CLINICAL TRIALS TRANSFORMATION INITIATIVE

CTTI RECOMMENDATIONS: DATA MONITORING COMMITTEES

DEFINITIONS

- **Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB)** – A group of individuals who review accumulating trial data by treatment group in order to monitor patient safety and efficacy, ensure the validity and integrity of the trial, and make a benefit-risk assessment.
- **External DMC** – An independent group of individuals that conducts these activities outside of the sponsor organization.
- **Internal DMC** – A group of individuals that conducts these activities within the sponsor organization.
- **Data Coordinating Center (DCC)** – A group whose role is to facilitate the collection and quality control of trial data as specified in the protocol
- **Statistical Data Analysis Center (SDAC)** – A group whose role is to prepare statistical analyses of accumulating data, and prepare and present reports of data to the DMC; this group may be within or separate from the organizational structure of the DCC

Note: While these recommendations focus on external DMCs, many principles described may also apply to internal DMCs.

INTRODUCTION

DMCs traditionally have been used to monitor masked, randomized, controlled, multicenter trials that evaluate interventions intended to reduce major morbidity or mortality, whether sponsored by industry, government, or other entities. However, use of DMCs is not dependent entirely on study size or study phase, but rather on the nature and extent of risk to trial participants. In addition, DMCs add transparency, and their use may enhance the credibility of trials among both patients and clinicians. DMCs typically oversee the conduct of a single trial but they are occasionally asked to review multiple related trials.

The criteria for when a DMC is necessary are not well defined, and may vary substantially depending on the type of sponsor and their perceived need for independent trial monitoring and oversight. Furthermore, the roles and responsibilities of DMCs invariably overlap to some extent with those of other trial oversight groups. Nonetheless, DMCs hold a unique place in trial oversight. Although DMCs have been established for decades, their use in increasingly varied types of trials has led to diverse perspectives on how they should operate. While there may be reasons for DMC operations to vary somewhat according to the clinical trial setting, we offer the following general recommendations and guiding principles pertaining to external DMCs:

Role of the DMC

1. DMCs should be used when there is a need to periodically review the accumulating unmasked safety and efficacy data by treatment group, and advise the trial sponsor on whether to continue, modify, or terminate a trial based on benefit-risk assessment.
2. DMC members should be independent of the trial sponsor and should be provided with adequate resources and flexibility to perform their role of assessing benefit-risk (e.g., performing ad hoc analyses as needed, having full access to accumulating unmasked study data).
3. The rationale for use of a DMC, and the roles, responsibilities, and operational structure of the DMC, should be addressed in a Charter agreed to by the sponsor and the DMC prior to patient enrollment. [See Appendix I for examples of activities that may or may not fall within the remit of a DMC.]
4. The DMC and the SDAC preparing reports for the DMC should have access to all accumulating study data by treatment group beginning at trial initiation. The SDAC should have the flexibility to perform additional analyses that may be requested by the DMC.

DMC Composition

1. Clinician(s) with expertise in the medical area under study, and statistician(s) knowledgeable about clinical trials and statistical monitoring plans are essential members of a DMC. Bioethicists and patient advocates may make important contributions to some DMCs. Other types of expertise may be needed in some trials (e.g., pharmacology, toxicology, behavioral science, etc.).
2. DMC members should have experience in clinical research, and preferably clinical trials.
3. Senior researchers with expertise in the area under study will often have some prior connection with the study sponsor and/or investigators, and may therefore not be considered completely free from conflict of interest or the perception of conflict of interest. When these connections appear minor (e.g., prior DMC service for the same sponsor for a different product several years in the past), they can be dealt with by disclosure to the sponsor and other DMC members.
4. At each meeting, DMC members should report any activities or connections with sponsors, investigators, and/or other parties that could be perceived as a conflict of interest. If any such activity or connection is deemed to undermine the member's independence, that member may need to resign from the DMC.

Communication

1. SDAC report to the DMC

a. The SDAC should receive a scheduled transfer of accumulating data from the DCC, rather than only at regularly scheduled DMC reviews, to ensure they can meet Charter-driven responsibilities. A specific yet flexible schedule for transfer of accumulating data should be described in the Charter.
b. The format of the SDAC report to the DMC should be agreed upon prior to the first DMC interim analysis meeting.
c. Reports should include graphical presentation of the relevant data to summarize the information contained in the tables.
d. Flexibility should be permitted in the SDAC analyses and report format to accommodate changes as the trial progresses.
e. The lead SDAC statistician should be present at all DMC meetings and be well-versed in the trial protocol, including the statistical analysis plan.

2. In general, the SDAC should anticipate and be responsive to the needs of the DMC. To facilitate this, there should be a mechanism described in the charter for communication between the lead SDAC statistician and DMC, as needed, throughout the conduct of the trial.
3. Lines of communication between the DMC and trial sponsor should be specified in the Charter, and should follow suggested best practices. [See Appendix II]
4. DMC members and the SDAC statisticians should have an in-depth introduction to the study prior to patient enrollment. They need to be familiar with 1) the study design, 2) trial- or program-specific information, and 3) interim analysis plan.
5. DMC trial recommendations and proposed modifications should be provided to a steering committee or sponsor leadership group authorized to act on those recommendations, and not to those directly involved with implementation of the trial. The Charter should specify how disagreements between the sponsor and the DMC are to be managed.
    a. If the sponsor agrees with the DMC recommendations, the sponsor should report the major DMC recommendations to regulatory bodies and IRBs within an appropriate time period after the recommendations are made. Minor operational recommendations need not be reported to regulatory bodies or IRBs.
    b. If the sponsor does not agree with the DMC recommendations, the sponsor and DMC should first try to come to resolution. However, if a resolution is not reached, then the sponsor should make the final decision. That decision, along with supporting rationale and the DMC's written recommendations, should be provided to regulatory bodies and IRBs within an appropriate time period after the recommendations are made. IRBs and regulatory bodies may act independently based on their assessment of the disputed information.
6. DMC meeting minutes and reports should be made available to the sponsor and regulatory bodies at the end of the trial, as needed.

DMC Charter

1. Roles, responsibilities and operational issues (e.g., format and frequency of meetings) should be clearly outlined in a succinct, well-organized, jargon-free, non-legalistic Charter that empowers rather than handicaps the DMC, and allows flexibility in DMC operations and recommendations, while ensuring that the perspectives of sponsor and/or investigators are appropriately represented.
2. Communication processes between the DMC and sponsor must be clearly described in the DMC Charter.
3. In the rare circumstances when communication between the DMC and regulatory bodies is deemed necessary, the process for this communication should be clearly defined and agreed to by the DMC and sponsor.
4. The DMC Charter should include a summary of the statistical interim analysis and study monitoring plan, which serves as a guide for DMC recommendations.
5. Additional documents that should be provided to the DMC, but are not part of the Charter, include the trial protocol and statistical analysis plan.
6. See Appendix IIIa and IIIb for DMC Charter general content and additional specific content to consider, respectively.

Training

The work of DMC members and SDAC statisticians is complex. Preparation requires a combination of training and experience. Sole reliance on on-the-job training is not feasible due to the complexity of the role and size of the currently available pool of candidates.

1. Training should include:
    a. Review of the fundamentals of DMCs (e.g., via books, courses at professional meetings, and/or on-line content)
    b. Review of published case studies
2. The inclusion of one or more members without prior DMC service on each DMC (including closed sessions) is encouraged, such that continued development of new DMC members can occur through apprenticeship and mentoring.
3. Professional societies/organizations with an interest in the role and function of DMCs should develop and maintain databases of experienced DMC members and their relevant expertise.
4. DMC members should submit interesting and instructive DMC case studies to peer-reviewed journals in compliance with confidentiality provisions described in the DMC Charter. This will increase awareness of issues and challenges that can arise during the conduct of a clinical trial.

Appendix I. Specific DMC Responsibilities[1]

DMCs must:

Periodically review the accumulating unmasked safety and efficacy data by treatment group, and advise the trial sponsor on whether to continue, modify, or terminate a trial based on benefit-risk assessment, as specified in the DMC Charter, protocol, and/or statistical analysis plan.

It is recommended that DMCs:

1. Review the protocol and statistical analysis plan, contribute to the DMC Charter, and become familiar with pertinent background information prior to participant enrollment.
2. During conduct of the trial, DMCs should periodically review by treatment group and in an unmasked fashion:
    a. Primary and secondary outcome measures,
    b. Deaths
    c. Other serious and non-serious adverse events,
    d. Benefit-risk assessment
    e. Consistency of efficacy and safety outcomes across key risk factor sub-groups.
3. Periodically review, and make comments as necessary, during conduct of the trial related to:
    a. Recruitment progress,
    b. Quality and timeliness of data collection,
    c. Adherence to the protocol (e.g., missing data).
4. Provide their recommendations to the steering committee or a sponsor contact not involved in trial operations in a timely fashion, both in writing and perhaps verbally.

DMCs may:

1. At the initial DMC meeting, offer feedback to the sponsor on protocol issues that would enhance the ability of the DMC to carry out their responsibilities.
2. Review specific adverse events individually if deemed necessary (e.g., if a specific safety issue arises).
3. Request unscheduled DMC meetings without having to notify sponsor or investigators.
4. Request additional unplanned analyses without having to notify sponsor or investigators.

[1]There may be exceptions to these responsibilities due to variation among trials.

5. Review data that has not yet been cleaned and/or adjudicated.

It is recommended that DMCs not:

1. Adjudicate study endpoints under any circumstance.
2. Routinely review all adverse events individually.
3. Have a role in redesigning the trial after reviewing unmasked data.

Appendix II. Best Practices for DMC Meetings and Meeting-Related Communication

In addition to the CTTI DMC Project Recommendations, the following best practices may also be considered:

1. All attempts should be made to hold the first DMC meeting in person, before initiation of patient recruitment, to allow DMC members the opportunity to get to know one another, and to review the DMC Charter, trial protocol, and planned SDAC report templates.
    a. Discussions between the trial sponsor and DMC should be held to provide adequate trial context and summarize existing knowledge about the intervention being investigated.
2. Sponsor attendees should be limited to the sponsor trial leaders during the open session of the DMC meeting.
3. The content and duration of the open session after DMC meetings should be limited.
4. DMC members should have minimal sponsor interactions outside the formal DMC meeting open session.
5. Annual face-to-face meetings should be held; other meetings can be held via web- or teleconference.
6. DMC meetings should be held at a neutral location (e.g., not at the trial sponsor or particularly luxurious locations).
7. DMC members should not have discussions about the trial outside of DMC meetings.
8. DMC written recommendations to the trial sponsor should be conveyed with the minimal amount of information necessary to provide clarity.
9. If verbal debriefings are held following meetings or issuance of DMC recommendations, the minimal amount of information necessary to provide clarity should be provided.
10. Provide a period for written comments from the sponsor to the DMC rather than holding a verbal debriefing by the DMC following issuance of recommendations and/or suggested trial modifications.

Appendix III a. Sample DMC Charter Table of Contents

- **Introduction**
  Provide title and objectives of the trial including the interventions; include a reference to the synopsis or figure of the clinical trial design in the protocol. Provide a concise description of the DMC Charter scope.

- **DMC Roles and Responsibilities**
  Provide a broad statement of DMC goals as well as the specific roles of the DMC.

- **DMC Composition**
  List the DMC membership and individual titles. Also, provide the SDAC institution/vendor and role.

- **Governance and Relationships**
  Describe the governance and relationships of the DMC and other trial committees/stakeholders. Indicate the DMC decision-making authority is advisory, DMC conflict of interest disclosure and plan for ongoing evaluation of conflict of interest.

- **Independence**
  Affirm the independence of DMC members from the trial sponsor and investigators. Indicate that the DMC has the flexibility to request additional analyses and conduct unscheduled DMC meetings if needed. For government-sponsored trials, indicate that the DMC has the flexibility to meet in closed or executive sessions that do not include staff from the government entity sponsoring the trial.

- **Prior to the First Interim Analysis**
  Describe the DMC involvement in the protocol review process and any issues specific to the finalized protocol (e.g. participants, intervention, or regulatory issues). Describe DMC meetings prior to the first interim analysis including review of the DMC Charter.

- **Organization of DMC Meetings**
  Provide expected frequency of DMC meetings including flexibility to have ad hoc meetings, if required. Describe the meeting format (e.g. face-to-face, teleconference) and meeting sessions (e.g. open, closed, executive [2]), including the attendees.

[2] Open: DMC members, SDAC representatives, sponsor, and lead investigators
Closed: DMC members and SDAC representatives
Executive: DMC members only

- **Documentation, Confidentiality & Communication**
  Outline the material available in the open session (e.g. recruitment, data quality) and the confidential information available in the closed session (e.g. efficacy and safety tables, listings and figures) and the masking of the SDAC Report to the DMC. Indicate to whom the DMC communicates recommendations.

- **Decision-Making**
  Indicate when DMC members that are present constitute a quorum and how recommendations will be achieved. Outline potential DMC recommendations, reference statistical methods for decision-making (e.g. statistical analysis plan) and whether methods are binding or non-binding for recommendations.

- **Reporting**
  Indicate process for recording, archiving, and distributing DMC minutes. State how DMC recommendations and sponsor responses are communicated to stakeholders (e.g., IRBs, investigators); and how to resolve disagreements between the DMC and sponsor.

- **After Study is Completed**
  Provide plans for acknowledgement of the DMC in planned publications. After the trial is made public, indicate constraints on DMC members regarding disclosure or discussion of their deliberations during the trial.

- **Appendix**
  - Research Design Synopsis/Figure
  - DMC Contact Information including the SDAC
  - Figure: Relationship between DMC, trial committees and other stakeholders (e.g., IRBs, investigators, regulatory agencies)
  - SDAC Report: Planned Tables, Listings, and Figures
  - Data Sources Memorandum (completed for each SDAC Report)
  - Process for executing revisions to the Charter
  - List of abbreviations

Appendix III b. DMC Charter Points for Consideration

Additional content for consideration:

DMC Composition

- DMC membership and size (see Appendix for contact information)
- DMC Chair's role/checklist
- Replacement of DMC members
- DCC role[3]:
  - Collection and review of case report forms
  - Ensuring completeness and accuracy of the data collected
  - Providing collected data to the SDAC
- SDAC role:
  - Receipt of collected data from the DCC
  - Preparation of the SDAC Report and presentation to the DMC
  - SDAC statistician responsibilities before, during and after DMC meetings
- Trial sponsor/management group role:
  - Ensuring resources available to DMC to achieve designated functions
  - Communicating regulatory information to the DMC
  - Selection of the DMC and SDAC

Documentation, Confidentiality & Communication

- Material available in open sessions (e.g. recruitment, data quality)
- Material available in closed sessions includes efficacy and safety tables, listings and figures (include mock-up of tables and figures).
- Material periodically reported to the DMC (e.g. actual versus predicted enrollment, events of clinical interest)
- In double-masked trials, masking of the DMC reports
- Documentation/checklist of DMC process during and after the trial
- Documentation of data sources for the SDAC Report
- Distribution of material to DMC relative to timing of DMC meeting
- Maintaining confidentiality of DMC material
- Responsibility for providing information that is external to the trial under investigation
- To whom the DMC communicates recommendations
- Retention/disposition of DMC material

[3] The DCC and SDAC may exist as a single entity, particularly in the case of NIH-sponsored trials

Appendix (Additional Documents)

- Confidentiality agreement
- Conflict of interest statement
- Details for planned interim analysis(es)
  [if not contained in the protocol or separate statistical analysis plan]
- DMC Chair checklist of responsibilities
- Agenda topics for DMC meeting prior to first interim analysis
- Checklist of required DMC documentation during and after trial completion
- SDAC statistician responsibilities before, during and after the DMC meetings

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Bibliography

1. DeMets DL, Furberg CD and Friedman LM (eds). *Data monitoring in clinical trials: a case studies approach*. New York: Springer, 2006.

2. Clinical Trials Transformation Initiative. Data Monitoring Committees: project summary, https://ctti-clinicaltrials.org/our-work/ethics-and-human-research-protection/data-monitoring-committees/ (accessed 23 February 2016).

3. Ellenberg SS, Fleming TR and DeMets DL. *Data monitoring committees in clinical trials: a practical perspective.* Hoboken, NJ: Wiley, 2002.

4. Food and Drug Administration, *Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees*. 2006: Silver Spring, MD.

5. Grant AM, Sydes M, McLeer S, Clemens F, Altman DG, Babiker A, Campbell MK, Darbyshire J, Elbourne D, Parmar M, Pocock S, Spiegelhalter D, Walker A and Wallace S. Issues in data monitoring and interim analysis of trials (the DAMOCLES study). *Health Technol Assess* 2005; 9 (7).

8. Organization, review, and administration of cooperative studies (Greenberg Report): a report from the Heart Special Project Committee to the National Advisory Heart Council, May 1967. *Control Clin Trials* 1988; 9: 137-148.