# Health Research Council of New Zealand

# [Template for] Data Monitoring Committee Charter – *[Insert Trial Name]*

1. Introduction

This Charter is for the Data Monitoring Committee (‘DMC’) for:

***[Insert Trial Name and Acronym]* (*[Insert HRC Reference e.g. 16/xxx])***

**Trial Registration Number: *[Insert Trial Registration Number]***

**Objective of the trial:**

***[Insert short summary of trial objectives]***

***[Insert diagram of trial timeline here]***

The purpose of this document is to define the primary roles and responsibilities of the ***[insert trial name]*** DMC, its relationship with other trial committees, its membership and the purpose, format and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines for implementation by the DMC, and an outline of the content of the Open and Closed Reports required by the DMC. This document includes a principal Terms of Reference for all trial-specific DMCs governed by the Health Research Council (‘HRC’) Data Monitoring Core Committee (‘DMCC’) (Appendix A).

1. Primary Responsibilities of the DMC

The ***[insert trial name]*** DMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMC will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the selection/recruitment of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedure for data management and quality control.

The DMC will provide advice to the clinical trial leadership group, hereafter referred to as the Steering Committee (‘SC’). The SC will be responsible for promptly reviewing the DMC recommendations, deciding whether to continue or terminate the trial; and determining whether amendments to the protocol or changes in study conduct are required.

The ***[insert trial name]*** DMC will report to the DMCC. The DMCC will be responsible for the activity and good practice of the ***[insert trial name]*** DMC and the DMCC will report on meeting frequency, attendance by members, conflicts of interest and any significant recommendations made by the trial DMC.

The DMC are required to act in accordance with the HRC Statutory and Standing Committees General Principles.

3. Organisational Diagram

The following diagram shows the relationships between DMC and other committees and functional areas involved in the trial. ***[Add additional relationships for the specific trial]***

Health Research Council of New Zealand (HRC)

**4. Membership of the DMC**

Other DMCs

***[Insert functional areas related to SC, e.g. DHB, advisory committee, sponsor other than HRC, and host institutions]***

Health and Disability Ethics Committee (HDEC)

Trial-Specific Data Monitoring Committee (DMC)

Steering Committee (SC)

Data Monitoring Core Committee (DMCC)

4.1 Members

Membership principles of trial-specific DMCs are outlined in the Terms of Reference in Appendix A. The members of the ***[insert trial name]*** DMC are as follows:

***DMC Chair*** Professor Thomas Lumley (Biostatistician)

 Department of Statistics

 The University of Auckland

 Private Bag 92019

Victoria Street West

Auckland

 t.lumley@auckland.ac.nz

|  |  |  |  |
| --- | --- | --- | --- |
| **DMC Members** | **Date****Appointed to DMC** | **Expertise** | Location |
| Professor Tim Dare |  | Ethicist | Department of PhilosophyUniversity of Auckland |
| Dr Ben Hudson  |  | General Practitioner | Department of General Practice University of Otago |
| Professor Dr Suetonia Palmer  |  | Clinician | Department of NephrologyChristchurch Hospital |
| Dr Mark Webster |  | Clinician  | Department of CardiologyAuckland City Hospital  |
| Dr Yalu Wen  |  | Biostatistician | Department of StatisticsUniversity of Auckland |
| Associate Professor Conroy Wong |  | Clinician | Department of Respiratory MedicineMiddlemore Hospital  |

|  |  |  |  |
| --- | --- | --- | --- |
| ***[Insert details of augmented member}*** |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Steering Committee Membership** | **Trial Start Date** | **Expertise** | Location |
| ***[to be completed by SC]*** |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

***Address for All Correspondence:***

Lana Lon

Secretary to the DMCC

Health Research Council of New Zealand

PO Box 5541

Victoria Street West

Auckland 1142

New Zealand

llon@hrc.govt.nz

4.2 Conflicts of Interest

The DMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, professional or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMC.

The DMC members should be independent of the trial and the investigators. They should not own stock in companies having products being evaluated by the clinical trial. Any competing interest, whether real or potential, should be declared. The DMCC will be responsible for deciding whether these competing interests materially impact members’ objectivity. DMC members must act in accordance with the State Services Commission Standards of Integrity and Conduct and the HRC Policy on Conflict of Interest.

The DMC members will be responsible for advising fellow members and the DMCC of any changes in competing interests that occur during the course of the trial. Any DMC members who develop significant conflicts of interest during the course of the trial should resign from the DMC.

DMC membership is to be for the duration of the clinical trial. If any member leaves the DMC during the course of the trial, the DMCC, in consultation with the DMC and the SC, will promptly appoint a replacement.

**5. Terms of reference and specific roles of the DMC**

***Terms of reference***

The Terms of Reference for all Trial-Specific DMCs are included in Appendix A of this document.

***Specific roles of the* *[insert trial name]* *DMC***

To undertake to review the trial’s progress by:

* Assessing data quality, including completeness (thereby encouraging collection of high quality data
* Monitoring recruitment figures and losses to follow-up
* Monitoring compliance with the protocol by participants and investigators
* Monitoring evidence for treatment differences in the main efficacy and safety outcome measures – and thus recommending action when/whether the main trial question has been answered
* Monitoring evidence for treatment harm (e.g. toxicity, SAEs, deaths) in a timely way, receiving prompt reports of SUSARs and taking appropriate action to ensure patients’ safety.
* Recommending whether the trial should continue to recruit or follow-up (see section on recommendations to the Steering Committee)
* Recommending any major changes to the protocol where necessary (e.g. changes to recruitment procedures, inclusion criteria, endpoints, data collection)
* Advising on and/or endorsing any major protocol modifications suggested by the investigators or sponsors
* Assessing the impact and relevance of any external evidence provided
* Monitoring the compliance with previous DMC recommendations
* Considering the ethical implications of any recommendations made by the DMC

The DMC will report its recommendations to the SC, and once the response to these recommendations is received, will, if necessary, send the DMC recommendations, with the SC responses and DMC review of the appropriateness of the SC responses, to the HRC (or study sponsor) and the *[insert appropriate ethics committee].*

All DMC members will have sight of the protocol/outline before agreeing to join the DMC. DMC members should be constructively critical of the on-going trial, but supportive of the aims and methods of the trial.

6. Timing and Purpose of the DMC Meetings

6.1 Organisational Meeting

The initial meeting of the DMC 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 standard operating procedures for the role and functioning of the DMC, and to discuss the format and content of the Open and Closed Reports that will be used to present trial results at future DMC meetings.

The Organisational Meeting will be attended by the DMC, the lead trial investigators, the trial statistician, and the data manager. Representatives of the sponsors may also attend. Before the meeting, the DMC will be provided with the drafts of the clinical trial protocol, the Statistical Analysis Plan, the DMC Charter template, and the current version of the case report forms. The DMC will also receive the initial draft templates of the Open and Closed Reports. Agreement on the format and content of reports will ensure the DMC is receiving the necessary data on the trial progress.

6.2 Monitoring meetings

DMC meetings will take place every 6 months. The first meeting must be in person (It is noted that under COVID this may not be possible). All subsequent monitoring meetings can be by ZOOM. However, at the discretion of the DMC, the study team may be requested to have discussion in person when required.

The Principal Investigator (PI), or nominee, must attend open sessions of the DMC meetings. It may also be useful for other members of the SC and the trial manager to attend the open sessions.

The trial statistician provides the link between the database and the DMC, and they are the only person outside the DMC to have access to unblinded data (data from closed reports) during the trial. They are responsible for the production of the DMC reports, will attend both the open and closed sessions of the DMC meeting to talk the DMC through the report. They may also participate in some DMC discussions.

The first meeting of the DMC should take place during the early stage of recruitment, to review early safety information, to review factors relating to quality of trial conduct, and to review information provided to the DMC.

Further meetings are planned around the standard DMCC meeting dates in April and October, until the trial has 6 months left to completion. ***[Insert number]*** of these meetings will involve formal review of interim statistical analyses.

After completion of its monitoring role, the DMC offers to provide comment on the final results of the study, in order to provide any additional insights they may have gained through the monitoring process. Comment could be provided on the final statistical report or a draft publication.

Every effort should be made for all DMC members, the trial PI and the trial statistician to attend meetings. The Secretary to the DMC will attempt to ensure a date is chosen to facilitate this. If, at short notice, any DMC member cannot attend, the meeting may still take place as long as a quorum of four people are present, including the DMC Chair. Expertise of the quorum should include a statistician, the primary reviewer and a DMC member with the specific expertise in the area of the trial (see Appendix A). If the DMC is considering recommending a major action after such a meeting the DMC Chair should talk to the absent members as soon as possible after the meeting to confirm agreement. If consensus cannot be reached, a further meeting by teleconference with the full DMC should be held.

7. Procedures to Ensure Confidentiality and Proper Communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMC has sole access to evolving information from the clinical trial regarding comparative efficacy and safety data, aggregated by treatment arm. An exception will be made to permit access for the trial statistician who will be responsible for serving as a liaison between the database and the DMC. A nominated member of the DMC ***[insert name]*** will be provided immediate access on an on-going basis to patient-specific information on Suspected Unexpected Serious Adverse Reactions (SUSARs) and or Serious Adverse Events (SAEs). The report of all SUSARs and SAEs must be made to the Secretary to the DMC no later than 5 working days after the event.

Procedures will be implemented to ensure proper communication is achieved between the DMC and the trial investigators and sponsor. A format for Open Sessions and Closed Sessions will be implemented to provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial. The intent of this format is to enable the DMC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMC and others who have valuable insights into trial-related issues.

7.1 Closed Sessions

Sessions involving only DMC members and the independent statistician who generated the Closed Reports (called Closed Sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMC will be unblinded in its assessment of safety and efficacy data.

At a final Closed Session, the DMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.

7.2 Open Session

In order to allow the DMC to have adequate access to information provided by study investigators, a joint session between these individuals and DMC members (called an Open Session) will be held between the Closed Sessions. This session gives the DMC an opportunity to query these individuals about issues that have arisen during their review in the initial Closed Session. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved. These individuals will either be present in person at the DMC meeting or be provided a telephone link.

Identification and circulation of external evidence (e.g. from other trials or systematic reviews) is not the responsibility of the DMC. The PI will take responsibility to collate such information and provide it to the DMC.

7.3 Open and Closed Reports

For each DMC meeting, Open and Closed Reports will be provided (See Section 8 for outlines of the content of these reports). The trial statistician, ***[insert name of trial statistician],*** will prepare these reports.

Open Reports, available to all who attend the DMC meeting, will include data on recruitment and baseline characteristics and pooled data on eligibility violations, completeness of follow-up and compliance.

Closed Reports, available only to those attending the Closed Sessions of the DMC meeting, will include analyses of primary and secondary efficacy endpoints, subgroup and adjusted analyses, analyses of AEs and symptom severity, analyses of laboratory data, and Open Report analyses that are displayed by intervention group.

The Open and Closed Reports should provide information that is accurate, with follow-up that is complete to within two months of the date of the DMC meeting. The Reports should be provided to the Secretary of the DMCC, 10 working days before the date of the meeting.

7.4 Minutes of the DMC Meeting

The DMC will prepare minutes of their meetings. Two sets will be prepared: The Open Minutes and the Closed Minutes.

The Open Minutes will describe the proceedings in the Open Session of the DMC meeting. These minutes will be circulated in a timely manner to the Principal Investigator and the study statistician. The Principal Investigator is responsible for distribution of the Open Minutes to other members of the SC. It is necessary that these minutes do not unblind the efficacy and safety data if the DMC is not recommending early termination.

The Closed Minutes will describe the proceedings from all sessions of the DMC meeting, including the listing of recommendations by the Committee. Because it is likely that these minutes will contain unblinded information, it is important that they are not made available to anyone outside the DMC. The study statistician will receive minutes of the sections of the closed sessions they attend, and it is vital that these are kept confidential. Copies will be archived by the Secretary to the DMC for distribution to the Principal Investigator, sponsor, and regulatory authorities at the time of study closure.

7.5 Recommendations to the Steering Committee (SC)

At each meeting of the DMC during the conduct of the trial, the DMC will make a recommendation to the SC to continue or to terminate the trial. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in the Charter.

The SC is jointly responsible with the DMC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the study made by the DMC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue or to stop the trial based on the DMC recommendations.

The SC will provide responses to DMC recommendations within 25 working days of receipt of the recommendations. These responses will be sent to the Secretary of the DMC. The DMC will, if necessary, forward copies of DMC recommendations and the responses to those recommendations to the HRC ***[or insert other primary trial sponsor]*** (as primary trial sponsor) and the appropriate Ethics Committee, along with a brief comment on DMC concurrence with the response. (In particular where DMC recommendations are not adopted, the DMC will comment on whether or not they consider the justification provided by the SC adequate).

The DMC must be notified, via the Secretary of the DMC, of all proposed changes to the protocol or to study conduct. DMC consensus must be sought on all substantive changes to the protocol or study conduct prior to their implementation.

The SC may communicate information to their senior management. Information in the Open Report and any DMC recommended alterations to study conduct or early trial termination in instances in which the SC is in agreement with the recommendation may be disclosed. The SC will maintain confidentiality of all information it received other than that contain in the Open Reports until after the trial is completed or until a decision for early termination has been made.

7.6 HRC Reporting Requirements

Each meeting of a trial-specific DMC will be reported to the HRC in the DMCC minutes, as meetings of the DMCC will coincide with trial-specific DMC meetings. The meeting will be noted as ‘The DMCC took part in the *[insert trial name]* DMC and will send recommendations by letter.’ Any recommendation to stop a trial must be reported to the HRC Board.

Updates on the progress and monitoring of each trial will be provided to the DMCC at their biannual meetings. Any issues of risk to trial participants, trial integrity, or to the HRC must be raised at these meetings and, if necessary, the HRC will be informed.

8. Statistical Monitoring Guidelines

***[This section is to be completed by the Steering Committee Statistician and is trial specific. The information should be collated from the Statistical Analysis Plan and list of Open and Closed reporting elements.]***

***[The DMC Charter should specify the statistical monitoring procedures that will be used by the DMC to guide their recommendations regarding termination or continuation of the trial. These procedures should include guidelines relating to early termination for benefit, as well as guidelines for termination when evidence indicates the experimental intervention has an unfavourable benefit-to-risk profile.]***

***[The DMC may also be asked to ensure procedures are properly implemented to adjust study sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.]***

9. Content of DMC’s Open and Closed Reports

9.1 Open Statistical Report: An Outline

***[Below are some of the minimum requirements for an Open Statistical Report. These may be adapted depending on the nature, subject and duration of the trial.]***

* One-page outline of the study design, possibly with a schema
* Statistical commentary explaining issues presented in Open Report figures and table
* DMC monitoring plan and summary of Open Report data presented at prior DMC meetings
* Major protocol changes
* Information on patient screening
* Study accrual by month and by institution
* Eligibility violations
* Baseline characteristics (pooled by treatment regimen)
	+ Demographics
	+ Laboratory values and other measurements
	+ Previous treatment usage and other similar information
* Days between randomisation and initiation of treatment
* Adherence to medication schedule (pooled by treatment regimen)
* Attendance at 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)
* Completeness of data (pooled by treatment regimen)

9.2 Closed Statistical Report: An Outline

***[Below are some of the minimum requirements for a Closed Statistical Report. These may be adapted depending on the nature, subject and duration of the trial.]***

* Detailed statistical commentary explaining issues raised by Closed Report figures and tables (by coded treatment group, with codes sent to DMC members by a separate mailing)
* DMC monitoring plan and summary of Closed Report data presented at prior DMC meetings
* Repeat of the Open Report information, in greater detail by treatment group
* Analyses of primary and secondary efficacy endpoints
* Subgroup of adverse events and overall safety data
* Analyses of lab values, including basic summaries and longitudinal analyses
* Discontinuation of medications
* Information on crossover patients

Appendix A

**Trial-Specific Data Monitoring Committees**

*(March 2015)*

**Terms of Reference**

1. The primary function of a Health Research Council (‘HRC’) Trial-Specific Data Monitoring Committee (‘DMC’) is to provide data and safety monitoring to either a HRC-funded trial or trial identified as suitable for monitoring by the Data Monitoring Core Committee (‘DMCC’). The DMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial.
2. To provide protocol advisory review for those trial being monitored.
3. To provide both recommendations based on the progress and accruing data of the trial and advice on the conduct of the trial to the Steering Committee (‘SC’). This will include a recommendation about stopping or continuing the trial.
4. To provide updates to the DMCC to ensure good clinical practice is in place for each trial.
5. To offer comment on the final results of the study, in order to provide any additional insights which may have been gained through the monitoring process.
6. To monitor and provide recommendations that will enhance the integrity and credibility of the study.

**Membership Composition**

A DMC may comprise of up to eight members appointed on the recommendation of the DMCC. Membership expertise must include a biostatistician, an ethicist and two clinicians or health professionals, one with strong clinical trial experience. Membership should include members who have varied professional interests in order to minimise conflict of interest.

Each DMC requires a minimum DMCC membership of 4. The DMC may additionally appoint up to 2 Augmented Members who are specialists in the field of the clinical trial. The Chair of the DMCC formally invites any new augmented members recommended by the DMCC and membership will be confirmed by the Chief Executive of the HRC. Trial DMC members do not become DMCC members and will be released once the monitoring of the trial is complete.

**Term of Office**

Term of office is for the duration of the clinical trial. DMCC members of a DMC specific to a clinical trial may retain their membership in the DMC after their end of term in the DMCC until the end of the clinical trial and this will be at the discretion of the Chair of the DMCC.

**Process for Appointment of Committee Members**

The Chair of the DMCC formally invites the proposed member recommended by the Committee and confirmed by the Chief Executive of the HRC.

**Secretary** Ms Lana Lon

**DMC Quorum** 4 people including the Chair, a statistician, the primary reviewer and a DMC member with the specific expertise in the area of the trial

**Meetings per annum** Two meetings every year which may include one in-person meeting

**Committee Fees and Allowances**

Meeting fees and travel expenses for Committee members will be in accordance with standard HRC practice.

**Reports to** DMCC