



Trans Tasman Radiation Oncology  
Group Limited  
ACN 132 672 292

## **TROG POLICY STATEMENT**

# **Guidelines for Data Monitoring Committees**

**TPS E9**

**Version 2: 22<sup>nd</sup> January 2013**

(Always refer to the TROG website to check for the current version of this policy)

### **TROG Central Operations Office**

Level 5, MHA Building  
Calvary Mater Newcastle  
Locked Bag 7 HRMC NSW 2310  
Tel: + 61 2 40 143 911  
Fax: + 61 2 40 143 902  
Email: [trog@trog.com.au](mailto:trog@trog.com.au)  
Website: [www.trog.com.au](http://www.trog.com.au)

## Contents

1. DATA MONITORING COMMITTEES.....	3
1.1 Membership .....	3
1.2 DMC Terms of Reference .....	3
1.3 Meetings.....	4
1.4 Responsibilities.....	4
1.5 Methodological Implications of DMC analyses on Trial Analyses .....	5
1.6 Reporting of Meeting Outcomes and Recommendations .....	5
2. REFERENCES .....	6
Appendix 1: Template Data Monitoring Committee Terms of Reference .....	7

## 1. DATA MONITORING COMMITTEES

The European Medicines Agency (EMA) 'Guideline on Data Monitoring Committees'<sup>1</sup> (adopted by the TGA), defines a Data Monitoring Committee (DMC) as “a group of independent experts external to a study assessing the progress, safety data and, if needed critical efficacy endpoints of a clinical study. In order to do so a DMC may review unblinded study information (on a patient level or treatment group level) during the conduct of the study. Based on its review the DMC provides the sponsor with recommendations regarding study modification, continuation or termination”.

A DMC must be formed for all randomised Phase II and Phase III clinical trials **before the trial is open to accrual**. The Trial Management Committee (TMC) is responsible for the appointment of DMC members.

IDMC, DSMB, IDSMB, DMC or SDMC are all acronyms for the same functional group. [D = Data; S = Safety; M = Monitoring; I = Independent; B = Board; C = Committee].

### 1.1 Membership

The DMC will be independent of the TMC and consist of a minimum of 3 members, at least 2 of who will be Radiation Oncologists and 1 of who will be a statistician. Multidisciplinary trials should also include a specialist from each of the involved disciplines. In the case of inter-group or trials with international collaboration consideration should be given to a broad representation.

Experience is essential for DMC members to perform their task effectively. Potential DMC members should not only have scientific expertise relevant to the indication being studied, they should also have practical experience with conducting clinical trials and a good understanding of the problems and limitations of clinical trials. In order to facilitate the work of a DMC it is helpful that some of the members, at least the DMC chair, to have served on a DMC previously<sup>1</sup>.

For TROG-led trials ie. TROG is the sponsor, the TMC may request the advice from the TROG Scientific Committee (TSC) regarding potential members.

A DMC must be fully functional before enrolment starts to enable it to respond to any safety signal.

### 1.2 DMC Terms of Reference

The DMC should have written operating procedures documenting the role, composition and proceedings of meetings and maintain written records of all its meetings<sup>2</sup>. The operating procedures should also describe how the integrity of the trial with respect to preventing dissemination of unblinded trial information is ensured.

- Please refer to Appendix 1 for a template Terms of Reference document.

- A copy of the final trial specific Terms of Reference must be submitted to TROG.
- Any Conflict of Interests (COI) of the DMC members must be declared. TROG recommends that COI is included as a standing agenda item and declared at the beginning of each DMC meeting. Alternatively a 'Conflict of Interest form' may be signed by each DMC member and submitted to TROG. Please refer to TROG Policy Statement TPS C5 '*Conflict of Interest Policy*'.

### 1.3 Meetings

The frequency of DMC meetings will depend on any statistical plans specified and otherwise on trial events. It is recommended that the DMC meet at least biannually either in person or by teleconference.

### 1.4 Responsibilities

The Trial Chairperson and TMC bear the final responsibility for the conduct of the trial. This responsibility cannot be transferred to a DMC.

The DMC responsibilities include:

- i. Review accrual, to recommend whether a poorly accruing trial should be prematurely closed to patient entry as it is unlikely to meet its accrual objectives in a reasonable timeframe or whether accrual in the trial should continue and the protocol amended to reflect this change.
- ii. Review protocol compliance, patient withdrawal, and losses to follow up, in order to review potential problems with respect to patient compliance or trial feasibility/quality and make recommendations as appropriate
- iii. Review all toxicity data and provide recommendations for any actions. These recommendations may result in amendments to the protocol (including the Patient Information Sheet and Consent Form), early closure or suspension of the trial or one, or more, of the trial arms. Review of toxicity by the DMC is in addition to that of the Trial Chairperson and TMC, who have primary responsibility for monitoring toxicity. The early closure criteria section of the protocol should be referenced in any report provided by the DMC.
- iv. To recommend whether it is ethical to continue randomising patients when there are potential differences in treatment efficacy and/or safety and toxicity, or conversely when there may never be any difference in efficacy.
- v. Review all planned interim analyses, in confidence, and make recommendations to the TMC about continuing, modifying or stopping the trial.
- vi. Recommend and review protocol amendments including but not limited to:
  - a. changes to any treatment arm
  - b. changes to sample size calculation or accrual target

*Such amendments must not violate the concepts behind the original trial protocol.*

- vii. Review of information from other trials which may influence the design or conduct of the trial being monitored
- viii. Review of the final analysis
- ix. Effective communication of all recommendations

## **1.5 Methodological Implications of DMC analyses on Trial Analyses**

Inflation of Type I error\* as well as a possible bias in the future conduct of a clinical trial are the major methodological problems in connection with DMC activities.

If a DMC monitors the primary parameter of the statistical analysis with the option to stop early, the impact on the Type I error is obvious and there are statistical methods (e.g. group sequential designs) available to account for this properly. In such a situation the DMC's Terms of reference shall clearly describe the statistical methods to be applied for analysis. These methods must comply with the statistical methods outlined in the trial protocol. The trial protocol must describe the provisions planned to avoid an inflation of the Type I error.

The EMEA Guideline on Data Monitoring Committees<sup>1</sup>, as adopted by the TGA, and the ICH Harmonized Tripartite Guideline: Statistical Principles for Clinical Trials<sup>3</sup> should be referred to for further information.

## **1.6 Reporting of Meeting Outcomes and Recommendations**

### **1.6.1 Data Monitoring Committee**

If changes in the trial conduct are recommended by a DMC, sufficient information must be provided to allow the TMC, in consultation with the TROG Scientific Committee (TSC), to decide whether and how to implement these recommendations.

The DMC shall provide blinded reports to the Trial Chairperson and the TMC. Reports shall be blinded to specific study information, as required by the protocol, and all patient information de-identified. A copy of the final report should also be provided to the TSC.

### **1.6.2 Trial Management Committee**

The implementation of any DMC recommendation is the responsibility of the TMC in consultation with the TSC. The TMC shall therefore review the DMC report and prepare recommendations based on the report. The TMC is responsible for forwarding the original DMC report and any further TMC recommendations to the TSC.

---

\* In a hypothesis test, a type I error occurs when the null hypothesis is rejected when it is in fact true; that is it is wrongly rejected

#### 1.6.3 TROG Scientific Committee

The TSC shall review the recommendations provided by the TMC and DMC and provide feedback on the recommendations back to the TMC.

The process described at 1.6.2 and 1.6.3 shall be repeated until the TMC and the TSC are satisfied with the recommendations.

The TMC shall notify the DMC, and any collaborating groups, of the final recommendations.

#### 1.6.4 Trial Coordinating Centre

The Trial Coordinating Centre shall be responsible for notifying Trial Sites of the recommendations (if required) and coordinating protocol amendments that may arise from the recommendations.

#### 1.6.4 Trial Sites

Trial Sites shall be responsible for directly notifying their approving Human Research Ethics Committee and/or Research Governance Officer and all trial participants of any new information arising from the recommendations.

## 2. REFERENCES

1. Guideline on Data Monitoring Committees. European Medicines Agency. EMEA/CHMP/EWP/5872/03 Corr. 27 July 2005. (Adopted by TGA January 2006)  
<http://www.tga.gov.au/pdf/euguide/ewp587203final.pdf>
2. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA comments (DSEB July 2000). <http://www.tga.gov.au/pdf/euguide/ich13595.pdf>
3. ICH Harmonized Tripartite Guideline: Statistical Principles for Clinical Trials (ICH E9). Available at: <http://www.tga.gov.au/pdf/euguide/ich036396en.pdf>

**Appendix 1**  
**Data Monitoring Committee**  
**Terms of Reference - Template**



---

<b>Protocol Title:</b>	
<b>TROG Trial No.</b>	
<b>Date of Document:</b>	

### 1. Introduction

The purpose of these operating procedures is to define the roles and responsibilities of the Data Monitoring Committee (DMC), delineate qualifications of the membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of the reports.

The DMC will function in accordance with the principles of the following documents: Guideline on Data Monitoring Committees. European Medicines Agency. EMEA/CHMP/EWP/5872/03 Corr. 27 July 2005. (Adopted by TGA January 2006) <http://www.tga.gov.au/pdf/euguide/ewp587203final.pdf> and Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA comments (DSEB July 2000). <http://www.tga.gov.au/pdf/euguide/ich13595.pdf>

Abbreviations and definitions to be used in the operating procedures:

DMC – Data Monitoring Committee

TMC – Trial Management Committee

TSC – TROG Scientific Committee

### 2. Responsibilities of the DMC

- a) Review accrual, to recommend whether a poorly accruing trial should be prematurely closed to patient entry as it is unlikely to meet its accrual objectives in a reasonable timeframe or whether accrual in the trial should continue and the protocol amended to reflect this change.
- b) Review protocol compliance, patient withdrawal, and losses to follow up, in order to review potential problems with respect to patient compliance or trial feasibility/quality and make recommendations as appropriate
- c) Review all toxicity data and provide recommendations for any actions. These recommendations may result in amendments to the protocol (including the Patient Information Sheet and Consent Form), early closure or suspension of the trial or one, or more, of the trial arms. The early closure criteria section of the protocol should be referenced in any report provided by the DMC.

- d) To recommend whether it is ethical to continue randomising patients when there are potential differences in treatment efficacy and/or safety and toxicity, or conversely when there may never be any difference in efficacy.
- e) Review all planned interim analyses, in confidence, and make recommendations to the TMC about continuing, modifying or stopping the trial.
- f) Recommend and review protocol amendments including but not limited to:
  - I. changes to any treatment arm
  - II. changes to sample size calculation or accrual target*Such amendments must not violate the concepts behind the original trial protocol.*
- g) Review of information from other trials which may influence the design or conduct of the trial being monitored
- h) Review of the final analysis
- i) Effective communication of all recommendations

### **3. Membership of the DMC**

#### **3.1 Members**

The DMC will be independent of the TMC and consist of a minimum of 3 members, at least 2 of who will be Radiation Oncologists and 1 of who will be a statistician *[change numbers as required]*. The DMC is an independent multidisciplinary group consisting of biostatisticians and clinicians that, collectively, has experience in the management of patients with *[fill in disease]* and in the conduct and monitoring of randomised clinical trials.

The members of the DMC are:

DMC Chair:  
DMC Member:  
DMC Member:  
DMC Statistician:  
*[add others]*

#### **3.2 Quorum**

A quorum of members must be present before a meeting can proceed. At least three (3) members will form the quorum, a Radiation Oncologist, a statistician and if applicable a specialist of an involved speciality.

#### **3.3 Terms of Office**

The term of office for each member will be in accordance with the trial period (i.e. before the trial is open to accrual to the review of the final analysis).

#### **3.4 Vacant Positions**

If any members leave the DMC, the Trial Chair in consultation with the TMC will promptly appoint a replacement.



### 3.5 Chairperson

The Chairperson shall be selected by the Trial Management Committee for the trial period.

The Chairperson's responsibilities will include:

- Guiding the meeting according to the agenda and time available;
- Ensuring all discussion items end with a decision, action or definite outcome; and
- Reviewing and approving the draft minutes before distribution;
- Discussing recommendations arising from the DMC meeting with the Trial Chair.

### 4. Declaration of conflict of interest

At the commencement of each meeting, DMC members will be required to declare any conflict of interest they may have in relation to any of the agenda items for that meeting.

DMC members will have no major apparent financial or intellectual conflict of interest that could prevent them from objectively reviewing the trial protocol, interim and final data and giving advice to the TMC.

The DMC members will be responsible for advising the Chair of the DMC of any changes in consulting agreements or financial interests that occur during the course of the trial. Any DMC member who develops significant conflicts of interest during the course of the trial should resign from the DMC.

## 5. Organisation of DMC Meetings

### 5.1 Meeting Frequency

*[Change as required]*

*The frequency of DMC meetings will depend on any statistical plans specified and otherwise on trial events. It is recommended should that the DMC meet at least biannually either in person or by teleconference.*

### 5.2 Meeting Format

*[Change as required]*

*Closed sessions: Members of the DMC and the trial statistician (for some or the entire meeting)*

*Open sessions: Members of the DMC and the trial statistician, Trial Chair, Central Trial Co-ordinator and others by invitation.*

*The format of the meetings may follow:*

- 1. Open session: Introduction and any "open" parts of the report*
- 2. Closed session: DMC discussion of "closed" parts of the report*
- 3. If necessary, further discussion with other attendees on any matters arising from the previous session(s).*

### Suggested Meeting Agenda Items

1. Apologies
2. Declaration of Conflict of Interest
3. Review of Trial Data
  - a. Recruitment
  - b. Protocol Compliance
  - c. Toxicity/SAE

- d. Major Protocol Amendments proposed (ie. early termination, increase in sample size)
- e. Interim/Final Analysis
- f. Review of relevant external trial results
- 4. Recommendations
  - a. Recruitment
  - b. Trial Continuation
  - c. Ethical Considerations
  - d. Protocol Amendments
- 5. Next Meeting

### **5.3 Remuneration**

Members of the DMC will be supported with:

*[insert remuneration to be given eg. Members will be reimbursed reasonable travel expenses]*

### **5.4 Secretariat Support**

Secretariat support in preparation of each meeting will be supplied by the Trial Coordinating Centre.

This support will include

- Preparation of agendas and issuing notices for meetings
- Ensuring all necessary documents/data requiring discussion or comment are distributed to DMC members in a timely manner
- Arrangement of venue, travel, accommodation bookings or teleconference details as required
- *[insert any further support to be given]*

## **6. Trial documentation and procedures to ensure confidentiality and proper communication**

### **6.1 The responsibilities of the trial statistician**

The trial statistician will produce (or oversee the production of) the report to the DMC and will participate in DMC meetings, guiding the DMC through the report, and participating in DMC discussions.

### **6.2 Intended content of material to be available in open sessions**

*[Change as required]* Open sessions: Accumulating information relating to recruitment and data quality (eg data return rates, treatment compliance, completeness of follow-up) will be presented. Total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC. Data reviewed in open sessions remains blinded and is presented as aggregated data.

### **6.3 Intended content of material to be available in closed sessions**

*[Change as required]* Closed sessions: In addition to all the material available in the open session, the closed session material may include safety data by treatment group. It may include efficacy data by treatment group, depending on the planned interim analysis. Data reported by treatment group should be blinded where possible, unless the DMC requests otherwise.

## 6.4 Minutes of the DMC Meeting

To maintain DMC independence, an elected DMC member will be responsible for

- Recording the meetings minutes
- Completion of the 'blinded' report
- Sending the report to the Trial Chair, TMC and the Trial Sponsor.

Two sets of minutes will be prepared: open minutes and closed minutes. The open minutes will describe the proceedings of the open session of the DMC meeting and present all recommendations by the DMC. It is critical that these minutes do not unblind the efficacy and safety data if the DMC is not recommending early termination.

Closed minutes will describe the proceedings from all sessions of the DMC meeting including a list of all recommendations by the committee. These minutes are available only to the members of the DMC during the course of conduct of the trial. Copies of the closed session minutes will be archived by the DMC Chair and the primary trial statistician.

## 7 Recommendations

The DMC will report to the TMC after each meeting. The DMC is to supply the Trial Chair and TMC with a 'blinded' report of the DMC's findings and recommendations. The TSC, representing the trial sponsor TROG, should also be copied in on this correspondence.

The DMC will make a recommendation to the TMC to continue or prematurely terminate the trial. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines according to this operating procedure. The recommendation to suspend enrolment will either be for permanent enrolment suspension or enrolment pending protocol modification.

Recommendations by the DMC regarding the study protocol will be made to the Trial Chair and the TMC. The DMC will be notified about changes to the protocol or to trial conduct. DMC agreement will be sought in all substantive recommendations or changes to protocol or to trial conduct prior to implementation.

## 8. Statistical Monitoring Guidelines

The primary endpoint of this trial is <primary endpoint>. The primary analysis will <analysis plan>.

Interim analysis will be performed after finalised data are available for <number> and <number> patients. The results of interim analyses will be reviewed by the DMC who will not disclose any of the efficacy results unless an early stopping decision is made.

<Statistical plan/details>.