STANDARD OPERATING PROCEDURE 12

GCP defined responsibilities

Part 3: Data Monitoring Committee

Version:	4.0	Effective Date:	20 October 2023
Issue Date:	6 October 2023	Review Date:	20 October 2025
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Revision Chronology:	Effective date:	Reason for change:
Version 4.0	20 October 2023	Biennial review: Change of title and linked to SOP 12 parts 1 & 2. Minor amends to text for clarification. Addition of information relating to observers attending DMC meetings
Version 3.0	13 May 2021	Biennial review: Update to reflect format of new SOP template structure. Minor text changes.
Version 2.2	10 April 2019	Biennial review: Clarification of meeting quoracy and timings. Definition of potential members. Updated DMC charter. Minor text changes
Version 2.1	11 July 2016	Biennial review: Splitting of timing and purpose into 2 sections. Minor text changes. Clarification re: who should attend DMC, prepare, and store reports (3.3.3 and 3.3.6). Deletion of graphic (3.3.5).
Version 2.0	26 February 2014	Format change to describe DMC procedures and to comply with SOP 1. Template Charter document produced.
Biennial review March 2010		No Changes.
Version 1.1	20th March 2008	Addition of cover page to state author and approver.
Version 1.0	March 2006	

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1 Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to describe the responsibilities for members of Data Monitoring Committees (DMCs), how they operate and their interactions with other oversight committees.

The responsibilities of those involved in Trial/Study Management Groups (T/SMGs) and Trial/Study Steering Committees (T/SSCs) are covered in Parts 1 and 2 of this SOP respectively.

This SOP applies to all University of Warwick staff working on Randomised Controlled Trials (RCTs) requiring independent oversight of activities. It is also applicable to research studies managed by WCTU who have an external sponsor where use of Warwick SOPs has been agreed.

2 Definitions

Oversight Committee	A group responsible for making sure that an activity is done correctly and legally.
Data Monitoring Committee	A group of researchers (statisticians, clinicians, health economists, other methodologists), external to the trial team, whose role as a committee is to safeguard the interests of participants by independently assessing the safety and efficacy data produced by an ongoing trial.
Open session	Sessions involving both independent and non-independent members, to review accumulating data on data quality, recruitment, patient safety, and other key data on the progress of the trial
Closed session	Sessions involving only DMC members and the Trial Statistician(s) who generated the Closed Reports. Allows discussion of confidential, potentially unblinded data from the randomised controlled trial, including information about the relative efficacy and safety of interventions.

3 Background

The DMC forms part of the oversight arrangements in place for a trial to ensure appropriate conduct on behalf of the sponsor and funding body.

The DMC is advisory to the Trial/Study Steering Committee (T/SSC). The T/SSC is responsible for promptly reviewing the DMC recommendations, to advise whether to continue, modify or terminate the trial, and to determine whether amendments to the protocol or changes to trial conduct are required.

4 Procedure

4.1 Responsibilities

Trial Statistician(s)	• Preparation of reports for open and closed sessions of the DMC. • Attend open and closed sessions of the DMC meetings. • Take minutes at open meetings (if required) and closed meetings. • If required, perform unmasking for the DMC.
Trial Manager	• Assist Trial Statistician(s) with preparation of open report (if required). • Attend open sessions of the DMC meetings. • Take minutes at open meetings (if required).
Chief Investigator (CI)	• Nominate suitable independent members to the funding body, if NIHR funded. Or as requested by non-NIHR funders. • Attend open sessions of the DMC meetings.
Funding Body	• Assess the independence of nominated members • Formally invite nominees to be included on the committee

4.2 When?

Nominations/invitations to form a trial's DMC should be considered as early 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 first DMC meeting should be held early in trial set-up, before the start of recruitment if possible, and is often combined with a meeting of the T/SSC. DMC meetings are usually aligned with the dates of the trial's T/SSC meeting to ensure DMC recommendations are reviewed and taken into consideration. Subsequent DMC meetings will usually be held annually, but more frequently if necessary, with the agreement of the committee. Frequency of meetings should be in line with the trial/study risk assessment.

A final DMC meeting will usually be held upon the availability of the final trial data, following the final data lock, and cleaned datasets being made available to Trial Statistician(s). If the trial is terminated based on the recommendations of the DMC, no subsequent DMC meetings are required.

4.3 How?

4.3.1 Remit of DMC meetings

The DMC will review:

- Trial Protocol
- DMC Charter
- Safety Review
- Open Reports
- Closed Reports including interim analyses
- Relevant evidence from other trials
- Statistical Analysis Plan (when appropriate)

Any recommendations the DMC make should be communicated directly to the TSC, via the Chairs of both committees.

A template DMC Charter is available (T38). This can be amended to the requirements of the individual trial and should be signed by all members.

4.3.2 Composition of a DMC

A DMC must be comprised of at least three independent members. At least one member should be an appropriately qualified clinician, and one member should be an appropriately qualified statistician. The independence and expertise of the nominated members should be assessed by the funding body upon CV review. Other appointments should be made in line with the particular requirements of the trial. For example, if a trial has a considerable economic evaluation component, then a health economist may be required.

Members of the DMC may wish to invite an observer to the Open session of the meeting, who will not contribute to discussions but attends as a learning exercise. The observer should be approved by the Chair and should be a named individual who has completed the T61 Confidentiality Statement for Oversight Committee Observers form. Observers do not have voting rights.

4.3.3 Attendance

DMC meetings require the attendance of the independent DMC members and the Trial Statistician(s). The CI(s) and Trial Manager(s) are strongly recommended to attend the open session(s) to provide input to the discussion of clinical and administrative issues with the DMC respectively. Full details of requirements should be included in the committee Charter.

DMC membership is to be for the duration of the trial and members are expected to attend all meetings. If any members leave or fail to attend consecutive meetings, the CI and funding body will liaise to appoint a replacement.

A DMC meeting must have at least 66% of independent members in attendance to be quorate. If the Chair is unable to attend, and the meeting cannot be rearranged, then the meeting may go ahead with an "Acting Chair" from the remaining members of the committee if this approach has been agreed by the committee.

If a meeting is not quorate then the meeting should be re-arranged to ensure quoracy. If there is an immediate urgency then the reports can be circulated via email and comments be made in confidence and returned to the Chair within a stipulated timeframe in place of a formal meeting i.e., have a 'virtual meeting,' however, it is recognised that this is not ideal and should be avoided as far as is practicably possible.

4.3.4 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 Charter containing a 'DMC member's disclosure agreement' and a 'confidentiality agreement.' Any DMC members who develop significant conflicts of interest during the course of the trial should declare and subsequently resign from the committee to be replaced with an appropriate independent member to meet the requirements of the committee.

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(s) will be the only trial team member(s) to have access to the interim data and are responsible for presenting reports to 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.

4.3.5 Open and Closed Reports

	Open Reports	Closed Reports
Prepared by	Trial Statistician/Trial Manager	Trial Statistician
Presented by	Trial Statistician/Trial Manager*	Trial Statistician
Content	Recruitment data Baseline Characteristics Eligibility violations Completeness of Follow-up Compliance pooled over treatment arms	Analyses of primary & secondary efficacy endpoints Analyses of safety data Sub-group analyses (If applicable) Analyses of AE/SAE(s) Analyses of laboratory data (If applicable) Open Report analyses that are displayed by masked intervention group
Circulated to	Trial team/DMC members	Trial Statistician/DMC members

See Appendix 1 for outlines of the proposed content of these reports.

*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.

Maintenance of blinding should be ensured through careful preparation of the Open Report which may also include the total number of SAEs reported and details of those SAEs.

All results should be presented by masked treatment group to maintain blinding. In the event a DMC need to see unmasked data (e.g., for planned interim analysis or Suspected Unexpected Serious Adverse Reaction (SUSAR) reviews) then the unmasking should be undertaken by the Trial Statistician(s) only. See SOP 41 'Blinding & Unblinding in Research Studies' for further information.

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. Further details on preparing datasets for DMC reports are given in SOP 15 'Information Handling' and T46 (Confirmation of Data Snapshot/Lock Form). The reports should be provided to DMC members optimally no later than one week prior to the meeting date.

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 DMC chair is responsible for communicating these recommendations to the T/SSC.

4.3.6 Minutes of the DMC meeting

The Trial Statistician, Trial Manager or other delegated trial team member will 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 prepared by the Statistician or Trial Manager, circulated to members of the DMC, the funding body (if required/on request) and key trial staff as appropriate, then filed in the Trial Master File (TMF).

The **Closed Minutes** will describe the proceedings from the closed sessions and should include the listing of recommendations by the Committee. These minutes should be prepared by the Trial Statistician(s), are confidential, and should not be made available to anyone outside the DMC. A copy should be kept by the statistician preparing the reports and stored securely in accordance with SOP 15 'Information Handling'. while the study is ongoing, with the location noted in the TMF map. Once the study completes and blinding is no longer needed to be maintained then they can be combined with all other documentation for archiving.

4.3.7 Recommendations to the Trial/Study Steering Committee (T/SSC)

Following each DMC meeting, the DMC Chair should communicate with the T/SSC Chair, potentially with assistance from the trial team and statisticians as required. This should happen as soon as possible with the agreed recommendations clearly stated. This document should be circulated to all independent DMC members and approved prior to sending to the T/SSC Chair. 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 T/SSC. The T/SSC will be responsible for deciding whether to continue or stop the trial based on the DMC's recommendations.

List of abbreviations

AE	Adverse Event
CI	Chief Investigator
DMC	Data Monitoring Committee
NIHR	National Institute for Health and Care Research
QA	Quality Assurance
RCT	Randomised Controlled Trial
R&IS	Research & Impact Services
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
T/SMG	Trial/Study Management Group
T/SSC	Trial/Study Steering Committee
WCTU	Warwick Clinical Trials Unit

Templates

T38	DMC Charter
T46	Confirmation of Data Snapshot/Lock Form
T61	Confidentiality Statement for Oversight Committee Observers form

Appendix 1: Recommended Content of DMC open and closed reports

Open Statistical Report: An Outline

- One-page outline of the trial design, possibly with a flow diagram
- 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 (if applicable)
- Major protocol changes
- Information on patient screening
- Trial accrual by time and by institution
- Eligibility violations
- Baseline characteristics
    - 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 over randomised arm)
- Attendance at scheduled visits (pooled over randomised arm)
- Reporting delays for key events (pooled over randomised arm)
- Length of follow-up data available (pooled over randomised arm)
- Participant treatment and trial status (pooled over randomised arm)

Closed Statistical Report: An Outline

- Detailed statistical commentary explaining issues raised by Closed Report figures and tables. (Where practical by randomised arm, with codes sent to DMC members by a separate mailing (See SOP 15, Part 1, 'Data Handling' for clarification on transferring data electronically).
- Summary of Closed Report data presented at prior meetings (if applicable)
- Repeat of the Open Report information, in greater detail by randomised arm
- 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