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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.

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1. PURPOSE

The purpose of this guidance document is to assist researchers in determining whether their research requires independent safety monitoring by a Data and Safety Monitoring Board (DSMB). 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 (see Appendices for the link).

2. RESPONSIBILITY AND SCOPE

It is the responsibility of the Principle Investigator (PI) of the study together with the Trial Steering Committee (TSC), or the Trial Management Group (TMG) where there is no TSC, to make the final decision regarding whether a DSMB is required for a trial and, if considered needed, to appoint members of the DSMB and to ensure that a charter detailing the roles and responsibilities of the DSMB is developed and followed. Establishing a DSMB may also be requested as a prerequisite for ethical approval.

3. 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.

4. PROCEDURE

4.1. INTRODUCTION

For the purpose of this document, the term Data and Safety Monitoring Board (DSMB) will be used. However, it should be noted that there exist various other terms for such a committee, including Data Monitoring Committee (DMC) and Data and Safety Monitoring Committee (DSMC).

The guidelines for Good Clinical Practice of the International Conference on Harmonization (ICH GCP) give the following definition for the body tasked with monitoring a trial: “A DSMB is an independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints and to recommend to the sponsor whether to continue, modify, or stop a clinical trial”. Note that in trials where there is no external sponsor, the DSMB should make its recommendations to the PI and through the PI to the TMG and/or TSC.

Clinical trials frequently extend over a long period of time and so it is important to ensure that there is no unavoidable or increased risk of harm for trial participants and that there remains genuine uncertainty about the most beneficial treatment (equipoise). However, it is also important to ensure that a clinical trial continues for sufficient duration to answer its primary scientific question. It can be difficult to make an objective assessment of these issues as part of the trial team with an invested interest in the trial. Hence monitoring of the trial should be conducted by a group of people independent of the trial (i.e. a DSMB), where 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. An independent DSMB helps to protect the integrity of trial monitoring and the credibility of trial results.
The DSMB may also formulate recommendations relating to: the selection, recruitment and retention of participants; participant management; improving adherence to protocol-specified regimens; and procedures for data management and quality control.

When setting up a DSMB, the TSC/TMG in collaboration with the DSMB, decide the nature of the monitoring 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 arises during the trial
- The accumulating safety data from the trial
- The critical efficacy endpoint(s) of the trial

Note if monitoring of efficacy by the DSMB is required, the interim analyses of this data should be pre-specified in the study protocol

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).

### 4.2. ASSESSING THE NEED FOR A DSMB

Not all clinical trials require independent monitoring. DSMBs add administrative complexity to a clinical trial and require resources to set-up the committee, coordinate meetings and prepare reports for meetings.

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 safety concerns in at least one trial arm
- Trials of any size primarily comparing rates of mortality, major disease morbidity or other 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, since the PI 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.

#### 4.2.1. Is DSMB review practical?

Setting up a DSMB is non-trivial and takes time, as it involves sourcing appropriate members (see section 4.3) as well as a statistician (ideally a statistician 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 as by the time the review is complete most or all of the participants will have completed their active treatment.

4.2.2. 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, 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.

4.3. 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 content 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 PI 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.

4.3.1. Composition of the DSMB

Relevant qualifications and experience is 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. A quorum for each meeting should be decided upon and detailed in the DSMB’s Charter.

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 PI 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 course of 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.

4.3.1.1. Independence of the DSMB

To allow for an unbiased assessment of trial data:

- Members of the DSMB must be completely independent from the conduct of the trial, should be independent of members of the TMG, and must not have a direct interest in the trial outcome, or on whether or not the trial continues. To maximise independence, DSMB members should where possible be recruited from beyond Melbourne Children’s.

- It is important that there are no conflicts of interest for any of the members of the DSMB. Potential candidates for a DSMB membership should have no financial interest in the outcome of the trial or of a competing trial. Other aspects should also be taken into consideration when assessing a possible conflict of interest. For example the planned authorship of DSMB members in publications on trial results might impact the independence of the DSMB and is a non-financial conflict of interest. Other potential conflicts of interest could include intellectual interests (contributed to protocol development) or patient interest (treating trial participants, evaluating participant outcomes). Declaration of a conflict of interest is an ongoing process; it should be completed at the time of joining the DSMB and prior to each DSMB meeting.

- A potential DSMB member must not serve in parallel on the DSMB of another trial in the same indication.

4.4. MONITORING ACTIVITIES CONDUCTED AND OVERSEEN BY A DSMB

4.4.1. 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. A large number of protocol violations/deviations 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 which 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. 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.
4.4.2. 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).

An adverse event (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.

When interpreting the safety data, the DSMB should use the accumulating clinical data to differentiate (serious) AEs 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 AE 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 AE/SAE reports.

4.4.3. 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 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 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 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 PI.

### 4.4.4. 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.

### 4.4.5. 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 PI and through the PI 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 PI, it is important that the DSMB does not release any information about the treatment assignment of participants or any treatment arm comparisons.

The implementation of any DSMB recommendation is the responsibility of the PI and, through the PI, to the TSC or TMG. If any recommendation of the DSMB is 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).

### 4.4.6. DSMB CHARTER

The roles and responsibilities, membership and processes of the DSMB should be detailed in a Charter that is agreed by both the TSC/TMG and the members of the DSMB prior to the initiation of the trial (see Appendix 1 for a template). A charter is important to ensure that the DSMB and the TMG/TSC are in agreement regarding the roles and the responsibilities of the DSMB. It is also important for the integrity of the study. 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 PI 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, PI and TSC/TMG

5. Extent of data monitored at clinical sites before safety data review meetings

6. Statistical guidelines and report

7. DSMB meetings
   - Types of meetings
   - Schedule of meetings
   - Open and closed sessions
   - Voting
   - masking (blinding) policies for DSMB members and PI/TSC/TMG

8. Procedures for providing recommendation major to PI/TSC?TMG

9. Meeting minutes and retention

10. Safety analysis plan – templates of tables and listings to be reviewed during DMC meetings

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

5. GLOSSARY

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.

**PI:** The Principal Investigator is the person responsible for the overall conduct of the research project and is usually the person ‘driving’ the trial.

**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 Trial Management Group is a group of people who oversee the day-to-day conduct of a clinical trial. This group should include the key individuals responsible for the everyday management of the clinical trial, such as the PI, 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; adherence to good research practices.

**TSC:** Trials may employ a Trial Steering Committee. This is a committee whose members are responsible for the oversight of a trial. This usually includes the PI and other key members of the TMG and often includes external members who are independent of the trial conduct. The aim of this committee is to provide overall supervision and guidance regarding the trial. Such a committee is often only used for trials that are large, complex or potentially controversial, or where there is a need to include key stakeholders in oversight of the trial.
6. 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/


Wombat Perinatal Trials Toolkit: Establishing a data monitoring committee (DMC)

National


International


7. APPENDICES