DSMB

One of the most significant characteristics of a DSMB is its ability to provide independent review of clinical trial data. Independence is defined as having no involvement in the design and conduct of the trial, except through a role on the DSMB, and having no financial or other connections to the Sponsor-Investigator or other trial organisers that could influence (or be perceived to influence) objectivity in evaluating trial data. When establishing a DSMB, the primary consideration is to ensure that members have **no vested interest in the outcome of the trial** and are therefore free from material conflicts of interest. **Declaration of a conflict of interest is an ongoing process; it should be declared on joining the DSMB and prior to each DSMB meeting and recorded in the minutes of each meeting.**

For most investigator-initiated clinical trials, DSMB members may be from (or affiliated with) the same institution but (as outlined above) must have no vested interest in the trial outcome. However, DSMB members should where possible be recruited external to Melbourne Children's in order to maximise independence.

3.3.1.2.1. CONFIDENTIAL DISCLOSURE AGREEMENTS (CDA)

When a member of the DSMB is employed by an external institution and being provided MCRI's confidential information (e.g. Trial data, patient information, etc.), the Institutions for each DSMB member must sign a CDA. The CDA must be signed by an authorised representative of the institution, not the individual member of the DSMB (unless they are authorised to sign on behalf of their institution).

Please refer to the template DSMB CDAs in Appendix 2 and 3. Investigator's may amend the template as required and forward the new draft to MCRI Legal for review and approval before arranging signatures.

3.4. MONITORING ACTIVITIES CONDUCTED AND OVERSEEN BY A DSMB

3.4.1. MONITORING TRIAL CONDUCT

High quality conduct of a trial is essential in order to protect participants and produce data that is accurate and valid. When reviewing the trial progress, the DSMB must consider whether study conduct is of high quality and whether it is ethical to continue the trial. In

performing its task, a DSMB should consider essential parts of trial conduct such as protocol adherence and participant withdrawal. Protocol deviations that require exclusion of the participant from the per-protocol analysis, serious breaches or a large number of participants who have withdrawn from a trial are often indicators of possible problems with respect to safety, efficacy, or the feasibility of trial procedures and these may render the trial unethical. In particular, imbalances between treatment groups with respect to these occurrences can directly impact the trial outcome as this can lead to a bias in the treatment comparison.

The reports to the DSMB should include data on any deviations resulting in exclusion from the per protocol analysis, details of serious breaches, discontinuations from study treatment, withdrawals from study follow up procedures and safety events.

If major problems with the trial conduct are observed, the DSMB should consider possible recommendations to the TSC/TMG to improve the quality of the trial. In extreme cases, the DSMB may wish to suggest that the trial be halted or stopped due to quality issues.

3.4.2. MONITORING SAFETY

In most cases, safety monitoring will be the major task for the DSMB. This will generally involve monitoring of adverse events (AE) and in particular serious adverse events (SAE), Suspected Unexpected Serious Adverse Reactions (SUSAR), Urgent Safety Measures (USM) as well as Significant Safety Issues (SSI).

- An AE is defined as any untoward medical occurrence in a study participant, regardless of whether or not it is thought to be related to study procedures or to a study intervention (e.g. an experimental drug or device; a behavioural intervention; a procedural intervention).
- An SAE is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
- A SUSAR is an adverse reaction that is both serious and unexpected.
- A USM is a measure taken in order to eliminate an immediate hazard to a participant's health or safety.
- An SSI is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

When interpreting safety data, the DSMB should use the accumulating clinical data to differentiate (serious) AEs, SUSARs and USMs associated with the trial interventions from those with other aetiologies.

It is advised to consider available catalogues such as MedDRA (Medical Dictionary for Regulatory Activities) for the classification of (serious) AEs. MedDRA is the AE classification dictionary endorsed by the International Conference on Harmonisation (ICH).

In multinational trials, the DSMB needs to understand potential cultural, political and medical/surgical practice issues that may affect safety data.

The decision on whether to recommend continuation of the trial based on safety is often made using clinical judgement and there are commonly no specific "stopping rules" regarding safety; this should be pre-defined in the DSMB Charter. The DSMB Charter will also define who can be unmasked to study group assignment in reports detailing participant AEs, SAEs, SUSARs and USMs.

3.4.3. MONITORING EFFICACY

In some situations, the DSMB may be asked to monitor efficacy. Reasons for monitoring efficacy might be for futility (where the interim data suggest that the trial is not going to provide an answer to the question of interest), checking the assumptions for sample size calculation, or for monitoring for superiority (where one intervention is far superior to another in which case it is not ethical to continue with the less favourable intervention).

If the DSMB is required to monitor efficacy, it is important to provide a "stopping rule" as guidance for the DSMB regarding when to recommend that the trial be stopped. For example, in a superiority trial it would be important to define what would be a large enough difference (or evidence of a difference) between the treatment groups to warrant stopping the trial. In the same way, stopping rules for futility can be defined. Any stopping rule should be pre-determined in the trial protocol and in the DSMB Charter and should be agreed between the members of the TSC/TMG and the DSMB. A stopping rule should take into the number of interim analyses of the data that are planned. If the data are reviewed frequently this inflates the Type I error (i.e. the chance of finding a difference between the interventions when there really is no difference), and hence some adjustment for this should be made in defining the stopping rule. If a stopping rule is applied to justify discontinuation of the trial due to evidence of futility, the global (over all planned assessment) Type I error rate needs to be adjusted to account for the interim 'looks' at the data.

The DSMB's Charter should clearly describe the statistical methods to be applied for analysis of the efficacy data. These methods must comply with the statistical methods outlined in the trial protocol.

The MCRI Clinical Epidemiology and Biostatistics Unit (CEBU) can be contacted for further advice on stopping rules.

If stopping rules are used, they should be used as a guideline by the DSMB rather than an absolute rule; the DSMB should take into account the safety data from the trial as well as external evidence from other trials in deciding whether a recommendation is made to stop the trial or not. Reasons should be recorded in cases where the stopping rule is disregarded by the DSMB.

Even if the trial protocol does not specify an interim analysis to assess efficacy, a 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. In such cases, the DSMB may request to receive efficacy data additional to the available safety data. This will need to be approved by the Sponsor-Investigator.

3.4.4. CONSIDERATION OF EXTERNAL DATA

As the trial continues, new results from other research in the same indication may be released. It is important that such information is taken into consideration by the DSMB when providing a recommendation regarding further trial conduct to the TSC/TMG. It is the responsibility of the TSC/TMG to ensure that any such external evidence is made available to the DSMB. However, such external information should be assessed very carefully by the DSMB and a decision to recommend stopping or modifying a clinical trial based on external information should be taken under exceptional circumstances only.

3.4.5. MAKING RECOMMENDATIONS

Based on the results of the monitoring activities, the DSMB should make recommendations regarding further trial conduct. Such recommendations may include: continuing a trial; terminating a trial (due to futility, or overwhelming benefit or harm in one arm); or modifications to conduct of the trial (e.g. eligibility criteria changes, increase or decrease of number of patients to be recruited, changes in dose and/or dose schedules). With regard to the latter such modifications should not violate the concepts behind the original trial protocol. Any recommendation made by the DSMB should be communicated to the Sponsor-Investigator and through the Sponsor-Investigator to the TSC/TMG. Sufficient information should be provided from the DSMB to allow a decision on whether, and how, to implement the DSMB recommendations. In reporting back to the Sponsor-Investigator, it is important that the DSMB does not release any information about the treatment assignment of participants or any treatment arm comparisons.

The Sponsor-Investigator is responsible for implementing any DSMB recommendations.. If any recommendations are not implemented, a detailed memo justifying the reasons for not implementing the recommendation must be promptly forwarded to the DSMB and also to the Human Research Ethics Committee (HREC).

3.4.6. DSMB CHARTER

The roles and responsibilities, membership and processes of the DSMB should be detailed in a Charter that is agreed upon by both the TSC/TMG and the members of the DSMB prior to the initiation of the trial (see Appendix 1 for a template). It is the responsibility of the Sponsor-Investigator to ensure that a template Charter is in place for the DSMB when it is established.

The Charter is important for the integrity of the study. As the DSMB may have access to unblinded treatment information, there is potential to introduce bias to future trial results; the Charter should make transparent the procedures involved in all decision-making. The Charter also:

- Describes how and when the DSMB will interact with non-DSMB members;
- Documents the procedure for meetings to review unblinded efficacy and safety data by treatment group, at which the, Sponsor-Investigator and trial team will not be present (closed meetings); and meetings to discuss its conclusions and recommendations with the Sponsor-Investigator (open meetings);
- Confirms that the DSMB and the TMG/TSC agree regarding the roles and the responsibilities of the DSMB.

The TSC/TMG should prepare and provide an initial draft of this charter to the DSMB for its review and comment. An agreed charter should be signed by all DSMB members as early as possible, but at the latest before participant enrolment starts. The charter should document the following:

1. Scope of DSMB responsibilities
   - Safety monitoring
   - Efficacy monitoring and data interim analyses (if required)
   - Publication review
   - Confidentiality

2. Membership of the DSMB including qualifications and individual responsibilities
   - Chairperson responsibilities
   - Responsibilities of the Sponsor-Investigator and the TSC/TMG
   - Contact information
3. Details of the Data Analysis Centre / independent statistician who will prepare the reports for the DSMB including their responsibilities and contact information
4. Communication and data flow among DSMC, Sponsor-Investigator and TSC/TMG
5. Extent of data monitored at clinical sites before safety data review meetings
6. Details of the planned DSMB meetings
   - Types of meetings
   - Frequency of meetings (least annual is recommended) and the schedule of meetings
   - Open and closed sessions
   - Voting
   - Masking (blinding) policies for DSMB members and Sponsor-Investigator/TSC/TMG
7. Details of what will be in the DSMB report(s) and any stopping rules that should be applied in providing recommendations
8. Procedures for providing recommendation major to Sponsor-Investigator/TSC/TMG
9. Details of who will co-ordinate meeting minutes and document retention

Detailed information for each of these sections of the DSMB charter are provided in the DSMB Charter templated associated with this SOP.

4. GLOSSARY

CDA: Confidential Disclosure Agreement

CEBU: Clinical Epidemiology and Biostatistics Unit

CRDO: Clinical Research Development Office

CLINICAL TRIAL: Any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between an intervention and a health outcome.

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.

HREC: Human Research Ethics Committee

ICH GCP: International Conference on Harmonization - Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting and reporting trials that involve the participation of human subjects. The objective of ICH GCP is to facilitate mutual acceptance of clinical data by regulatory authorities.
The principles of Good Clinical Practice have their origin in the World Medical Association's Declaration of Helsinki.

NHMRC: National Health and Medical Research Council. An independent statutory body within the portfolio of the Commonwealth Minister for Health and Ageing responsible for allocating funding for and directing health and medical research, ethics and advice.

MELBOURNE CHILDREN'S: this term is used to encompass The Royal Children's Hospital, Murdoch Childrens Research Institute and Department of Paediatrics University of Melbourne.

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.

PRINCIPAL INVESTIGATOR (SITE): The Site Principal Investigator is the person responsible for the overall conduct of the research project at a study site.

PROTOCOL VIOLATION: A protocol violation is a deviation from the protocol which affects participant safety.

RCT: A Randomised Clinical Trial is a clinical trial where participants are randomly allocated between one or more treatment (intervention) groups so that each person has an equal chance of being in the different groups.

SOP: Standard Operating Procedures are documents that provide definitions and formats for quality systems documentation, detailing procedures and work instructions.

TGA: Therapeutic Goods Administration. The role of the TGA is to provide a national framework for the regulation of therapeutic goods in Australia and to ensure their quality, safety and efficacy.

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.

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.

5. REFERENCES

Melbourne Children's:

CEBU website http://www.mcri.edu.au/research/core-facilities/cebu/

CRDO website http://www.mcri.edu.au/research/core-facilities/clinical-research-development-office/

RCH Research Ethics and Governance website http://www.rch.org.au/ethics/

National

NHMRC National Statement on Ethical Conduct in Human Research (NHMRC, 2007 and all updates) https://nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018

NHMRC Guidance: Data Safety Monitoring Boards (DSMBs) (EH59, November 2018)
https://nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1

Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6 (R2) - annotated with TGA comments https://www.tga.gov.au/publication/note-guidance-good-clinical-practice

International

FDA Guidance for clinical trial sponsors. Establishment and operation of clinical trial data monitoring committees. US Department of Health and Human Services. Food and Drug Administration, March 2006
http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

MRC Guidelines for good clinical practice in clinical trials March 1998
http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/

6. APPENDICES

APPENDIX 1: CRDO Data and Safety Monitoring Board Charter Template

Available on the CRDO website (Launching Pad: Research Oversight)

APPENDIX 2: Template DSMB CDA with fee

Available on the MCRI intranet (Legal Template and Form Library)

Ensure you contact MCRI Legal prior to finalising any CDA and/or sending them to any external party for review and signature.

This template has generated and is maintained by the MCRI Legal Department. Please contact Legal directly if you have any questions about this document.

APPENDIX 3: TEMPLATE DSMB CDA WITHOUT FEE

Available on the MCRI intranet (Legal Template and Form Library)

Ensure you contact MCRI Legal prior to finalising any CDA and/or sending them to any external party for review and signature.

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APPENDIX 4: Example Decision Making Tree for Establishment of a DSMB

From NHMRC Guidance: Data Safety Monitoring Boards (DSMBs) (EH59, November 2018) https://www.nhmrc.gov.au/guidelines-publications/eh59