New FDA Guidance on Data Monitoring Committees (DMCs) and Recommended Unblinded Data Reporting Practices for Effective Clinical Trial Oversight

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Abstract

The new FDA draft guidance on Data Monitoring Committees (DMCs) aims to update recommendations after nearly two decades, replacing the 2006 guidance. With evolving technology, study design shifts, and advancing industry standards, DMCs play an increasingly vital and complex role in clinical trials. This poster highlights key aspects of the updated FDA guidance, outlining the latest recommendations for DMC oversight, conduct, and best practices to consider when planning DMC involvement in clinical studies. It further offers recommendations for effectively reporting unblinded data to DMCs, facilitating informed decision-making to protect patient safety, upholding scientific integrity, and meeting economic needs of the sponsor.

Significant changes in DMC role and practice since 2006

- Increased use of DMCs in global and multiregional trials
- Increasing use of DMCs in trials of modest size and trials beyond those involving serious morbidity and mortality (trials of rare diseases, trials with vulnerable populations, etc.), and in earlier phase trials for serious diseases or conditions
- More often, the same DMC will oversee an entire clinical trial program rather than a single clinical trial
- DMC charters are becoming longer and more detailed
- Expanding functions of a DMC – for example review of aggregate safety reports for trials under IND application

Draft FDA guidance on DMCs: What's new?

- **Clear and detailed expectations for DMC Charters**
- **Minimum key sections to include:**

✓ Committee Composition: criteria for selecting members, description of roles (voting vs. nonvoting), procedures for managing conflicts of interest, and processes for member additions, removals, or disbanding.

✓ Meeting Information: information about frequency and format of meetings, conditions for ad hoc meetings, who will create the specific reports and have access to them, handling of meeting minutes for open and closed sessions, and definition of a quorum of DMC members.

✓ Planned Analyses and Data Protection: schedule and basis of planned interim analyses as described in the protocol/SAP, analyses associated with prespecified safety considerations.

✓ Data Confidentiality: how and at what frequency unblinded analyses will be prepared, how blinding will be maintained, procedures and strategies to maintain confidentiality in transmission of data, reports, and open/closed session meetings.

- **Final analysis SAP for CSR and planned analyses for DMC are distinct**
- CSR SAPs focus on primary and secondary endpoints and outline pre-specified statistical methods and provisions for interim analyses to assess early success or futility. The analyses are intended for clean data, following predetermined interim database locks or final locks.
- However, DMCs require flexibility to request additional exploratory or sensitivity analyses beyond the SAP's scope.
- **Emphasis on access to unblinded efficacy data**
- The new guidelines emphasize the need for the DMC to have access both safety and efficacy regardless of pre-planned interim analyses.
- To make informed recommendations, DMC members need to evaluate safety data in the context of comparative efficacy information to properly assess risk-benefit of the intervention.
- **Expanding functions of the DMC**
- The guidelines acknowledge pros and cons of a program-wide DMC
- Use of DMC in adaptive clinical trial designs
- Use of DMC to identify when further investigations of safety data and possible notification to regulatory agencies (IND rule) through aggregate safety review

DMC challenges and best practices to ensure the DMC's independence and effectiveness

- **DMCs are responsible to protect the safety of study participants, ensure ethical conduct of the clinical trial, and make crucial recommendations to the sponsor whether to continue, modify, or terminate the trial.**
- DMC members must perform these duties independently and effectively and require support from the sponsor and the independent statistical reporting group (ISRG).
  - An expert panel representing academia, industry and government sponsors, and regulatory agencies convened in 2017 (Fleming, 2017) to discuss some important challenges DMCs face, including:
    - Lack of access to unblinding safety and efficacy data throughout the clinical trial. DMC members must be able to make benefit-risk assessments with safety and efficacy summaries.
    - Rigid expectations and limitations set by overly prescriptive DMC Charters. The DMC Charter should provide guiding principles to the DMC while allowing for flexibility (e.g., ad hoc meetings, assessment of safety in the context of benefit-risk, and encourage discussion and consensus among members rather than a strict voting format)
    - DMC reports provided by the ISRG can vary widely in length and content. DMC reports must be both comprehensive and comprehensible. The report should facilitate efficient review by the DMC members, providing a complete picture of all potentially relevant data without overwhelming them with unimportant minutiae.
- **Operationally, how does this work?**
  - Collaboration is necessary between DMC members, sponsors, and the ISRG. All parties should be involved in the creation and approval of the DMC Charter.
  - Open lines of communication between clinical, statistical, and programming personnel during DMC SAP and mocks creation.
  - Conflicts of interest should be outlined in the Charter and acknowledged at every closed session.
  - Routine transfers of all available data to the ISRG, not only planned before the DMC meetings. If the DMC makes an ad hoc request, the ISRG should be able to respond without a special data transfer, which can potentially alert the sponsor to a safety concern/closed session discussion and threaten the integrity of the trial.
  - Flexibility and adaptability of the ISRG to meet the DMC's evolving requests as data accumulates, along with collaboration and trust among the sponsor, DMC, and ISRG.

Other reporting considerations

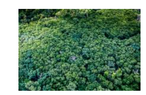
- DMC reports will evolve throughout the study. Changes to the report depend on the maturity of the data, the questions raised by the DMC members, foreseen or unforeseen safety signals, analyses on certain populations, or any other analyses the DMC members deem important.
- When providing high level summaries or text summaries, the ISRG should present the data in an unbiased manner.
- Contracts between sponsors and reporting groups often conflict with the need to deliver appropriate reports, specifying fixed DMC meeting numbers, variable analyses per meeting, or defined page limits. These contracts discourage effective DMC reporting.
- Most DMC members appreciate an executive summary at the start of a report, though some argue the reporting statistician, not the DMC itself, decides its relevance. The reporting statistician should defer to the DMC on whether to include an executive summary and its content.
- Reports should be structured to facilitate efficient review (under 100 pages), includes executive summary.
- Sponsors should select reporting groups based on expertise, not only cost.

Conclusions

- The new FDA draft guidance for DMCs is a great step forward toward harmonizing DMC conduct across clinical trials and underscoring important best practices.
- All clinical trial team members can benefit from understanding when and how DMCs are used in clinical trials and how they can contribute to ensuring patient safety and trial integrity.

The ideal DMC report

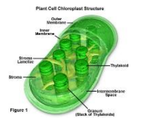
- **Structurally, the ideal report should utilize a "top-down" approach**
- Forest > tree > leaf > chlorophyll
- For especially dense sections (e.g., AEs), begin with an overview of data and then drill into details.
- Utilize innovative graphics for the 'forest.' DMCs need to begin navigating the data most efficiently. See example 'White Blood Cell Count' figure, which can provide quick visual inspection of lab analytes by DMC members.
- Executive summary tables at the beginning of each report, with comparison of executive summaries from the previous report (See Table 2, (Buhr KA, 2018))



- Volcano plot
- Dot plot

- Adverse events summary table

- Table of SAEs
- Table of Grade 3+ AEs by SOC/PT



- Profile plots
- AE listings
- Subject narratives

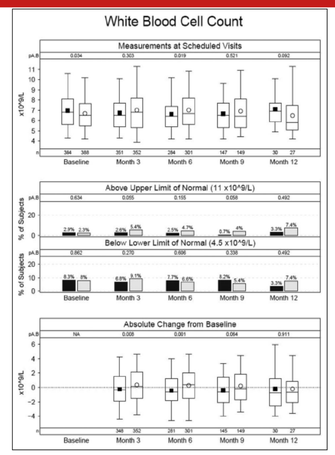


Table 2. Sample Executive Summary.

	Group A n (%)	Group B n (%)
Randomized and treated (Table 6)	xxx	xxx
Off treatment (Table 7)	xx (xx)	xx (xx)
Off study (Table 7)	xx (xx)	xx (xx)
Deaths (Table 18)	xx (xx)	xx (xx)
Subjects with adjudicated CV events		
MACE (Table 24)	xx (xx)	xx (xx)
CV death (Table 24)	xx (xx)	xx (xx)
MI (Table 30)	xx (xx)	xx (xx)
Stroke (Table 31)	xx (xx)	xx (xx)
Heart failure (Table 32)	xx (xx)	xx (xx)
Subjects with unrefuted CV events		
MACE (Table 28)	xx (xx)	xx (xx)
MI (Table 30)	xx (xx)	xx (xx)
Stroke (Table 31)	xx (xx)	xx (xx)
Subject-level adverse events		
Malignancy (Table 37)	xx (xx)	xx (xx)
Hepatotoxicity (Table 40)	xx (xx)	xx (xx)
Benign prostatic hyperplasia (Table 41)	xx (xx)	xx (xx)
Infection SAE (Table 50)	xx (xx)	xx (xx)
Mean ± SD change in vitals/ laboratories at week 24		
Systolic blood pressure (mmHg; Table 55)	x.x ± x.x	x.x ± x.x
Total cholesterol (mmol/L; Table 57)	x.x ± x.x	x.x ± x.x
Laboratories above upper limit of normal (ULN) or below lower limit of normal (LLN) at any time, n (%)		
Hemoglobin above ULN (Table 69)	xx (xx)	xx (xx)
Sodium above ULN (Table 72)	xx (xx)	xx (xx)
Potassium above ULN (Table 72)	xx (xx)	xx (xx)
Calcium below LLN (Table 72)	xx (xx)	xx (xx)

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; SAE, serious adverse event.

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