DATA MONITORING COMMITTEES IN CLINICAL TRIALS

Guidance for Research Ethics Committees

Contents

Introduction ................................................................. 2
1 What is a Data Monitoring Committee? ......................... 2
2 Which trials require Data Monitoring Committees? .......... 3
3 Why should the REC be interested in the Data Monitoring Committee? .............................................. 4
4 Might the Data Monitoring Committee assume a different name? ............................................................ 4
5 Who sits on Data Monitoring Committees? .................... 5
6 How is the role and function of the Data Monitoring Committee described? ......................................... 5
7 Does the Data Monitoring Committee need to be independent? .............................................................. 5
8 What does the REC need to know about the Data Monitoring Committee? ............................................. 6
9 How often should interim safety and efficacy data be monitored? ......................................................... 6
10 Where could I read more about Data Monitoring Committees? .............................................................. 7
11 Where can the REC obtain further advice if required? ................................................................................ 7

References ................................................................................................................................. 7

Appendix 1: Headings from the DAMOCLES template DMC charter ......................................................... 9
1. INTRODUCTION ................................................................. 9
2. ROLES AND RESPONSIBILITIES ........................................ 9
3. BEFORE OR EARLY IN THE TRIAL ..................................... 9
4. COMPOSITION ................................................................. 9
5. RELATIONSHIPS ............................................................. 9
6. ORGANISATION OF MEETINGS ...................................... 10
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION ................................................................. 10
8. DECISION MAKING .......................................................... 10
9. REPORTING ................................................................. 10
10. AFTER THE TRIAL .............................................................. 11
DATA MONITORING COMMITTEES IN CLINICAL TRIALS

Guidance for Research Ethics Committees

Matthew R Sydes\textsuperscript{1,2}; David Neal\textsuperscript{3};
\textsuperscript{1} MRC Clinical Trials Unit, London; \textsuperscript{2} formerly Cambridgeshire 4 REC; \textsuperscript{3} Deputy Director (Policy), National Research Ethics Service

Introduction

The primary responsibility for monitoring the safety of participants in clinical trials lies with the trial sponsor. Some types of clinical trial are also subject to regulatory oversight. In particular, the safety of clinical trials of investigational medicinal products (CTIMPs) and clinical investigations of medical devices (CIMD) within the EU is fully assessed by the relevant Competent Authorities (CA) prior to giving authorisation. CAs also maintain an overview of emerging safety issues through review of safety reports and access to global safety data. In the UK, these responsibilities lie with the Medicines and Healthcare products Regulatory Agency (MHRA).

In this context, the responsibilities of the Research Ethics Committee for monitoring the safety of regulated trials are limited. However, when giving an ethical opinion the REC needs to be assured that the safety and well-being of participants will be protected during the trial. It should be satisfied that sponsors have adequate monitoring arrangements in place, and kept informed about emerging issues that may have ethical implications, such as a need to inform participants or seek further consent.

The respective roles of MHRA and RECs are described in the Memorandum of Understanding\textsuperscript{1} agreed between MHRA, NRES, GTAC and AAPEC under the Clinical Trials Regulations, and in equivalent arrangements between MHRA Devices Division and NRES\textsuperscript{2}. This guidance supplements those agreements by explaining the role of the Data Monitoring Committee (or equivalent group) in monitoring a trial, when a formal DMC may be established by the sponsor, and the assurances the REC requires when reviewing the trial.

The guidance is equally relevant to clinical trials of investigational medicinal products (CTIMPs) and all other types of randomised clinical trial, including those not subject to regulatory oversight where the REC has a more significant role in reviewing safety-related issues. For example, it would be relevant to trials of surgical interventions or radiotherapy.

The guidance has been developed in consultation with the Clinical Trials Collaboration Group, which oversees the Memorandum of Understanding\textsuperscript{1}, and the National Research Ethics Advisory Panel.

1 What is a Data Monitoring Committee?

A Data Monitoring Committee (DMC) is a group of people that reviews accumulating data in a clinical trial and advises the sponsor (directly or indirectly) on the future management of the trial. It mainly reviews safety and efficacy data but may also see
quality and compliance data. (Other titles may be used, see section 4 below.) The DMC is usually privy to interim comparisons by arm and sees data in a format that is not normally widely shared beyond the core statistical team.

This guidance applies to the function of monitoring interim data; this role may, indeed, not involve a formal committee. The guidance relates to whoever is performing the data oversight function on the sponsor’s behalf throughout the trial.

2 Which trials require Data Monitoring Committees?

Some form of monitoring interim data should always be considered but many trials will not require a DMC or other formal arrangements. There is no statutory requirement under the Medicines for Human Use (Clinical Trials) Regulations 2004 for the sponsor to appoint a DMC, and where a DMC is appointed it has no statutory role.

A DMC is not required if it is not possible for it to make a contribution to the trial, e.g. where the trial would recruit and follow-up over only a short period or where the likely risks are known to be minimal or where the trial protocol would not be modified regardless of the interim data.

Trials which normally require DMCs or other formal monitoring arrangements would be those involving subjects with life-threatening illnesses or vulnerable populations and/or with significant potential risk of harm, or unknown or uncertain risks. Formal DMCs are of most value in trials with long-term or survival-based outcome measures (e.g. overall survival or disease-free survival). These types of outcome measure tend to be more common in randomised controlled trials (particularly in areas like cancer, cardiology, etc) and less common in phase I or phase II trials.

The outcome of deliberations about whether a DMC is required should always be recorded in the trial documentation. Plans to establish a DMC or put other formal monitoring arrangements in place should be described in the protocol.

Examples of trials where the sponsor would be expected to establish a formal DMC are shown in the box.

Example 1: A randomised controlled trial to assess whether patients with lung cancer live longer if they take a new chemotherapy agent.

A trial is planned to assess whether a new biological therapy, R1, should be given in addition to standard treatment with chemotherapy, C, for patients with small cell lung cancer. The current standard treatment is associated with a number of toxicities. Data from Phase I and II studies of R1 in patients with lung cancer and early phase III data from colorectal cancer suggest that R1 may cause some of the same unwanted side-effects as C. The investigators have named overall survival as their primary outcome measure as they hope that the combination of C+R1 will help patients to live longer. However, they are concerned that the side-effects may be additive or multiplicative. The trial plans to recruit 1200 consenting patients over 4 years and allocated half to each trial arm. Patients will be followed up for survival. The main analyses are expected 6 years after the start of recruitment. An Independent Data Monitoring Committee (IDMC) will meet 6-monthly for the first 2 years to review unblinded safety and efficacy data; the IDMC will determine the frequency of future meetings.
3 Why should the REC be interested in the Data Monitoring Committee?

The REC will receive some interim data about clinical trials in progress reports, annual safety reports and expedited reports of serious adverse events (SAEs), including any suspected unexpected serious adverse reactions (SUSARs) occurring in CTIMPs at UK sites. However, the REC is not responsible for assessing this data. As a voluntary body it lacks the resources and expertise to undertake in-depth monitoring and the data it receives are partial. It therefore relies on assurances from the sponsor that it has adequate monitoring arrangements in place for monitoring the safety and ethical conduct of a clinical trial. The DMC is an important component of these arrangements.

The DMC has access to much more information than the REC: usually seeing aggregated and comparative safety information including spontaneously-reported SAEs during the trial and routinely collected toxicity information, all by allocated treatment.

Commonly in CTIMPs, the DMC will see all of these data in the context of global safety data including non-UK SUSARs and SUSARs in other trials of an IMP conducted by the sponsor.

As well as safety information, in some cases the DMC will also see accumulating efficacy data and is usually the only body to see this interim data. The DMC has the clearest picture of the emerging balance of risks and benefits within the trial. Finally, the DMC will be able to interact with the trial team at meetings and quickly seek clarifications of the data or confirm their understanding of the data.

4 Might the Data Monitoring Committee assume a different name?

Formal Data Monitoring Committees appear under various other names, including “Data and Safety Monitoring Committee” (DSMC), “Data Monitoring and Ethics Committee” (DMEC) and “Trial Monitoring Committee” (TMC); many variants have been used e.g. the “committee” is often replaced by “board” (e.g. DSMB).
It is important to note that the ethical conduct of the trial, based on accumulating data, is at the heart of the DMC discussions. This is explicitly recognised in the name DMEC, although the name may be a little close to (Research) Ethics Committees. Each of the names emphasises some of the roles of the DMC (e.g. monitoring, safety, ethics), perhaps at the expense of others (e.g. balancing safety against efficacy). For this reason, Data Monitoring Committee is commonly preferred.

5 Who sits on Data Monitoring Committees?
DMC members are usually experienced trialists. A formal DMC usually consists of 3 or more people comprising clinicians and at least one statistician. The optimal size needs to balance the positives of larger groups (full range of skills, wide range of opinions, low risk of dominance) with the positives of smaller groups (availability of members, convenience and cost of meetings, less reluctance to express views, less risk of conflict, less potential for bias towards riskier decisions). Some DMCs cover a large number of trials, some cover only one. Many trials units note a lack of experienced people available to serve on DMCs.

6 How is the role and function of the Data Monitoring Committee described?
The role and function of the DMC should be well described in writing before the DMC reviews any trial data. This can be described in a Charter which covers the membership, the roles and remit, what recommendations are permissible, how often the DMC meets, how decisions are reached, whether they are advisory or executive, who they report to (how and when) and when they may reflect on their experiences.

The DAMOCLES group provided one possible template charter and the areas this covers are listed in Appendix 1. In some ways, the most important point is just that the charter exists and that the DMC role is described. In many trials, this will not be available at the very start of the trial: for long-term trials, the DMC may not meet for the first time until a year after the trial has opened; the trial team will likely (and appropriately) prioritise their efforts on starting the trial and will return to the DMC charter closer to when it is required.

It is the sponsor’s responsibility to ensure that a Charter is in place for the DMC when it is established. While the REC should be assured about the proposed role and function of the DMC at the time of the ethical review, it does not need to receive a copy of the Charter or approve it.

7 Does the Data Monitoring Committee need to be independent?
The presence of a DMC can be important for the credibility of a trial; the DMC protects against potential (unconscious) bias from investigators and from the sponsor. In many cases, an independent Data Monitoring Committee is recommended. If the DMC is independent it is useful to reflect this in the name: IDMC. Indeed, the use of an independent DMC should be the default position.

However, this is not always required. For some trials, e.g. a low-risk, short-term, randomised phase II trial, it might be appropriate for a non-independent committee or group within the same trials unit or company to review the data, provided that they are not members of the trial team. The remit and function of the committee should still be clearly described.
If the DMC is independent, it should be documented who the members are independent of and what is really meant by “independence”. The trial team should ensure that any potential competing interests are declared; members may be able to make rational conclusions in the context of competing interests but their presence can damage the credibility of the trial.

DMC meetings to review unblinded data will be “closed” meetings at which the sponsor and trial team will not be present. The DMC may also hold “open” meetings with the sponsor to discuss its conclusions and recommendations.

8 What does the REC need to know about the Data Monitoring Committee?

The primary responsibility for the safety of participants in CTIMPs and other types of trial lies with the sponsor. The responsibility of the REC is to ensure that the sponsor has appropriate arrangements in place to monitor the safety and welfare of participants during the trial.

To satisfy itself about this, the REC should be assured of the following:

- Whether a formal Data Monitoring Committee is to be convened
- If a formal DMC is not to be convened, whether this is justified given the nature of the trial and the interim monitoring plans in place
- If a DMC is to be convened, whether it will be independent and what its role and function will be.

This information should be included in the answer to the question in Part A of IRAS about safety monitoring and stopping rules. This question (currently A75) is enabled for all CTIMPs and other types of clinical trial. On-line guidance is available for applicants on the information required by the REC.

The REC does not require a copy of the DMC charter or a list of members before giving a favourable opinion.

The REC should bear in mind that many trials are international and that sponsors may not be able to act upon any proposed modifications to arrangements for interim monitoring or the detailed set-up of the DMC.

Where a formal DMC is to be convened, the sponsor should notify the REC of any recommendations made by the DMC and provide summary reports of interim analyses where appropriate. It is not considered necessary for the REC to see the minutes of all DMC meetings.

9 How often should interim safety and efficacy data be monitored?

The more often data are reviewed, the more likely that any one review will happen at a time when there is an imbalance in outcomes between treatment arms that has arisen just by chance. There is a risk that multiple reviews can lead to over-interpretation of “interesting” accumulating results.
It is better to look periodically at data with sufficient gaps so that a meaningful amount of new data can accumulate between meetings. There are a number of formal statistical “stopping rules” (stopping guidelines) which can support this and help to protect against over-interpretation.

10 Where could I read more about Data Monitoring Committees?

Much has been written about Data Monitoring Committees and interim monitoring which cover in depth the topics touched upon here. The NHS HTA-funded DAMOCLES project reviewed the literature, undertook surveys and performed detailed interviews before publishing recommendations in 2004. The full HTA report provides much detail about the findings. A short paper in *The Lancet* provides a template charter for DMCs from the DAMOCLES project. The [European Medicines Agency](https://www.ema.europa.eu) and [Food and Drug Administration](https://www.fda.gov) have each published guidance which is available online. Finally, two highly experienced clinical trialists, Susan Ellenberg and Jay Herson, have each published books about Data Monitoring Committees. Further sources are available.

11 Where can the REC obtain further advice if required?

The sponsor is primarily responsible for providing the REC with the information and assurances it requires about data monitoring arrangements. Where concerns arise and further expert advice is needed, options available to the REC include:

- MHRA Clinical Trials Unit, for safety issues in a CTIMP
- MHRA Devices Division, for safety issues in a CIMD
- NRES National Research Ethics Advisers, for ethical issues arising on initial review or during the trial
- Other expert referees, where appropriate.

The REC’s operational manager can facilitate any requests for advice. The MHRA should always be consulted if the REC is considering giving an unfavourable opinion on a CTIMP or CIMD because of concerns about safety or safety monitoring arrangements, including any disagreement with the sponsor about the need for a DMC or its role and remit.

References


Appendix 1: Headings from the DAMOCLES template DMC charter

1. INTRODUCTION
   • Name (& Sponsor’s ID) of trial
   • Objectives of trial, including interventions being investigated
   • Outline of scope of charter

2. ROLES AND RESPONSIBILITIES
   • A broad statement of the aims of the committee
   • Terms of reference
   • Specific roles of IDMC

3. BEFORE OR EARLY IN THE TRIAL
   • Whether the IDMC will have input into the protocol
   • Whether the IDMC will meet before the start of the trial
   • Any issues specific to the disease under study
   • Any specific regulatory issues
   • Any other issues specific to the treatment under study
   • Whether members of the IDMC will have a contract

4. COMPOSITION
   • Membership and size of the IDMC
   • The Chair, how they are chosen and the Chair’s role. (Likewise, if relevant, the vice-Chairman)
   • The responsibilities of the IDMC statistician
   • The responsibilities of the trial statistician
   • The responsibilities of the trials unit team
   • The responsibilities of the Chief Investigator and other members of the Trial Management Group (TMG)

5. RELATIONSHIPS
   • Relationships with Chief Investigators, other trial committees (e.g. Trial Steering Committee (TSC) or Executive Committee), sponsor and regulatory bodies
   • Clarification of whether the IDMC is advisory (make recommendations) or executive (make decisions)
   • Payments to IDMC members
   • The need for IDMC members to disclose information about any competing interests
6. ORGANISATION OF MEETINGS

- Expected frequency of IDMC meetings
- Whether meetings will be face-to-face or by teleconference
- How IDMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session

7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION

- Intended content of material to be available in open sessions
- Intended content of material to be available in closed sessions
- Whether or not the IDMC will be blinded to the treatment allocation
- The people who will see the accumulating data and interim analysis
- Responsibility for identifying and circulating external evidence (e.g. from other trials/systematic reviews)
- To whom the IDMC will communicate the decisions/recommendations that are reached
- Whether reports to the IDMC be available before the meeting or only at/during the meeting
- What will happen to the confidential papers after the meeting

8. DECISION MAKING

- What decisions/recommendations will be open to the IDMC
- The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules
- How decisions or recommendations will be reached within the IDMC
- When the IDMC is quorate for decision-making
- Can IDMC members who cannot attend the meeting input
- What happens to members who do not attend meetings
- Whether different weight will be given to different endpoints (e.g. safety/efficacy)
- Any specific issues relating to the trial design that might influence the proceedings, e.g. cluster trials, equivalence trials, multi-arm trials

9. REPORTING

- To whom will the IDMC report their recommendations/decisions, and in what form
- Whether minutes of the meeting be made and, if so, by whom and where they will be kept
- What will be done if there is disagreement between the IDMC and the body to which it reports
10. AFTER THE TRIAL

- Publication of results
- The information about the IDMC that will be included in published trial reports
- Whether the IDMC will have the opportunity to approve publications, especially with respect to reporting of any IDMC recommendation regarding termination of a trial
- Any constraints on IDMC members divulging information about their deliberations after the trial has been published