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Key Insights on Data Monitoring Committees:

Summarizing the FDA Guidance.

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The FDA recently published a draft guidance on the Use of Data Monitoring Committees (DMCs) in Clinical Trials for consultation. Leveraging our substantial expertise in DMCs, a select group of Phastar statisticians thoroughly reviewed and provided insightful comments on the guidance. By contributing our specialized knowledge, we aim to help shape the future direction of regulatory standards in this critical area.

DMCs can be referred to by other names e.g., Data and Safety Monitoring Board (DSMB), or Independent Data Monitoring Committee (iDMC), but for the purpose of the guidance the FDA defines a DMC as:

> **"a group of individuals with relevant expertise that reviews accumulating data on a regular basis from one or more clinical trials and recommends to the sponsor whether to continue, modify, or stop a trial or trials."**

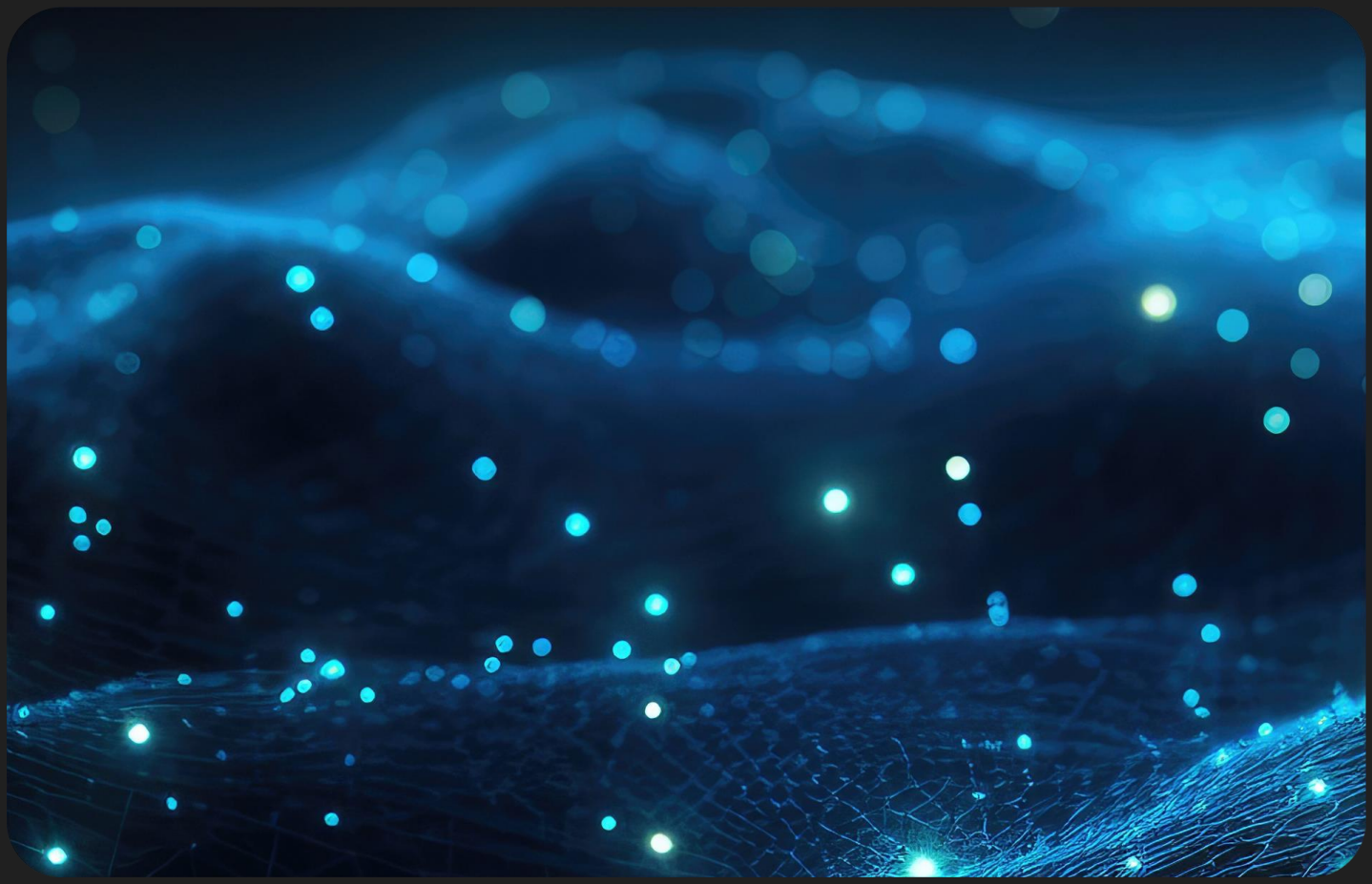
The FDA highlights significant changes in DMCs in practice since their 2006 guidance on *Establishment and Operation of Clinical Trial Data Monitoring Committees*, which this new guidance will replace. These are:

- Increased use of DMCs beyond conditions associated with significant morbidity or mortality (e.g., in vulnerable populations like neonates, for oncologic therapies with potentially serious risks, in rare diseases providing specialized expertise to evaluate the emerging efficacy and safety data).
- Increased number of program wide DMCs that oversee the drugs entire clinical development program.
- Increased use of DMCs to implement adaptive designs.

The draft guidance comprehensively covers a range of topics from determining when to use a DMC, the establishment of a DMC, to the responsibilities of a DMC and interim analysis and reports for DMCs. Five key areas that resonated with Phastar as we reviewed this guidance are summarized and discussed below.

1. Determining Whether to Use a DMC

The FDA strongly recommends establishing a DMC if patients are at risk of serious morbidity or mortality, or the product may cause serious unexpected adverse events (i.e., that may require aggregate safety evaluation across study arms to help determine causality). They are of value when there is limited experience in therapeutic area, or the study is in a vulnerable population. However, practicalities need to be considered in a short-term trial with rapid recruitment where a DMC may not have the opportunity to make a meaningful impact on the conduct of the trial.



2. Establishing a DMC

The Sponsor (or trial steering committee) generally appoint members of the DMC. Members need to have expertise in current clinical trials conduct, and clinicians need expertise in the clinical specialties relevant for the studies. DMCs should include at least one statistician knowledgeable about statistical methods for clinical trials including the methods anticipated for the study. DMC chairs should have experience serving on DMCs and be familiar with the FDA regulations for clinical trials.

- ✓ Members should not be involved in the design or conduct of the trial and have no significant financial or other important connections with the Sponsor (apart from compensation for DMC duties).
- ✓ Members should also have no other professional or financial relationships that could influence or be perceived to influence their objectivity in evaluating the data.
- ✓ No intellectual conflict of interest (such that they may not be able to review the data in fully objective manner).

The DMC should operate under a written DMC charter and the FDA guidance lists out the minimum elements that should be included. The charter should clearly describe:

- ✓ The purpose of the DMC,
- ✓ The specific questions expected to be addressed,
- ✓ Possible recommendations to be made to the sponsor during the trial.

3. The Key Role of an Independent Statistician

The DMC is often supported by an independent statistician/statistical group responsible for providing unblinded statistical analyses and reports to the DMC during closed sessions.

> Importantly, this independent statistician is not part of DMC, and the role is distinct from DMC statistician who is the voting member.

Conflicts of interest must be evaluated when choosing members. Whilst a DMC is established by Sponsor, it should be independent of the Sponsor and the trial conduct. The FDA guidance highlights that this independence from the Sponsor is critical as it ensures that the Sponsor interests do not influence the DMC and it enhances the DMCs objectivity and reduces potential for bias. From a Sponsor perspective this independence preserves the ability of the Sponsor to make trial modifications in response to external information without introducing bias.

The composition of the committee should include the roles of the members, and the procedures for assessing conflicts of interest. Meeting information such as planned frequency, format, and who may attend the open and closed sessions should be included. Consideration will need to be given to number of DMC members needed to achieve quorum, as well as their disciplines. Importantly, how the confidentiality and the blind of the data will be maintained needs to be documented, including who besides the DMC and independent statistician will have access to the interim data and reports.

4. DMC Responsibilities: Assessing Safety and Effectiveness

Safety monitoring of clinical trials is the most common purpose of a DMC. If the investigational product is found to credibly increase risk of serious adverse outcomes as trial endpoints, such as mortality, disease progression, or loss of organ function compared to the control, the DMC may recommend early termination of the trial.

However, the FDA recommend that DMC review the unblinded efficacy data for a benefit-risk assessment. They also recommended having a lower threshold for early stopping the investigational product for safety than those applied to early stopping for benefit. Other important aspects of safety monitoring including comparison of the adverse event rates (other than trial endpoints) in each treatment arm or monitoring serious individual events, where the DMC will make recommendations based on the serious adverse events by treatment arm provided from interim summaries.

Effectiveness and futility monitoring of investigational products from an interim analysis are other common purposes of a DMC. While it is desirable that clear evidence of effectiveness be identified as soon as possible, it is critical to provide prespecified criteria for early termination in the DMC charter and the statistical analysis plan (SAP) to minimize the chance of false benefit from multiple interim analyses during a trial of an ineffective product. If the new product is determined of to be of no benefit to subjects, DMC may recommend stopping the enrolment due to futility to protect subjects from further exposure to a potentially ineffective investigational product.

DMCs are also used for monitoring studies which have an adaptive design. This allows for prospectively planned modifications to one or more aspects of the design based on interim data analyses, in that prespecified criteria are set for stopping the trial for efficacy or futility, or modification in sample size, study arms (e.g., elimination of a particular dose or doses), randomization ratio, or restricting future enrolment to a prespecified subgroup (adaptive enrichment). If DMC take this responsibility, it should be pre-specified in the DMC charter.

A fundamental responsibility of a DMC is to make recommendations to the sponsor concerning the continuation of the trial. The FDA guidance indicates that both an oral communication and written recommendation to the Sponsor can be valuable.

For recommendations other than continuing the trial as designed, e.g., trial termination, trial continuation with major or minor modification or temporary suspension of enrolment, the DMC should provide clear and precise rationale, best with the minimum amount of data for the sponsor to make a reasonable decision about the recommendation. Sponsors may wish to develop internal procedures to limit the interim data released by a DMC after a recommendation until a decision is made regarding acceptance or rejection of the recommendation.

The DMC recommendations and rationale can be circulated to Institutional Review Boards, FDA, and/or other interested parties after the sponsor's review. Sponsors should discuss with FDA any proposed major protocol changes, based on review of interim data that were not planned for, before implementation, and submit such changes to FDA. Finally, it is the sponsor's decision to accept or reject the recommendation from the DMC.

5. Interim Data and Analyses

To protect the confidentiality of interim data and minimize bias on trial conduct, any unblinded safety and effectiveness data should be reserved for the DMC, **provided by an independent statistician/statistical group**, and should be discussed in the closed session among DMC members of a DMC meeting. On the other hand, data in aggregate (blinded) are provided to the sponsor and will be discussed in an open session of the DMC meeting.

Although the study SAP submitted to FDA focuses on the statistical methods of primary and secondary variables and sample size calculations, DMC may perform or request additional statistical analyses outside the study SAP to evaluate accumulated data or request sensitivity analyses. Analyses used by the DMC also include results of unblinded data analyses on both the primary endpoint of interest and imbalances in serious adverse events among the trial arms, thus the analyses in the DMC SAP may differ from those in the study SAP.

If a DMC serves as a program-wide safety assessment group involving multiple trials, the statistical analyses used to review safety data may vary accordingly but are unlikely to be part of the SAP submitted to FDA.

Key Takeaways on FDA Guidance on DMCs

Independence and Objectivity:

- Underlines the importance of the DMC's independence from the sponsor and trial management to avoid conflicts of interest.
- Suggests mechanisms to maintain objectivity and impartiality in the DMC's operations and decision-making.

Purpose and Scope:

- Clarifies the roles and responsibilities of DMCs in clinical trials.
- Emphasizes the importance of DMCs in ensuring the safety of trial participants and the integrity of the data.

DMC Composition:

- Recommends that DMCs be composed of independent experts with relevant clinical, statistical, and trial design expertise.
- Highlights the need for diversity in expertise to address various aspects of the trial.

DMC Charter:

- Stresses the necessity of a comprehensive DMC charter outlining the committee's responsibilities, procedures, and decision-making processes.
- Provides guidance on what should be included in the charter, such as meeting schedules, reporting procedures, and confidentiality agreements.

Operational Procedures:

- Recommends regular, pre-scheduled meetings and ad-hoc meetings as necessary to review accumulating data.
- Provides guidelines for the frequency and timing of data reviews to ensure timely and appropriate decision-making.

Data Review and Decision-Making:

- Details the types of data and interim analyses that DMCs should review, including safety, efficacy, and trial conduct data.
- Encourages DMCs to make recommendations on trial continuation, modification, or termination based on pre-defined criteria.

Communication and Reporting:

- Advises on the communication processes between the DMC, trial sponsor, and regulatory authorities.
- Highlights the importance of clear and timely reporting of DMC findings and recommendations.

Conflict of Interest Management:

- Provides guidance on identifying, disclosing, and managing potential conflicts of interest among DMC members.
- Suggests regular reviews of conflict-of-interest statements to maintain transparency and trust.

Training and Qualification:

- Recommends ongoing training for DMC members to stay updated on regulatory requirements, clinical trial methodology, and ethical considerations.
- Emphasizes the need for DMC members to have adequate qualifications and experience relevant to the trial.

Documentation and Record-Keeping:

- Stresses the importance of maintaining detailed records of DMC meetings, decisions, and recommendations.
- Provides guidance on the documentation requirements to ensure accountability and regulatory compliance.

Conclusion

The FDA guidelines set a minimum expectation for the establishment of DMCs and their operating procedures that can only help Sponsors designing and conducting clinical trials.

Whilst the prominent responsibility of the DMC is to help ensure patient safety, the FDA guidance is clear that the DMC should also have access to comparative efficacy data.

By utilizing a trusted independent statistician, Sponsors can ensure unblinded statistical analyses and reports can be reliably provided to the DMC during closed sessions.

References

Use of Data Monitoring Committees in Clinical Trials, Guidance for Industry, February 2024. https://www.fda.gov/media/176107/download.

Discover more insights on DMCs here