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Responsibilities of Data Monitoring Committees: Consensus Recommendations

Barbara E. Bierer, MD[1,2], Rebecca Li, PhD[1,2], Jonathan Seltzer, MD, MBA, MA, FACC[3], Lynn A. Sleeper, ScD[4], Elizabeth Frank, EDA[5], Charles Knirsch, MD, MPH[6], Carmen E. Aldinger, PhD, MPH[2], Robert J. Levine, MD[7], Joe Massaro, PhD[8], Amish Shah, JD[9], Mark Barnes, JD, LLM[2,9], Steven Snapinn, PhD[10], and Janet Wittes, PhD[11]

Abstract

Background: A data monitoring committee (DMC) has special responsibilities for protecting the safety of clinical trial participants. Few guidance documents are available that address the operations and mechanics of establishing, serving on, or reporting to a DMC. This article provides a practical guide to sponsors, institutions, and individuals responsible for, or serving on, a DMC. *Methods:* A workgroup of professionals from academia and not-for-profit and commercial organizations that included investigators, statisticians, patient advocates, and ethicists met to define the essential elements of planning, coordinating, and populating a DMC. All members of the group have formed, served on, advised, or worked with DMCs. *Results:* The group outlined the objectives and mechanics of running a DMC, including operational and practical considerations, membership characteristics, roles, members' liability, and indemnification. Further, it delineated the roles and responsibilities of each DMC member. *Conclusions:* The group recommended practices for each phase of the DMC process from inception through execution of a clinical trial, with appropriate considerations for confidentiality. The group's practical guidance should assist in comprehensive oversight of appropriate clinical trials and should help DMC members execute their obligations with greater assurance.

Keywords

safety data, clinical trials, oversight of clinical trials, human subject safety, multi-site clinical trials, Data Monitoring Committees

Introduction: Objectives and Background

A data monitoring committee (DMC)[i] is an independent panel of experts whose principal function is to review the conduct and data of an ongoing clinical study, typically one with a randomized and often blinded design, with particular emphasis on the safety of study participants. The DMC is composed of medical experts, biostatisticians, ethicists, and others with experience in the conduct of clinical trials and the therapeutic area of the study. Unlike other individuals and committees responsible for execution of a trial, members of the DMC are typically unblinded to aggregate or individual data by study arm during the conduct of the trial. The DMC provides independent advice, usually to the sponsor or its designee, on the continuing scientific validity and safety of the trial and the efficacy of the therapy under investigation. Many DMCs are given additional quality control responsibilities including, but not limited to, reviewing procedural aspects of the trial such as verifying that appointments, laboratory tests, and procedures are accomplished within designated time "windows"; examinations (eg, pathology of biopsies) are carried out by properly certified professionals; and assessing

[1] Division of Global Health Equity, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[2] Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard, Cambridge, MA, USA
[3] ACI Clinical, Bala Cynwyd, PA, USA
[4] Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
[5] Dana Farber Cancer Institute, Boston, MA, USA
[6] Pfizer, New York, NY, USA
[7] Yale University, New Haven, CT, USA
[8] Boston University, Boston, MA, USA
[9] Ropes & Gray, Boston, MA, USA
[10] Amgen, Thousand Oaks, CA, USA
[11] Statistics Collaborative Inc, Washington, DC, USA

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Corresponding Author:
Rebecca Li, PhD, Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard, 14 Story Street, 4th Floor, Cambridge, MA 02138, USA.
Email: rli@bwh.harvard.edu

Table 1. Responsibilities of Research Ethics Committees/IRBs, CECs, and DMCs.

	Research Ethics Committee/IRB	CEC	DMC
Purpose	To ensure protection of human subjects and that benefits are proportional to risks; to ensure the protocol is consistent with local standards	To determine whether patient data meet clinical endpoint criteria	To ensure patient safety; to perform formal efficacy and futility analyses
Governance	Government and institutional oversight	Protocol and CEC charter	DMC Charter
Location	Usually institution where research is conducted; central, single IRB also possible	Chosen by sponsor	Typically chosen by sponsor or, in the case of emergency ad hoc meetings, by DMC chair or by the reporting statistician
Composition of committee	Peers at institution and others, and membership guided by regulation	Clinical experts in disease area	Investigators in disease area, statistician, bioethicist, and other necessary experts
Scope	Generally to oversee all of an institution's human research studies	For a specific study	Typically for a specific study or drug development plan
Types of studies overseen	All studies involving human subjects	Studies with complex or subjective endpoints	Commonly phase III or pivotal trial, trials with potential significant morbidity and mortality; trials where risk of major adverse events is high
Decisional authority	To determine whether to initiate a study based on risk/benefit analysis; whether to continue the study; whether to require certain language in informed consent document	To determine whether data satisfy criteria of predefined clinical endpoints	To recommend either to continue the trial unchanged, to modify the protocol, or to halt a study based on safety or efficacy
Finality of decision	Decisions are final, but institution has authority to disallow a study that has research ethics committee/IRB approval	Decisions are final	Decisions are recommendations
How are studies reviewed?	Prospectively prior to study start and periodically thereafter	Throughout the course of the study; data are blinded	During the course of the study; data typically unblinded

Abbreviations: CEC, clinical endpoint committee; DMC, data monitoring committee; IRB, institutional review board.

whether certain attributes (eg, gender, race, body mass index, disease severity) are balanced. DMCs that are responsible for implementing interim analyses typically check that endpoints are being reported in a timely fashion and adjudication of endpoints appears to be proceeding quickly and accurately. The scope of a DMC might not be limited to the monitoring of a single trial; some DMCs review a set of trials that are part of a drug development program or a clinical research network.

DMCs differ from other committees that provide oversight to clinical trials (see Table 1). As often the only committee that has access to unblinded data in a double-blind trial, the DMC plays an important role in monitoring patient safety. The DMC communicates its recommendations to the sponsor or its designee who is responsible for making a final decision on whether to continue or stop the trial or modify the protocol. Thus, the appropriate constitution and organization of a DMC enhances the execution of safe clinical trials.[1]

Methods

In 2013, the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) embarked on a program to train international clinical trialists, statisticians, and regulators on the principles, processes, expectations, and responsibilities of DMCs, with particular attention to individuals in developing countries for trials occurring in their country. In the course of this effort, trainees requested a short practical guide for individuals who are establishing, serving on, or reporting to a DMC to supplement their training.[2] We assembled professionals from various fields to develop a practical, role-based guide for DMC operations and decision making.

A workgroup of 24 members defined the essential elements of planning, coordinating, and populating a DMC based on existing materials and their own experience. All members of the group had formed, served on, advised, or presented to DMCs. Materials were further refined iteratively. An initial set of training materials was piloted in 2013. Questions arising during subsequent training sessions led to modifications of materials that lacked clarity after each training session. Training sessions have been held in the United States, Korea, India, Japan, China, Thailand, and South Africa, with a total of more than 300 participants.

Results

Practical Considerations in Constituting a DMC

All interventional clinical trials require some form of monitoring to assess safety and quality of data but not all require a DMC.[ii] Trials sponsored by United States National Institutes of Health (NIH) require a data and safety monitoring plan that outlines the process for safety monitoring. Many early phase trials, many social and behavioral studies, and some short-term trials of low risk to participants do not require a DMC. The classes of trials likely to utilize a DMC include (1) large randomized multicenter trials, (2) blinded interventional trials, (3) all NIH-supported phase III interventional trials, (4) trials that expose the participants to a high-risk intervention or an intervention that has the potential for serious toxicity, (5) trials with outcomes of mortality or clinically deleterious morbidity (eg, heart attack, stroke, tumor progression), and (6) some trials conducted in a vulnerable study population (eg, children, pregnant women) or with the inclusion of participants who are unable to make informed decisions, who are at particularly high risk, or who are not literate.[3] In addition, a DMC may be useful where the sponsor may wish to stop the trial early if the interim data demonstrate either strong evidence of benefit or convincing evidence of lack of benefit. Statistical methods allow interim analyses to assess benefit in a way that preserves the statistical operating characteristics of the trial (ie, maintains nominal type I error rate and power).

The organization and membership of a DMC will often depend upon the nature of the trial, the DMC charter, and the expertise necessary for appropriate oversight of the specific trial. A DMC typically must have individuals with certain areas of expertise, including (1) the clinical disease under study, (2) interpretation of data from clinical trials, (3) ethical concerns relevant to the trial population, (4) statistical analysis and interim monitoring, (5) evaluation of safety, including of serious adverse event (SAE) reports, and (6) the regulatory environment in which the trial is conducted. DMC statisticians should be conversant in the specific planned statistical analysis of the trials they monitor. Occasionally, additional expertise is required. Examples include a safety concern that requires specific knowledge (eg, a neurologist to evaluate neurologic adverse events in the study of an oncology drug), knowledge of specific diagnostic techniques or biomedical engineering, or specific understanding of cultural and ethnic issues. Some DMCs include a patient advocate, that is, someone who has had the disease or who has a close family member with the disease. While any one member may be proficient in more than one area, the DMC membership collectively should have the expertise to review and address issues predicted to arise; ad hoc members may be added for unanticipated challenges.

The Sponsor-DMC Partnership

In addition to having functional expertise, the DMC must work well with the sponsor (or its designated liaison to the DMC). The DMC should review and abide by its charter, document their deliberations, and communicate effectively with the sponsor. In addition, DMC members must have sufficient time to, and dedicate the time to, review meeting materials in advance and to attend DMC meetings. The DMC is an advisory board, and as such, should explain the reasons for their recommendations. If a recommendation is not to make a change, the "explanation" should be succinct and not include information that could compromise the integrity of the trial.

Sponsors should form a DMC with whom they can work but one that will have sufficient stature to provide independent recommendations.[iii] Further, sponsors should anticipate both human and financial resources required to support the DMC.

DMC Communication and Documentation

The DMC charter (see below) should include a communication plan, specifying to whom the DMC reports and makes its recommendations. If the sponsor is a public agency (eg, the NIH or the Veteran's Affairs Administration in the United States, or the Medical Research Council in Great Britain), the DMC will generally report directly to that entity. On the other hand, if the sponsor is a commercial entity (eg, a pharmaceutical company), the reporting structure will depend on the trial and be specified in the charter. In many cases, the DMC reports directly to the commercial sponsor or the sponsor's designee. In other cases the DMC may report to an independent steering committee that has been granted authority by the sponsor to make decisions based on the DMC's recommendations. Communications between the DMC and the sponsor (or designee) may be privileged, thus encouraging direct and honest, but appropriately limited, exchange.[4] [iv]

The DMC chair should discuss expectations for communication and emphasize the imperative of confidentiality at the first meeting of the committee. The DMC, typically through the DMC chair, should only communicate with individuals as specified in the charter. DMC members should avoid *ex parte* communications and casual statements.[v] The chair should also discuss expectations regarding communication among the DMC members themselves and whether they may or may not independently consult with each other or members of the independent statistical group outside of convened committee meetings. The DMC chair should decide whether there should be written communications and to whom they should be addressed.

Communication between a DMC and other parties requires a balance of openness and confidentiality. The DMC must make its recommendations clearly and in a way that preserves the integrity of the trial. Thus, any communication should provide sufficient, but minimal, information for the sponsor (or designee) to consider the DMC's recommendations. Shared DMC meeting minutes are terse and often refer only to information that is available in open session[vi] (eg, "accelerate recruitment"), and its recommendations are concise and succinct (eg, "The DMC reviewed data from the trial and other

relevant information. On the basis of that review, the DMC sees no cogent reason to modify the trial.''). Or, for instance, if there is an imbalance of safety events across sites or suspicion of unblinding at a certain site, the DMC might recommend that the sponsor re-educate *all* sites on proper safety reporting and blinding procedures without disclosing the specifics of the concern. Some DMCs create closed session minutes that remain confidential until the trial is complete and is unblinded. Others create summary notes instead of minutes. Generally, neither the minutes nor the notes specify which members said what.

Frequently, research ethics committees/institutional review boards (IRBs), and sometimes regulatory agencies, wish to receive a letter signed by the DMC chair attesting to the fact that the DMC has met and summarizing the most important recommendations. In many studies, the chair then writes two letters—one very short document that the sponsor sends to the research ethics committees/IRBs and regulatory agencies (''The DMC met on XX date and sees no cogent reason to modify the trial at this time'') and a longer letter that amplifies and details the nature of any specific recommendations for the sponsor. Unless what the DMC recommends leads to a major change in the protocol or to stopping the study, no communication should divulge any information that could unmask the blind or the outcomes in the trial. DMC minutes should document the sponsor's responses to previous DMC's recommendations. In addition to bringing closure to outstanding items, such written documentation attests that outstanding issues have been addressed. It may be of particular value in response to subsequent external requests.

Whether the DMC reports its recommendations directly to the sponsor, or the sponsor has given responsibility to decide on DMC recommendations to a separate group, there may be circumstances where the DMC's recommendations are rejected. These situations should be quite rare, particularly when the recommendation is in response to what the DMC perceives as risk of harm to study participants, and will typically reflect a fundamental disagreement in interpretation of the data.[vii] The DMC should be informed of this decision but has no authority to overturn it; often, such disagreement represents an opportunity for the sponsor to clarify data or present additional data or explanation, and the DMC might modify its recommendation. In rare circumstances when disagreement persists, the DMC might consider taking the rather drastic step of resigning from the study; even in this event, DMC deliberations remain confidential.

DMC Membership and Liability

Because DMC members may be individually and jointly liable for committee recommendations, all members should be comfortable with the insurance provisions that cover their participation. Sponsors should describe the financial liability that members might incur if they agree to serve, and corporate sponsors should include provisions for indemnification and legal costs in their contracts with DMC members.[4] In these provisions, the sponsors should include procedures to minimize potential conflicts of interest between sponsors and DMC members.[viii] Many government sponsors, however, do not possess such insurance; therefore, DMC members may wish to seek their own professional insurance and ascertain whether these insurance premiums are reimbursable.[5]

Process: Practical Suggestions for Each Phase of the DMC

Ideally, sponsors should convene the DMC and hold an inaugural (''kickoff'' or ''organizational'') meeting prior to enrolling the first participant in the trial. Such a meeting should include not only the DMC members but also the reporting statistical group. If a kickoff meeting prior to the start of the study is not possible, the first meeting should be held as early as feasible after the trial commences. All members of the DMC (excluding ad hoc members) will be involved in the following phases:

A. Development and review of the charter

Every DMC should have a written charter that delineates its responsibilities, the roles of its individual members, and the standard operating procedures for the conduct of the committee (see Table 2). Prior to the first meeting, the sponsor or designee should provide members with a draft charter for review.[ix] The DMC should review the draft at its first meeting. The charter should empower the DMC to evaluate the trial data effectively. Appropriate safeguards should be in place with respect to access to and communication of ongoing results of the trial.[x] Questions or clarifications concerning the charter should be addressed at the first DMC meeting.

B. Kickoff meeting

DMCs should hold a kickoff organizational meeting in which all DMC members participate. The meeting should include discussion of the rationale of the trial, the information known about the intervention under study thus far, finalization of the charter, the sponsor's rationale for the DMC, and expectations of the DMC. The sponsor should describe prior relevant interactions with regulatory bodies. For multiregional trials, the sponsor should explain special regulatory requirements in the countries where the trial is being held.[xi] The kickoff meeting allows the opportunity to explore what actions the DMC might take in hypothetical scenarios.

C. Periodic and follow-up meetings

All DMC members should be prepared to attend periodic and ad hoc meetings, many of which are held by teleconference or videoconference. Prior to any meeting, DMC members should have reviewed all distributed information (eg, meeting minutes, the DMC report, serious adverse events) (see Table 3). DMC members should be prepared to discuss potential issues at the start of the open session if the issues are ones that can be discussed with the sponsor present, and at the closed session for

Table 2. The Basic Elements of a DMC Charter.

Topic	Elements
Overview	• A general description of the DMC's role • A brief summary of the study design • Organizational structure of the trial, detailing the relationship of the DMC to other committees and parties involved in the trial • Methods for amending the DMC charter, if any
Membership	• Description of the responsibilities of each DMC member • Procedures for replacement of DMC members • Definition of a quorum
Communication and meetings	• Procedures to ensure confidentiality and appropriate communication • Meeting types, frequency, schedule, and purpose (safety review only, or review of both safety and efficacy) • Description of various meeting formats (open session, closed session, executive session) • Address(es) for correspondence • The process for taking and archiving minutes • Record retention and document archives
Data monitoring	• Planned format for data presentation of results • Plan for communication and review of adverse events • General description of planned statistical monitoring, focusing on procedures for decision making at the time of an interim look or adaptive design decision (without stating the decision rules for stopping or adaptation specific to the trial)
Reporting	• Nature and format of the recommendations to sponsor and the steering committee • Method and extent of communications among sponsor, medical representatives of the sponsor, investigators, research ethics committee/IRB (if any), and regulatory bodies (if applicable)

Abbreviations: DMC, data monitoring committee; IRB, institutional review board.

Table 3. Study Data Provided to a DMC for Review.

1	Summary of recruitment and likely ability to achieve target sample size
2	Data quality and completeness, including regional or site differences
3	Protocol adherence
4	Validity of assumptions concerning the study design
5	Safety of the study intervention
6	Efficacy of the study intervention (especially at planned interim looks)
7	Newly published research in the field that may impact the conduct of the trial or the ethics of continuing to randomize patients

Abbreviation: DMC, data monitoring committee.

issues that should not be discussed with the sponsor present. DMC meetings are focused on problems; the minutes should capture issues and their resolution to facilitate preparation of future meetings. Procedures for calling for special follow-up meetings should be defined. Review and discussion of the study data will allow the DMC to assess the integrity of the trial, the safety of research participants, and the appropriateness of continued random assignment.

D. Ad hoc or emergency meetings

DMC members must recognize that they may have to attend occasional ad hoc meetings. While rare, these meetings constitute a core responsibility. There is often little time to prepare for an emergency session; the questions and supporting analysis are discussed during the meeting. Emergency sessions are convened when significant new information may potentially cause the DMC to recommend modification or curtailment of the clinical trial or program.[xii]

E. Meeting format: open, closed, and executive sessions

Open sessions. The first kick-off meeting often has only an open session with representatives of the sponsor, the steering committee, the reporting statistical team,[xiii] and all members of the DMC present. In open sessions at subsequent meetings, the sponsor informs the DMC about the trial status and describes questions it would like the DMC to address. Full disclosure of the progress of the clinical trial program helps the DMC to perform its job effectively. The sponsor should provide up-to-date information about serious adverse events with particular attention to events that occurred since the study documentation was prepared (eg, events that occurred in the period between report preparation and the meeting itself). In addition, at this session, the DMC and sponsor may review an "open report" describing aggregate study conduct and safety data (eg, demographics, adverse events) for all treatment groups combined.[xiv]

Some DMC meetings end with a final open session during which the DMC presents its recommendations to the sponsor. If the DMC recommends a modification to the protocol, the sponsor needs to understand the rationale behind the recommendation, decide whether to accept the recommendation, and, if they do, move expeditiously to implement the change.[xv]

Table 4. Primary Responsibilities and Qualifications of DMC Members.[6,7]

	Responsibilities	Qualifications
All team members		
DMC members	• Review of DMC charter • Declaration of any conflicts of interest • Adequate preparation prior to meetings • Attendance and participation in DMC meetings • Understanding of specific role	• Freedom from, or management of, conflicts of interest with the study and the study sponsor other than payment for current service • Knowledge of protocol, statistical design, and parameters for recommendations for the trial • Appreciation of the requirements of confidentiality for membership • Experience in the area of ethical conduct of human subject research • Working knowledge of good clinical practices and clinical research
Reporting statistical team	• Independent of sponsor's statistician or statistical team • Prepares DMC statistical reports • Presents data at DMC meetings in a manner that is understandable • Understands study design, methodology for statistical stopping guidelines (stopping rules) • Interprets statistical data for DMC, and strives to simplify data to be concise and clear • Responsible for well-designed tables and graphs • Prepared to answer questions	• Advanced degree in statistics or biostatistics • Understanding of statistical principles for clinical trials (eg, International Conference on Harmonization E9 of Technical Requirements for Registration of Pharmaceuticals for Human Use) • Understanding of DMCs, statistical principles for interim safety analyses and other relevant methodologies • Detailed understanding of the protocol and the development program for the investigational product • Understanding of the therapeutic area under study
DMC administrator	• Responsible for DMC operations • Provides administrative support for chair, meetings, conferences • Ensures delivery and return of reports • Coordinates communication • Responsible for essential record-keeping	• Excellent managerial capabilities • High level of professional discretion • Project management experience • Clinical trials background helpful
Medical expert(s)	• Participates by contributing therapeutic area and disease-specific expertise	• Content expert in disease, therapeutic area, or patient population under study • Prior experience and familiar with clinical trials and research • Competence in good clinical practice • Prior experience and participation on DMCs preferred • Expertise in data analysis and study design preferred
DMC statistician(s)	• Focused on validity of experimental design, data quality and quantity • Familiar with design, execution and analysis of clinical trials, and procedures (eg, randomization, stratification) • Able to assess comparability across treatment groups • Able to conceptualize and calculate statistical power of, and necessary sample size implied by, a given design • Expert analytic methods relevant to data interpretation • Experience in best practices concerning acquisition, storage, and analysis of data	• Education and expertise in statistics, biostatistics, or relevant qualitative discipline, usually master's level or higher • Expertise in methods for sequential analysis of clinical trials • Substantial experience in the design and conduct of clinical trials • Experience with DMCs and statistical methodology for interim analyses • Ability to explain to nonstatisticians on the DMCs the statistical methods relevant to the trial • Knowledge of the relevant scientific area of the trial helpful
Ethicist	• Contribute to deliberations, with emphasis on actions that have ethical implications[a] • Contribute to discussions of informed consent, equitable selection of participants, risks and benefits, privacy as appropriate	• Expertise in research ethics • Familiarity with concepts of product development through clinical trials • Prior experience serving on DMCs preferred • Understanding basic statistical analysis preferred

(continued)

Table 4. (continued)

	Responsibilities	Qualifications
Patient advocate*	• Consider design or conduct of study such that it is appropriate for participants • May be important in international settings or inclusion of vulnerable populations	• Membership in the population of trial participants or, in the case of a pediatric trial, a parent of a child who is a member of the target population. Population defined as (1) persons who are afflicted with, or susceptible to, a specific disease or (2) members of a specific cultural group. Patient advocate may serve. • Some formal training in clinical trial design and implementation • Should not be enrolled or a relative of, or have knowledge of, specific participants in the trial • In some cases (eg, limited cognitive incapacity), patient advocate or advocacy organization may be helpful
Sponsor team roles		
Sponsor-designated medical team	• Resource for the DMC regarding the conduct and safety of trial studies; clarify medical questions that arise	• Practical experience with the protocol and the program for which the DMC is constituted • Understanding of the rationale and philosophy of the DMC • Comprehensive knowledge of trial conduct • Comprehensive knowledge of blinded study safety profile • Significant experience to review and question the rationale of DMC requests
Sponsor clinical operations team	• Responsible for site monitoring, protocol adherence, and data quality • Implementation of appropriate data entry and quality control procedures • Adherence to good clinical practices • Remains blinded to study arm assignment	• Training in clinical trial design and conduct • Expertise in principles of good clinical practice • Detailed understanding of the protocol • Some medical training and/or understanding
Sponsor data management team	• Ensures the quality of the data for DMC reports • Works closely with clinical operations team above • Reviews site data • Sends queries to sites to clarify data anomalies	• Training in clinical trial design and conduct • Expertise in principles of good clinical practice • Detailed understanding of the protocol
Sponsor safety officer	• Either specialized role or part of medical officer's role • Ensures safety of investigational product • Familiar with the identified and potential risks of the product • Oversees classification (not adjudication) of safety events • Key role when DMC recommends trial modification	• Medical training • Expertise in clinical trial design • Understanding of assessing product safety through pharmacovigilance efforts • Understanding methods of assessing balance between benefits and risks • Detailed knowledge of the investigational product's safety
Sponsor statistician (trial statistician)	• Responsible for the statistical aspects of this design, including definition of statistical stopping guidelines • Performs final analysis of the study after unmasking • Participates in the publication of the results • Supports any regulatory submissions • Key role when DMC recommends trial modification based on a statistical analysis	• Advanced degree in statistics or biostatistics • Understanding of statistical principles for clinical trials (eg, International Conference on Harmonization E9 of Technical Requirements for Registration of Pharmaceuticals for Human Use) • Detailed understanding of the protocol and the development program for the investigational product • Knowledge of the therapeutic area under study

Abbreviation: DMC, data monitoring committee.

*Patient advocate is not a required member of most DMCs.

[a]Actions that have ethical implications include many considerations in which the interests of one group of stakeholders (eg, sponsors who wish to extend a trial for the collection of secondary endpoints) are in actual or potential conflict with those of another group (eg, participants who would benefit from termination of the trial and knowledge of the primary outcome). Patient advocate is not a required member of most DMCs.

Table 5. Roles of DMC Teams During Charter Development and Kick-Off Meeting, and in Subsequent Meetings.

Role	Role During Charter Development	Role During Kick-off Meeting	Role During Subsequent and Ad Hoc Meetings
All DMC members		• Review charter, protocol, investigators' brochure, and sample informed consent form • Freedom from bias • Attention to the areas of their own expertise	• Provide guidance to other members on their specific areas of expertise • Remain open to question areas of concern or confusion • Actively participate in discussion and decisions

Sponsor-designated medical team	• Review charter for:
	  • Integration of required DMC operational procedures with the sponsor's operations
	  • DMC philosophy and rationale consistent with sponsor needs and perspectives
	  • Role of the DMC is consistent with regulatory requirements
		• Participant and presenter
		• Explain the sponsor's goals to the DMC
		• Explains relationship of the program to the overall drug, biologic, or device development strategy
		• Medical information regarding the disease or condition being studied
		• Technical, preclinical, and available clinical information about the product being tested
		• Information about the clinical development program, if relevant
		• Specific regulatory issues relevant to the DMC's activities
		• Safety issues that may have arisen in preclinical or clinical testing or suspected from other products in the class
			• Focused summary of trial progress and the program
			• In collaboration with the trial statistician:
			  • Enrollment
			  • Blinded safety information
			  • Disclosure of apparent problem sites or investigators
			  • Variability among sites or protocols
			  • Preclinical or clinical information from other protocols or programs
			  • Address previous concerns raised by the DMC (but note DMC has unmasked data available to it, so limit discussions of masked data to issues that the DMC must address in closed sessions)

Sponsor clinical operations team	• Commitments for clean and timely data for the DMC reports	• Rare interactions with DMC	• Rare interactions with DMC
Sponsor data management team	• Commitments for clean and timely data for the DMC reports	• Rare interactions with DMC	• Rare interactions with DMC
Sponsor safety officer	• Guidance regarding evaluation of specific safety concerns • May help define safety guidelines • Primary responsibility for informing the DMC of the known safety profile of the product	• May inform the DMC of known safety profile of the investigational product • May provide guidance with respect to anticipated issues or events during the trial • If not present at kick-off meeting, other sponsor representatives will relate information	• May attend the open session of regular and ad hoc meetings • May provide new safety information of investigational product learned elsewhere • May discuss and help interpret blinded, pooled-group information on safety from the ongoing trial

(continued)

Table 5. (continued)

Role	Role During Charter Development	Role During Kick-off Meeting	Role During Subsequent and Ad Hoc Meetings
Sponsor statistician (trial statistician)	• Often a primary author of the DMC charter • Responsible for the statistical aspects of that document, including description of any statistical stopping boundaries • Responsible for plan for data presentations that will be provided to the DMC	• Key participant • May present the charter • Gain agreement on its contents or determine the modifications needed • Helps to ensure that nonstatistical DMC members understand statistical aspects of the study's design and the DMC's role	• Key participant • Will generally inform DMC of known data quality issues (because the sponsor's data management and clinical operations teams generally do not attend the DMC meetings) • With the independent statistician who prepared the interim report, will help explain the details of the statistical analysis to the DMC members
Reporting statistical team	• Whether team is selected before or after charter is written, should confirm that all statistical aspects are clearly defined and satisfy principles of good statistical design • Should agree with plan as outlined	• Ensures that the nonstatistical members of the DMC understand the statistical aspects of the study's design and the role of the DMC	• Attends open session of regular and ad hoc DMC meetings • Assumes a leadership role in closed sessions • Informs DMC regarding issues related to data quality and timeliness • Independent voice for DMC, particularly if reporting statistical team analysis differ from that described by the sponsor statistician • In closed session, amplifies discussion of the methodology used for the report and for the planned interim analyses • Answers questions from DMC
DMC administrator	• None	• Schedules committee meetings and ensures scheduling needs are met for the project • Maintains administrative details on all members of the DMC	• Oversees meeting logistics (timing, location, transportation, reimbursements, meals, etc) • May take minutes during open session and, if not a representative of the sponsor, closed sessions upon request • May document committee decisions • Coordinates the team to ensure they meet deadlines for database lock and data reporting to the DMC

Abbreviation: DMC, data monitoring committee.

Closed sessions. For industry trials, the participants of the closed session portion of the meeting include the DMC and the unblinded and independent reporting statistical team. For public-sector trials, the trial statistician and some sponsor representatives may attend as well.[xvi] During this session, the reporting statistical team presents trial results concerning safety by study arm. It will also present efficacy outcomes by study arms if an interim look at unblinded data is planned or if the DMC needs data on efficacy in order to assess the balance of risks and benefits.[xvii]

Executive session. For industry, only the DMC attends the executive session portion of the meeting.[xviii] The DMC may use this session to discuss the quality of the report and data being presented and to formulate its recommendations to the sponsor of the study.[xix]

Discussion: Practical Suggestions for Roles and Responsibilities Related to DMCs

The qualifications and responsibilities for DMC members must be based on the type and scope of the clinical trial. Roles should not be confused with individuals—some people are capable of filling more than one role and, conversely, some roles may require multiple people. We have segregated the roles into four classes: sponsor, the reporting statistical team, the administrator for the DMC, and the DMC itself. In the last class, we also describe roles of specific members of the DMC. For each class, we describe the role definition, qualifications, and involvement in the functioning of the DMC (see Tables 4 and 5).

The sponsor, the reporting statistical team, and the DMC each have specific and different responsibilities in order to protect the subjects in the study and to ensure that the study is conducted rigorously. DMCs are constituted for general safety surveillance, formal interim efficacy analyses, and central risk monitoring; there is flexibility in implementation. Regardless of its structure, an effective DMC must be a true partner of the clinical trial sponsor and the investigators. As in any partnership, the relationships have multiple interdependencies as well as potential conflicts, which must be identified and navigated successfully.

The independence of the DMC is central to the committee's operation. From the DMC's perspective, ''independence'' means that its remit is sufficiently flexible to execute its charge: to protect the safety of the participants and to ensure scientific validity.[xx] ''Independence'' for the sponsor implies that sponsors not influence the decision making of the DMC and freedom from conflicting interests in the DMC members themselves—for example, DMC members should not be selected for their future marketing potential. Sponsors typically compensate DMC members for their time, effort, and expertise; therefore, awareness of potential conflicts, other than this singular financial relationship, is particularly important. DMC members must disclose potential conflicts of interest before joining the DMC and at the start of each meeting. Examples of potential conflicts of interest include salary, consultancy, stock in either the company whose product is being tested or a competitor of that company, professional relationship with study investigators, and public positions indicating lack of equipoise. Some of these conflicts may be managed rather than disqualifying a prospective DMC member, but they must be disclosed transparently. ''Independence'' for the reporting statistical team suggests that their primary role and obligation is reporting to the DMC, not to the sponsor that provides its financial support. Unlike the trial statistician, members of the reporting statistical team are not typically involved in the final statistical analysis for the study.[xxi] The initial scope of work should include not only the analysis of expected adverse events and efficacy, but anticipate additional analyses that the DMC may request.

The US FDA issued a draft guidance (Safety Assessment for Investigational New Drug Application Safety Reporting, December 2015) that recommends sponsors institute a Safety Assessment Committee to review accumulating safety information in an unblinded fashion regularly across all trials in a development program.[7] This committee, if the guidance is enacted as currently envisioned, differs from a DMC in that its role is to recommend whether or not the sponsor should submit an Investigational New Drug (IND) safety report to the FDA. In contrast, the DMC's recommendations are focused on modifications of a trial. Most DMCs are not currently constructed to serve as safety assessment committees. If this guidance is finalized, it is likely that the function of these two committees will be complementary.

Conclusions

Over the past two decades, clinical trials have become increasingly global[8]; the composition and demographics of DMCs have not changed concomitantly. The pool of experienced DMC members outside of the US and EU has remained small. Country-specific regulations are beginning to appear. For example, the China FDA (CFDA), in its final ''Guidance for International Multicenter Clinical Trials (IMCT),'' suggests that studies with more than 20% of Chinese patients include experts from China in their DMC.[6]

While it appears to be important to include DMC members who appreciate the needs and expectations of diverse participants in the trials, it is usually not feasible to represent all regions in the membership of the DMC. That said, greater representation from participating nations is an important and achievable goal.[8] The MRCT Center has been training DMC members since 2012, selecting midcareer physicians, statisticians and ethicists with strong clinical trial experience to participate in a one-day training program with leading clinical trialists, physicians, and statisticians. This guidance, intended for DMC members newly embarking on their responsibilities, provides practical knowledge about the day-to-day responsibilities, terminology, and roles required for them to fulfill their duty to trial participants.

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Notes

i. A DMC is also known as a data and safety monitoring board (DSMB), a data and safety monitoring committee (DSMC), or an independent data monitoring committee (IDMC).
ii. Throughout this paper, we use the word *monitoring* to refer to the activities of DMCs. The word is also used to refer to a

sponsor's activities related to checking the performance of individual clinic sites.

iii. The DMC membership need not be composed exclusively of potentially overcommitted leaders in their fields, particularly if the DMC members need to devote significant time to the study. For instance, junior-level faculty who understand the clinical population and scientific issues of the trial often serve as valuable members of a DMC, even though their clinical trial experience or prior service on a DMC may be limited. Likewise, experienced clinical trialists can be valuable DMC members even if they lack particular expertise in the therapeutic area being studied.

iv. To underscore the responsibility to protect confidentiality, some charters specify labeling each e-mail or other communication, ''Confidential, do not forward or otherwise communicate.'' Some charters have other reminders to underscore the responsibility to protect the exchange. Some charters preclude the use of ordinary e-mail.

v. It is sometimes helpful to script responses should any DMC member be approached by an outside entity. For instance, a response might be, ''DMC members have an obligation to respect confidentiality. If you wish information, please contact *<the sponsor of the study at:>*.''

vi. For a definition and discussion of open and closed sessions, see the ''Meeting Format'' section.

vii. If recommendations are made upon interim analyses, it is not uncommon for the sponsor to reanalyze the data internally with a small group of statisticians prior to taking any action. This confirmatory analysis, one that the sponsor can depend upon, confirms accuracy and data quality, particularly since the DMC often must depend upon data that have not been audited and analyses only performed by the independent reporting statistical team.

viii. One suggested solution to minimize such conflicts is for the Sponsor to provide both indemnification of liability and the legal costs of a separate lawyer for the DMC member.[4] Another suggested solution is for sponsors to agree to pay for independent indemnification insurance for DMC members.[5]

ix. Indeed, potential members of a DMC should not agree to serve unless they have reviewed and approved the charter and believe that they will be able to follow its mandate.

x. For instance, the medical experts should assess if the planned data analyses are likely to be sufficient to adjudge clinical effects with an acceptable degree of certainty given the population and preclinical risk.

xi. For trials conducted in areas with less developed medical systems, DMCs should consider—if feasible—holding their kick-off meeting at one of the clinical sites so that members understand the practical difficulties of conducting clinical research, collecting data, and ensuring the quality of such data.

xii. If the issues are sufficiently complex to merit significant deliberation, it may be helpful to hold this meeting in person even though it may be difficult to schedule on short notice.

xiii. The role of the reporting statistical team may be fulfilled by one individual (the reporting statistician) but more often by a number of people who collectively serve as the reporting statistical team. Here we use the term ''reporting statistical team'' to reflect one or more individuals serving that function.

xiv. Often, the analyses provided to DMC members prior to the meeting reflect data that are several weeks, or even months, old. Providing timely data to the DMC is often challenging because current data may not have been ''cleaned'' or audited (ie, validated by source documentation); *data cleaning* (or *data scrubbing*) includes the removal of errors and inconsistencies from the database. Data quality issues occur in single data collections (eg, files and databases) as a result of misspellings during data entry, missing information, or other invalid data. Data cleaning is more important if multiple data sources are integrated into one database, as redundant data in different representations may result in duplicate or misclassified information. DMCs require information that is timely even if the data are not completely or perfectly accurate.

xv. For DMCs that report to representatives of the sponsor (eg, academic steering committees, CROs, government agencies) who do not attend the meetings, such a final open session is not usually held.

xvi. In this context, the ''sponsor'' provides funding for the study and is not involved in the actual design, conduct, or reporting of the study. For NIH trials, for instance, the sponsoring Institute will usually appoint an Executive Secretary to attend DMC meetings and that person is usually responsible for the minutes of this session. In addition, if efficacy data are not presented or are presented only in aggregate, other members of the NIH, such as the program officer or NIH statistician, may choose to attend.

xvii. If the examination of unblinded data is not planned during that specific closed session, the participants of the session will rely upon aggregate data.

xviii. For NIH trials, the executive secretary attends as well.

xix. In some circumstances, particularly when the reporting statistical team and the DMC are aligned, this formulation may occur during the closed session without the need for an executive session.

xx. The charter should reflect that flexibility. For instance, a DMC that is chartered to look only at safety may require data on efficacy in order to judge the ongoing balance of risks and benefits. The DMC should not view its flexibility, however, as freedom to explore its own interests in the trial data or redesign the study, but rather to apply an independent and rigorous approach to the primary goal of a DMC—ensuring participant safety and scientific integrity and validity.

xxi. The independence of the trial statistician from the DMC permits advice to and the engagement with the trial investigators without the knowledge of interim results or safety concerns, thus minimizing potential of even unintentional bias.

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