Advanced Clinical

INSIGHT BRIEF

Conducting an Effective Data Monitoring Committee: Five Strategies for Success

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Introduction

The first data monitoring committee (DMC) was established by a National Institutes of Health (NIH) external advisory group in 1967. The goal of a DMC is to ensure the ongoing safety of clinical trial participants by identifying experts who are not involved in the design and conduct of the trial to review the data for emerging issues. The initial focus was on large, randomized multicenter trials sponsored by federal agencies such as the NIH and Department of Veterans Affairs.

Expectations for DMCs are described in multiple guidance documents, from bodies such as the U.S. Food and Drug Administration, European Medicines Agency and Japan's Pharmaceuticals and Medical Devices Agency.

Cases Where DMCs Are Used

Use of DMCs has evolved and expanded over time, and their relevance should be considered during study planning, depending on indication; study endpoint, duration and population; and the type of drug being investigated. Today, DMCs are no longer restricted to government agency studies, and may be appropriate in cases with:

- Concerns about trial data monitoring and subject safety in large, long duration and/or multi-center trials
- Safety concerns that are unusually high, including trials involving
  - Life-threatening diseases
  - Study treatments with potential for serious toxicity
  - Vulnerable patient populations who are at elevated risk of death or other serious outcomes
- Mortality or major morbidity endpoints, which are now being used more frequently
- Issues in clinical trial conduct and analysis that may lead to inaccurate or biased results
- More complex study designs, such as the increasingly used basket and adaptive design studies
- Collaboration between industry and government, under the policies of government funding agencies

DMCs are typically not used for: single-center, open label, phase I/II trials where independent medical monitoring may be sufficient; phase I, open label, dose escalation trial with clear and objective criteria for stopping the dose escalation if unacceptable side effects are observed; or trials expected to accrue too quickly to enable a DMC to be set up.

DMC Composition

DMCs should have a limited number of members—ideally between three and seven—depending on phase, study complexity and level of risk. DMC members should have: scientific expertise in the relevant indication; practical experience with conducting clinical trials; an understanding of the problems and limitations of clinical trials; no financial ties to sponsors nor financial interest in the outcome of the study; no involvement with the conduct of the study; and no participation as a DMC member on a study in the same indication with a different sponsor.

At a minimum, the DMC should include a clinical expert in the disease area, a biostatistician, and an investigator with experience in conducting clinical trials.

Topics for DMC Review

The DMC reviews interim/cumulative clinical trial data for:

- Evidence of study-related adverse events
- Evidence of efficacy in accordance with pre-defined statistical plans
- Data quality, completeness and timeliness
- Investigator site performance
- Recruitment and retention compliance
- Protocol adherence
- Factors that might affect study outcome or compromise confidentiality of the data (such as protocol violations or unblinding)

The committee also examines external considerations such as scientific or therapeutic developments that may impact participant safety or study ethics.

DMC recommendations typically fall into the following categories:

- Protocol changes
- Suggestions to increase numbers of clinical trial sites and/or extend enrollment
- Suspension or early termination of the study based on:
  - Concerns about subject safety, inadequate performance or rate of enrollment
  - Objectives being met based on pre-defined statistical parameters
- Corrective actions for a clinical trial site with questionable performance or potential performance concerns

Strategies for Success

The section below discusses five key strategies for conducting an effective DMC.

Strategy #1: Timely Development of a Robust DMC Charter

The DMC charter documents pre-defined operating procedures for the DMC. At a minimum, these include a communication plan, an organizational diagram, a list of members, and details of roles, responsibilities, decision-making procedures, meeting frequency, format and documentation requirements. The planned statistical approach and data requirements are also specified and must be agreed upon with the sponsor.

Charter development is judged a success if a robust document is completed early, ideally before study initiation, and finalized well in advance of data analysis. Clarity in expectations and responsibilities is also important, with input from DMC members included, and regular review at defined intervals during trial conduct and updating as required.

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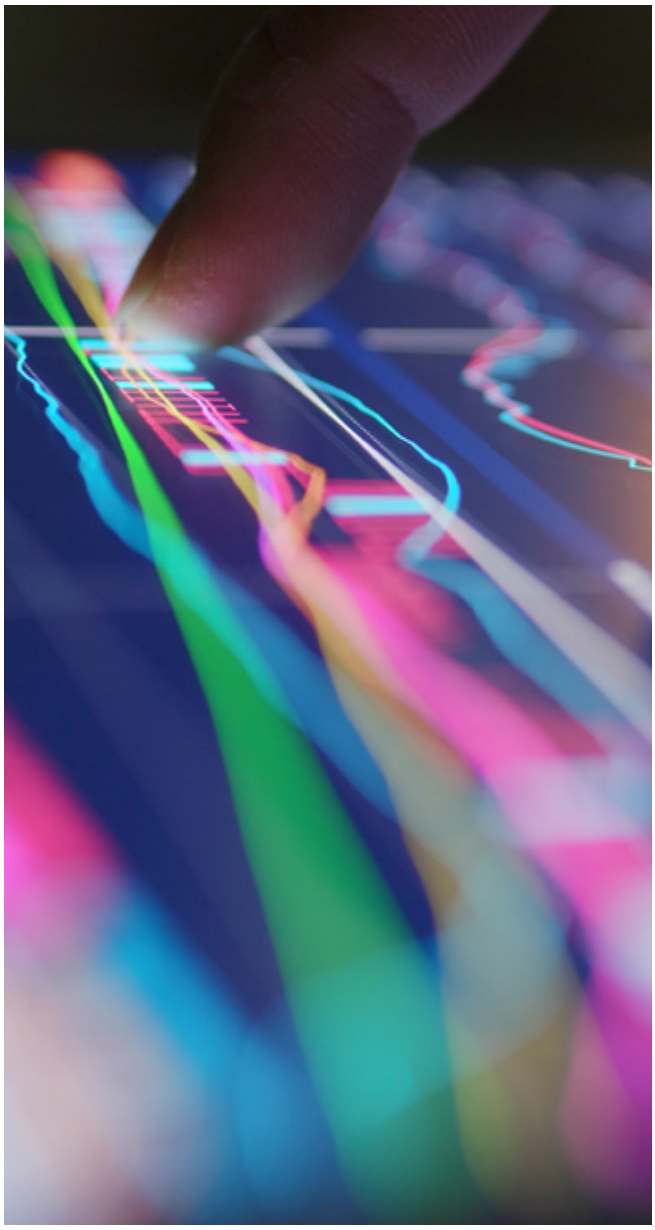
Strategy #2: Successful Planning for a DMC Meeting

The appropriate frequency of meetings varies based on factors including the rate of enrollment, the timing of scheduled interim analyses, and occurrence of any safety issues or unanticipated adverse events.

At the first meeting of the DMC, the charter is reviewed and discussed, attendees confirm that they have not had any changes in affiliation that might cause bias, and that all study-related documents have been shared.

Elements in meeting planning success include:

- **Providing an orientation** or holding a preparatory meeting
- Scheduling meetings **as far in advance** as possible
- **Coordinating activities** across all relevant functions, including data management (DM) data review requirements, including whether these are based on date or subject enrollment, and whether the data are expected to be clean
- **Identifying biostatistics deliverables**, including DMC report and tables, figures and listings (TFLs)



A successful DMC meeting requires timely delivery of study reports, data delivery outputs and all other required documentation.

- **Agreeing on deliverables**, including expected TFLs
- **Allowing time for data review** by DMC members prior to the meeting, with a minimum of five business days
- **Distributing the agenda** at least one week in advance of the meeting
- **Soliciting questions** from DMC members ahead of the meeting
  - **Establishing detailed timelines**, including data extraction date; materials distribution date; meeting date and time; minutes distribution, review period, planned finalization; and review of closed session recommendations with the sponsor
- **Creating a secure web portal**, especially for unblended data
- **Planning for emergencies** where committee members are unable to attend meetings

Strategy #3: Conducting a Productive Meeting

Types of sessions are defined in the charter. Open sessions may include study team members, investigators, and others, and focus on the progress and conduct of the study. The open report will include blinded and non-confidential data on topics such as recruitment, eligibility violations, and protocol compliance. Closed sessions are for DMC members only with the closed report including unblinded and confidential information such as key data points and an analysis of serious adverse events.

It is essential to ensure that there are separate links and distribution lists for open and closed session content. A full review of documentation is required by members who will be involved in developing recommendations. Other actions include the need to identify someone as being responsible for the minutes, allowing time for a thorough discussion of opinions and rationale between members, and for resolution of any discrepancies. All recommendations require a quorum.

A successful DMC meeting requires timely delivery of study reports, data delivery outputs and all other required documentation. Findings and recommendations should be discussed at the conclusion of the meeting with a detailed summary of discussions included in the meeting minutes. All protocols defined in the charter must be followed.

Strategy #4: Prompt Meeting Action Item Follow-Up and Closure

Post-meeting activities include sponsor reporting of DMC recommendations to regulatory bodies, and timely distribution of meeting minutes, which must be approved and distributed to all relevant parties. Documents from the DMC meeting should be filed, including the agenda and minutes, sponsor report, any materials shared with the DMC and any action items.

Characteristics of a successful meeting follow-up include rapid finalization of all reports, minutes and other documents, enabling the sponsor to distribute recommendations in a timely manner to all relevant parties, such as CROs, vendors and sites. Follow-up, tracking and resolution of all action items are essential, including recommended charter changes, data questions, TFL updates/ new requests and site inquiries. All next steps must be clear and taken without delay.

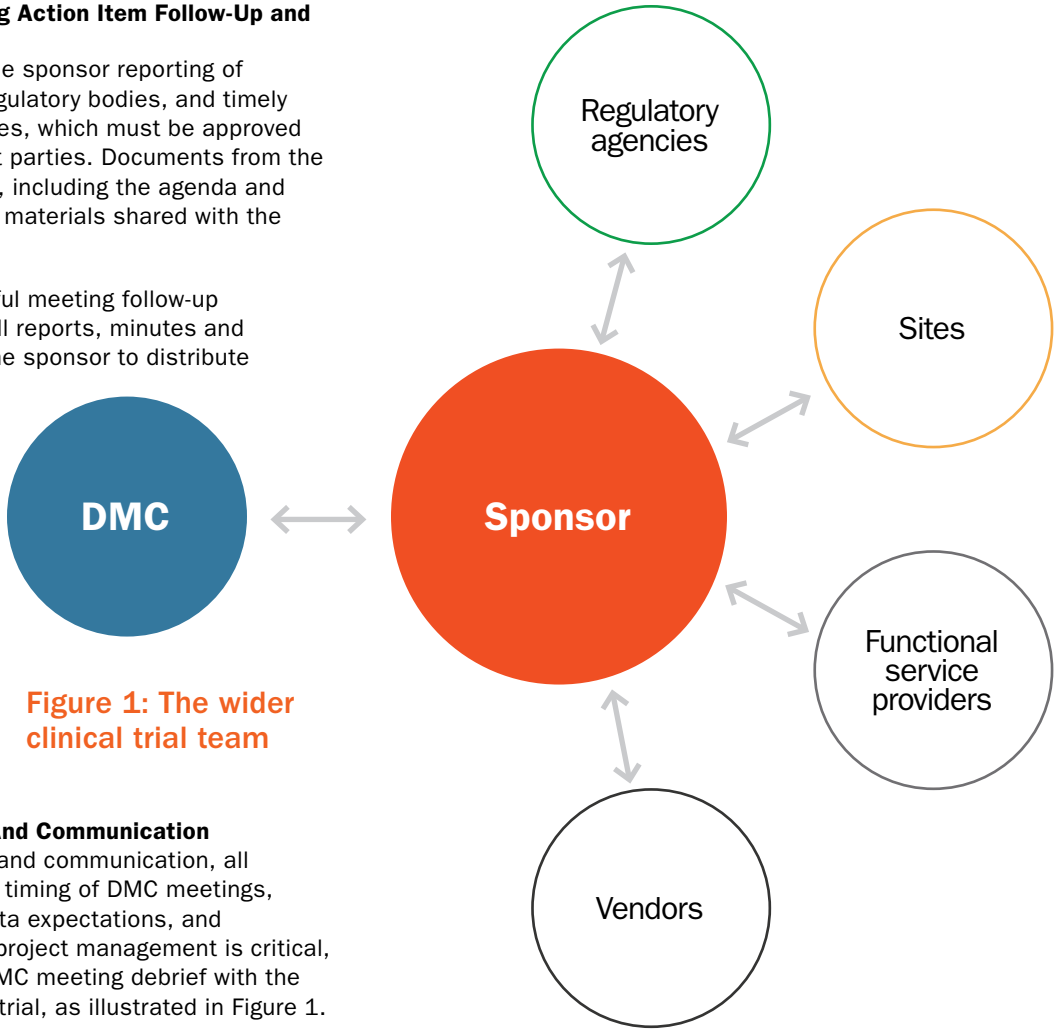


Figure 1: The wider clinical trial team

Strategy #5: Collaboration And Communication

For successful collaboration and communication, all parties must be aware of the timing of DMC meetings, roles and responsibilities, data expectations, and recommendations. Effective project management is critical, including coordination of a DMC meeting debrief with the wider team involved with the trial, as illustrated in Figure 1.

DMCs during the COVID-19 pandemic

During the COVID-19 pandemic, the increased risk of conducting studies has highlighted the importance of DMCs, which have been consulted about study suspensions due to site closures or subject reluctance to participate. DMCs have contributed to discussions on protocol changes designed to accommodate novel approaches to data collection and have collaborated with sites to determine whether remote clinical research might put subjects at risk. They have also been involved in studies of potential COVID-19 treatments and vaccines.

Conclusion

In conclusion, DMCs play a critical role in clinical research and are more important now than ever before, helping protect patient safety as the clinical trial design and research landscape evolves in response to the COVID-19 pandemic. When setting up a DMC, sponsors should consider collaborating with an experienced partner to implement the major strategies for success: timely development of a robust DMC Charter, planning and conducting a productive DMC meeting, prompt meeting action item follow-up and closure, and collaboration and communication.

Tracy Parker
VP of Biometrics

Tracy is a seasoned clinical researcher with 20 years of experience in multiple business functions, including biometrics, project management and proposal development. Her expertise includes cross-functional oversight, project management, risk management and mitigation, budget and proposal development and relationship management. She is dedicated to driving positive results, with a proven record of effective communication and collaboration within and across functions, building strong teams, driving initiatives and delivering with quality.

Jason Piontek
Director, Statistical Programming

Jason Piontek, Director SAS Programming, has over 15 years of clinical trial experience, having held roles from statistical analyst to manager of biostatistics. With experience leading single studies as well as large FSP programs, Jason's therapeutic expertise includes oncology, transplant and immunology, device studies, pediatrics/neonatology, cardiovascular, nephrology/urology, otolaryngology, psychiatry, psychology, pulmonary/respiratory diseases, dermatology and immunology/infectious diseases, including regulatory submission in several of these areas.

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