Operation of a Data Monitoring Committee

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Operation of a Data Monitoring Committee

1. Purpose
This Standard Operating Procedure (SOP) details the organisation, responsibilities, timing of meetings and remit of a clinical trial Data Monitoring Committee (DMC).

2. Background
A DMC is responsible for safeguarding the interests of participants in randomised controlled trials, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial.

The DMC is advisory to the Trial Steering Committee (TSC). The TSC is responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes to trial conduct are required.

For further information on DMC and TSC responsibilities, see SOP 12 ‘Definition of Responsibilities Part 2: For those Involved in the Oversight of the Trial’.

3. Procedure
3.1 Who?
The DMC is an independent multidisciplinary group consisting of statisticians and clinicians that, collectively, have experience in the management of patients with the disease/clinical problem being investigated and in the conduct and monitoring of randomised clinical trials. The DMC forms part of the oversight arrangements in place for a trial to ensure appropriate conduct on behalf of the funding body.

For trials funded by the National institute of Health Research (NIHR), the Chief Investigator (CI) is responsible for nominating suitable independent DMC members to the funding body. The funder will then formally invite nominees to be included on the committee.

Other funding bodies may have alternative/additional requirements which should be discussed and agreed during the trial set up period.

DMC meetings are usually attended by the DMC members, the trial statistician(s) and the CI. The Trial Coordinator may also attend.

DMC membership is to be for the duration of the clinical trial and members are expected to attend all meetings. If any members leave or fail to attend consecutive meetings, the DMC Chair, CI, funding body and TSC, will liaise to appoint a replacement.
3.2 When?
Nominations/invitations to form a trial’s DMC should be considered as early on in the trial set up period as possible. For NIHR funded trials, the DMC should be set up as soon as possible after the grant has been awarded.

The DMC should meet prior to the start of the recruitment period of a trial and at defined periods throughout the trial, usually annually.

3.3 How?
3.3.1 Timing and purpose of DMC meetings
The first DMC is usually held early in the trial, before the start of recruitment if possible, and is often combined with a meeting of the TSC. Subsequent DMC meetings will usually be held annually, but more frequently if necessary. The frequency of meetings will be determined by the DMC Chair in discussion with the CI.

The DMC will review:
- Trial Protocol
- DMC Charter
- Safety Review
- Open Reports
- Closed Reports including interim analyses
- Statistical Analysis Plan
- Relevant evidence from other trials

A final DMC meeting will usually be held upon the availability of the final trial data. If the trial is terminated based on the recommendations of the DMC, no final trial DMC meeting is required.

Any concerns or recommendations the DMC may have should be communicated directly to the TSC.

3.3.2 Procedures to Ensure Confidentiality and Proper Communications
DMC membership should be restricted to individuals free of apparent significant conflicts of interest (financial, scientific or regulatory). Members should sign a ‘DMC member’s disclosure agreement’ and a ‘confidentiality agreement’ or ‘Charter’. Any DMC members who develop significant conflicts of interest during the course of the trial should resign from the committee.

A template DMC Charter has been produced and can be found alongside this SOP on the Warwick Clinical Trials Unit’s web site:
http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/conducting/planning/sop/

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 trial. The trial statistician will be the only trial team member to have access to the interim data and is responsible for serving as a liaison between the database and the DMC.
Procedures should also be implemented to ensure proper communication is achieved between the DMC and the trial investigators, trial coordinating centre and sponsor. A format for Open Sessions and Closed Sessions should be implemented. 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.

### 3.3.3 Open and Closed Reports

For each DMC meeting, Open and Closed Reports will be provided (see Appendix 1 for outlines of the content of these reports). The Open Report contains only non-confidential information and is seen by the trial team as well as the DMC members; the Closed Report contains information that is confidential to the DMC and trial statistician and should not be made available to anyone else.

The Trial Coordinator and other members of the trial team may contribute to the presentation of the Open Report to the DMC. Relevant staff responsible for serious adverse event (SAE) monitoring will also be given a copy of the open report and may be present at the DMC open sessions.

Open Reports should be prepared by the statistician and made available to all DMC members. They should include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up and compliance. They may also include the total number of SAEs reported and details of those SAEs.

Closed Reports should only be made available to those attending the Closed Sessions of the DMC meeting and include analysis of primary and secondary efficacy endpoints, subgroup analyses, analyses of SAEs and AEs, analyses of laboratory data (if applicable), and Open Report analyses that are displayed by intervention group.

The Open and Closed Reports should provide information that is accurate and as up to date as possible, though it is recognised that interim analyses are based on data that may not yet have been checked and cleaned. The reports should be provided to DMC members approximately one week prior to the meeting date.

### 3.3.4 Open Sessions

In order to allow the DMC to have adequate access to information provided by trial investigators, a joint session between these individuals and DMC members (called an Open Session) will be held. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved.

### 3.3.5 Closed Sessions

These are sessions involving only DMC members and the trial statistician(s) who generated the Closed Reports and will be held to allow discussion of confidential, unblinded data from the clinical trial, including information about the relative efficacy and safety of interventions.

During the Closed Session, the DMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.
The following diagram shows the flow of information between the DMC and the other committees and functional areas involved in the trial.

3.3.6 Minutes of the DMC meeting
The trial statistician will usually record minutes of the meetings which should be circulated among DMC members and agreed. 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, and will summarise all recommendations made. Open minutes should be circulated to members of the DMC, the funding body (if required) and key trial staff as appropriate.

The Closed Minutes will describe the proceedings from the open and closed sessions, and should include the listing of recommendations by the Committee. These minutes are confidential and should not be made available to anyone outside the DMC. A copy should be kept by the statistician preparing the reports.

Reports, agendas and open and closed minutes should be archived with the rest of the trial documentation in the Trial Master File (TMF) at the end of the trial.

3.3.7 Recommendations to the Trial Steering Committee (TSC)
Following each DMC meeting, the Chair should draft a document making recommendations to the TSC. This document should be circulated to all DMC members and approved prior to sending to the TSC. The recommendations should include whether to continue, terminate or modify the trial and should be based primarily on safety and efficacy considerations.

Recommendations to amend the protocol or conduct of the trial made by the DMC will be considered and accepted or rejected by the TSC. The TSC will be responsible for deciding whether to continue or stop the trial based on the DMC’s recommendations.
Abbreviations used
CI  Chief Investigator
DMC  Data Monitoring Committee
NIHR  National Institute for Health Research
TMF  Trial Master File
SAE  Serious Adverse Event
SOP  Standard Operating Procedure
TSC  Trial Steering Committee
Appendix 1: Content of DMC open and closed reports

Open Statistical Report: An Outline

- One page outline of the trial design, possibly with a schema
- Statistical commentary explaining issues presented in the Open Report figures and tables
- DMC monitoring plan and summary of Open Report data presented at prior meetings
- Major protocol changes
- Information on patient screening
- Trial accrual by time 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 start of treatment
- Adherence to medication/treatment 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 trial status (pooled by treatment regimen)

Closed Statistical Report: An Outline

- 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 meetings
- Repeat of the Open Report information, in greater detail by treatment group
- Analysis of primary and secondary efficacy endpoints
- Subgroup analyses and analyses adjusted for baseline characteristics
- Analysis of adverse events and overall safety data
- Analyses of lab values, including basic summaries and longitudinal analyses
- Discontinuation of medications/treatments