Challenges and Opportunities in Data Monitoring and Trial Oversight

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Disclosure Statement

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Outline

- Define a DMC
- Brief history and current status
- Describe changes in landscape of trial oversight
- Identify major challenges facing DMCs
- Propose some possible remedies

Data Monitoring Committee

- An **independent** advisory group of experts assembled by a sponsor (public, private, or commercial) to review the ongoing conduct of a clinical trial, monitor efficacy and patient safety, and ensure the validity and integrity of the trial

- DMC = IDMC = DSMB = DSMC

- *FDA DMC Guidance* from March 2006 articulates FDA's thinking about the role and function of data monitoring committees in clinical trials

History of DMCs

- DMCs have been in existence since the early 1960s
- The concept of an independent data monitoring committee was brought into prominence in 1967 by the Greenberg Report

  Original charge:
  - Monitor conduct and safety of a single trial
  - Trials might be terminated because the intervention's benefit was clearly established, because of sufficient evidence of harm, because the trial was no longer viable or of interest, or for other compelling reasons
  - Initially used in large randomized multicenter trials that targeted improved survival or reduced risk of major morbidity

Changing Landscape

- Today's DMCs retain their original mandate but are being asked to fill a wider range of roles
  - DMCs may be internal or external to the sponsor
  - Use no longer restricted to controlled trials comparing rates of mortality or major morbidity (NIH, VA, and FDA policies may require their use in some additional contexts)
  - Responsibilities may also include reviewing data quality and other trial operations as well as providing ethical oversight

DMC Functions

- DMCs typically oversee a single trial but they are occasionally asked to review multiple related trials.
- Other emerging functions of DMCs include the monitoring of pragmatic clinical trials and perhaps even the entire portfolio of research related to an investigational product throughout its clinical development life cycle.
- Although DMCs have been established for decades, the transformation of the clinical trial landscape has created new opportunities as well as scientific and regulatory challenges in the oversight of clinical trials.

Clarifying roles and functions

- Evolving role of DMCs and emergence of other trial oversight committees with overlapping functions has led to confusion and unclear expectations between DMCs and other stakeholders (sponsors, CROs, regulators, investigators, patients)
- The apparent increase in use of DMCs has resulted in a mismatch between the need for and availability of qualified DMC members
- Concern regarding the lack of a coordinated plan for identifying and preparing the next generation of DMC members

Trial Oversight and Monitoring

- An overall study monitoring plan is essential for ensuring the safety, quality, and integrity of clinical research
- Sponsors of clinical trials evaluating FDA-regulated drugs, biologics, and devices are **required to monitor** their studies *(21 CFR 312.50 and 312.56 for drugs and biologics, and 21 CFR 812.40 and 21 CFR 812.46 for devices).*
- These requirements apply equally to privately and publicly sponsored research
- Routine monitoring of trial conduct does not always necessitate the use of a data monitoring committee

Trial Oversight and Monitoring

- Clinical trial oversight requires coordination and review by various diverse groups
  - focus on safety, quality, ethics, adjudication, operations, and logistics
- The roles and responsibilities of these oversight groups continue to evolve, and they invariably overlap to some extent
- Data monitoring committees (DMCs) hold a unique place among trial oversight bodies

Unique DMC Function

- DMCs periodically review the accumulating safety and efficacy data by treatment group (i.e., access to unmasked study data) and advise the sponsor on whether to continue, modify, or terminate a trial *based on risk-benefit assessment*
- They also play a critical role in assessing the validity and integrity of the trial to enhance its potential to generate reliable findings

DMC Composition

- DMCs should be composed of qualified individuals with knowledge of ethical principles and expertise in biostatistics, research methodology, and relevant areas of science and clinical medicine.
- DMC members must be independent of the sponsor and afforded adequate resources and flexibility to perform their duties.

The DMC Charter

- Roles and responsibilities of the DMC should be clearly delineated in a succinct, well-organized charter.
- It should be explicitly stated in the charter that the DMC must remain independent from the sponsor, and the sponsor must not have undue influence on DMC decision making.
- DMC members must be allowed to carry out their duties and fulfill their mission without hindrance or interference.

The DMC Charter

- The charter also outlines and defines
  - the planned communication process and contingency plans
  - the procedures to be employed by DMC members and relevant stakeholders throughout the course of the study.
- The charter is a valuable resource that should be used to empower rather than a legal document that handicaps the DMC.
- Above all, it should be an instrument that enhances the independence of the DMC and allows it to fulfill its mission unhindered.

Indicators of DMC independence

- Does the DMC have a clear and well-articulated charter that addresses the interests of DMC members?
- Is the DMC able to hold ad hoc meetings without triggering speculation or concern on the part of the sponsor or other stakeholders?
- Does the DMC have adequate resources and accommodations to carry out its duties and fulfill its mission?
- Are DMC findings and recommendations consistently shared with IRBs and regulatory bodies regardless of the sponsor's opinion or intent in regards to the DMCs advice?

When is a DMC needed?

- ***Factors that may influence the decision to use a DMC***
  - Risk level (define types of risks)
  - Trial phase, duration, or complexity
  - Type of study participants (e.g., vulnerable populations)
  - Type of study designs (randomization, blinding, control)
  - Type of study objectives
  - Type of study endpoints
  - Type of data analysis plan
  - Type of sponsor
  - Type of study settings (e.g., single center vs. multicenter)

When is a DMC needed?

- Criteria for when a DMC is necessary are not well defined
- May vary depending on the type of sponsor and their perceived need for independent trial oversight
- DMCs are most often used to monitor large, randomized, controlled, multicenter trials that evaluate interventions intended to prolong life or reduce major morbidity
  - These may be for industry-sponsored registrational trials or privately-sponsored trials of great public health importance
- Use of DMCs should not depend entirely on study size or phase of study but rather on the nature and extent of risk to trial participants
  - Other factors that may potentially influence the need for a DMC include the type of study endpoints and the overall duration and complexity of the trial.

Unresolved Issues

- ***How do we ensure that there is an adequate number of unbiased, competent, experienced, and well-trained DMC members to meet the growing demand?***
  - complexity of DMC work requires a combination of training and experience

- ***To what extent do internal and external DMCs differ?***
  - Roles and responsibilities
  - Composition and governance
  - Reporting and communication
  - Charters and degree of independence

Unresolved Issues

- ***How do we ensure that critical DMC recommendations and proposed trial modifications (i.e., risk-benefit findings and other significant issues related to trial operations) are provided by the sponsor to IRBs and regulatory bodies in a timely manner?***