



Trans Tasman Radiation Oncology  
Group Limited  
ACN 132 672 292

## TROG POLICY AND PROCEDURES

# Guidelines for Data Monitoring Committees

**TPP E9**

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

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## 1. Data Monitoring Committees

The European Medicines Agency 'Guideline on Data Monitoring Committees' has been adopted by the Australian Therapeutic Goods Administration (TGA).<sup>1</sup> A Data Monitoring Committee (DMC) is defined 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. Data Monitoring Committees also go under different names like Data Monitoring Board or Data Safety Monitoring Committee (Board)."

In accordance with ICH GCP Guidelines<sup>2</sup>, a DMC is mandatory for all randomised Phase II and Phase III TROG clinical trials and where TROG is the primary/lead trials group in the case of intergroup trials, DMCs will be formed for each TROG trial no later than the time of activation, with the Trial Management Committee (TMC) responsible for the appointment of members. The TMC may request the advice of the TROG Scientific Committee (TSC) regarding potential members.

### 1.1 Authority

The DMC will act as an advisory committee to the TSC.

### 1.2 Membership

The DMC will 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 the involved discipline.

Experience is essential for DMC members to perform their task in a proper way. 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, have served on a DMC previously<sup>1</sup>.

A Conflict of Interest form must be signed by DMC members in accordance with TROG policy.

### **1.3 Meetings**

The DMC should meet at least biannually either in person or by teleconference. Following a DMC meeting a summary report should be sent to the TSC. Contemporaneous 'blinded' reports will be sent to the Trial Chairperson, TMC and the collaborating group/s for their information.

### **1.4 Responsibilities**

When assessing the responsibilities of a DMC one should keep in mind that 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:

- 1.4.1 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.
- 1.4.2 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
- 1.4.3 Review all toxicity data and provide recommendations for any actions. These may include modification to the trial (including modification of the patient information 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.
- 1.4.4 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.

- 1.4.5 Review all planned interim analyses, in confidence, and make recommendations to the TSC about continuing, modifying or stopping the trial.
- 1.4.6 Review protocol amendments including but not limited to
  - a) changes to any treatment arm
  - b) changes to sample size calculation or accrual target
- 1.4.7 Review of information from other trials which may influence the design or conduct of the trial being monitored
- 1.4.8 Review of the final analysis

## **1.5 Reporting to the TSC**

Based on the results of the monitoring activities, a central responsibility of a DMC is to make recommendations on further trial conduct. Such recommendations include continuing or terminating a trial or recommending amendments to the trial. With regard to the latter such amendments should not violate the concepts behind the original trial protocol.

The proper communication of its recommendations is a major responsibility for a DMC. If changes in the trial conduct are recommended by a DMC, sufficient information should be provided to allow the TMC to decide whether and how to implement these recommendations (in collaboration with the TSC). The implementation of any DMC recommendation is solely the responsibility of the TMC. The TSC should be notified of the TMC decisions.

## **1.6 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 working procedures should clearly describe the statistical methods to be applied for analysis.

These methods have to comply with the statistical methods outlined in the trial protocol. The trial protocol has to describe the provisions planned to avoid an inflation of the Type I error.

The EMEA Guideline on Data Monitoring Committees, as adopted by the TGA, should be referred to for further information<sup>1</sup>.

## 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/docs/pdf/euguide/ewp/587203final.pdf>
  
2. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA comments (DSEB July 2000).