

The Role of Data Monitoring Committees and their Impact on Clinical Research Associate Responsibilities

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Abstract: *Clinical Research Associates (CRAs), or monitors, will benefit from understanding the draft guidance document published in November 2001 by the Department of Health and Human Services on the establishment and operation of Data Monitoring Committees (DMC). A DMC is an independent body composed of experts qualified to evaluate the scientific merit of a trial and analyze a trial's progress, with particular attention to safety and efficacy. Considerations for determining whether a DMC should be implemented include protecting subjects from risks, the practicality of a formal DMC, and the need to bolster the integrity of a study. A monitor's responsibilities are impacted when a trial implements the use of a DMC: more source documents may need to be retrieved, there may be stricter deadlines for collecting case report forms, visits may need to be planned according to designated timelines for DMC meetings, and there may be a need to prioritize which sites will require more attention. Understanding the role and functions of DMCs and how these may impact monitoring at the site level will help CRAs better understand their responsibilities in trials where DMCs are used.*

One of the many challenges clinical research professionals face is maintaining current knowledge about how clinical trials are designed and conducted, as well as how new regulations and guidelines impact roles and responsibilities. New guidelines and regulations are often implemented to better assure the protection of human subjects, minimize bias, and maintain ethical standards. Two recent examples include financial disclosure legislation (21 CFR 54) and new initiatives for gene transfer research sponsors (DHHS, 2000). The requirement for monitors to be qualified by training and experience (21 CFR 312.53, 2000) necessitates their awareness of new guidelines issued by regulatory agencies. This awareness increases professional knowledge and allows for a broader understanding of trends in the scope of clinical trials, i.e. "the big picture." Until recently, little was written in the ICH guidelines or the Code of Federal Regulations (CFR) regarding Data Monitoring Committees (DMC) (FDA, 2001). However, in November 2001, the Department of Health and Human Services (DHHS) published a draft guidance document for sponsors on the establishment and operation of DMCs (DHHS, 2001).

The promulgation of this document is no surprise. For the last several years, regulatory agencies have discussed how to better protect human research subjects. In May 2000, then-Secretary of the Department of Health and Human Services (DHHS) Donna Shalala announced that improved monitoring would be one of the new efforts implemented to improve the safety of human subjects in clinical trials. Although DMCs, also referred to as Data Safety Monitoring Boards (DSMB), have been required by the National Institutes of Health with certain clinical trials in government-funded research (DHHS, 2000), currently the FDA only requires a DMC as additional protection in emergency research where the informed consent requirements are waived (21 CFR 50, 2000). Because of increasing demands on Institutional Review Boards (IRB), the DHHS has discovered that an IRB alone is not always able to ensure optimal protection of human subjects in clinical research. In an April 2000 report from the Office of the Inspector General, the DHHS warned that "the capacity of IRBs to accomplish all that is expected of them is strained" (DHHS, 2000, p. 6). Partly due to overburdened IRBs,

increasing attention is being paid to the role of DMCs, particularly for multi-center trials and for those trials with significant risks to subjects. Regulatory agencies recommend that DMCs take an integral part in protecting human subjects and add scientific validity to a trial by providing expertise not commonly available on IRBs (DHHS, 2000).

What is a DMC?

A DMC is defined as a committee whose members are considered to be independent of those sponsoring, organizing, and conducting the trial. That is, they have had no previous involvement in the design of the trial, are not involved in its conduct except through their role on the DMC and have no financial or other important connections to the study sponsor or other trial organizers (DHHS, 2001, p. 18). A DMC is generally the only entity in a clinical trial that may be unblinded to data and treatment groups. Because of this, a major emphasis in the guidance document is that the "independence" of these committees from the sponsor is essential to safeguard the scientific validity of a clinical trial.

What does a DMC Do?

Just as monitors or CRAs assure adherence to good clinical practices by ensuring the protection of human subjects and the integrity of the clinical trial at the level of the research site (ICH, 1996), the sponsor can also charge these broad responsibilities to a DMC. One major difference is the DMC carries out the responsibility of protecting human subjects across all participating research sites, where the CRA and IRB have this responsibility at some of the sites. The DMC serves to “assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify or stop a trial” (ICH, 1996, section 5.5.2). Although their functions, tasks, and scopes of practice are obviously different, both the CRA and the DMC, like IRBs, have a common core value of protecting human subjects and all share in that responsibility (Figure 1).

The DMC meets to review cumulative trial data, formulate a statistical assessment, and make recommendations to the sponsor. The DMC evaluates the risk/benefit ratio and may recommend that a trial be stopped due to safety concerns, a strong efficacy profile in one arm of the trial, or “on the basis of futility – that is, when the probability, given the interim results, that the trial will ultimately be able to demonstrate the effectiveness of the investigational product is very low” (DHHS, 2001, p. 11). They also may suggest that the trial continue with changes. The sponsor may accept or reject the advice of the DMC. It is important to note that the sponsor should consult the FDA before making “certain types of changes to the protocol – e.g., changes in endpoints, changes in permissible concomitant medications or in dose/schedule of study medication ... [because these changes may] have substantial impact on the validity of the trial and/or its ability to support the desired regulatory decision” (DHHS, 2001, p. 23).

The IRB, DMC, and CRA all share the critical responsibility of protecting subjects.

What is the Composition of a DMC?

A DMC is composed of experts qualified to evaluate trial data and make decisions based on the continuing safety of the subjects, the assessment of efficacy, and the scientific merit of the trial. These committees should have at least three members and generally consist of at least one biostatistician, clinicians in the therapeutic field, and possibly other scientists (i.e. toxicologists, pharmacologists) who may be needed to assist in the evaluation (DHHS, 2001). Experts at an open public meeting on the FDA guidance document on Clinical Trial DMCs suggest that a DMC may need additional members to ensure better protection of subjects in trials with vulnerable populations or in international trials where cultural factors could be incorporated into the analysis. Additional members may include an ethicist, consumer advocate, or in a trial taking place in another country, a member from that country (FDA, 2001).

When is a DMC Used?

Traditionally, the pharmaceutical and device industries have not used DMCs; however, they are increasingly being used in trials with mortality and major morbidity endpoints, as well as in trials where it may be ethical to stop for efficacy (DHHS, 2001). In an open public meeting shortly after the DHHS published the draft guidance document for sponsors on clinical data monitoring committees, Dr. G. Campbell of the FDA’s Center for Devices and Radiologic Health suggested that “all clinical trials do require safety monitoring, ... [but not] every trial needs a formal committee that’s external to the trial organizers and to the investigators” (FDA, 2001, p. 9). Dr. Campbell states that three things should be considered when questioning whether a trial should have a DMC: 1) risks to subjects that may be best protected by an independent committee, especially pertaining to populations with increased risk of mortality/morbidity; 2) the practicality of a formal and independent DMC; and 3) if a DMC is needed to bolster the integrity of the study (FDA, 2001).

How does the Use of a DMC Impact CRA Responsibilities?

Before an analysis of trial data can be performed by a DMC, more responsibility is often placed on other clinical trial professionals to collect and process necessary information. Cathy Tyner, manager of the Clinical Event Validation & Adjudication (CEVA) Services at Quintiles, Inc., states that for trials where endpoint data may be somewhat subjective or interpreted in different ways (i.e. the criteria for a particular type of myocardial infarction), an endpoint committee is needed. These committees, also referred to as Clinical Event Committees (CEC), are comprised of clinical experts who assure the accuracy of the endpoints reported by the site and that the protocol-specific standards for the endpoint are actually met.

The processes of a CEC are closely linked to DMC processes. The CEC certifies the validity of the outcomes for endpoints that are captured in a clinical database. Information is extracted from this database for inclusion in a report provided to a DMC. CECs regularly require additional source documentation from the site. For example, in the case where a specific type of cardiovascular event is an endpoint, an endpoint committee may review laboratory/diagnostic reports, electrocardiograms, chest x-rays, echocardiogram reports, physical assessment findings, etc.

Therefore, when a DMC plans to meet to conduct an interim analysis of aggregate data, much preparation is needed. Clinical, data management, and safety/surveillance departments work to make the data as “clean” (meaning that the data entered into databases for the purposes of evaluation matches data on the Case Report Forms and source documents at the site) as possible. A CEC and CEVA services work to obtain adjudication for as many endpoints as possible before the DMC meeting. DMCs may also request that more information be provided if they see a trend with a particular adverse event; that is, in certain instances, they may evaluate some adverse events on a case-by-case basis, when there is a particular concern. Evaluating

events case-by-case is obviously more feasible on smaller scale studies, such as those of a phase II trial (C. Tyner, personal communication, February 18, 2002).

The processes of collecting, cleaning, and summarizing data, which are required before a DMC meets, impact clinical monitors in several ways: more source documents need to be copied and collected, and deadlines for collecting case report forms may be implemented to assure that a summary of information is provided for the DMC in time for its scheduled meeting. The overall goal is for the interval between current data and the DMC meeting to be as short as possible. Figure 1 (below) is a scenario of the chronological order of deadlines set before a DMC meets.

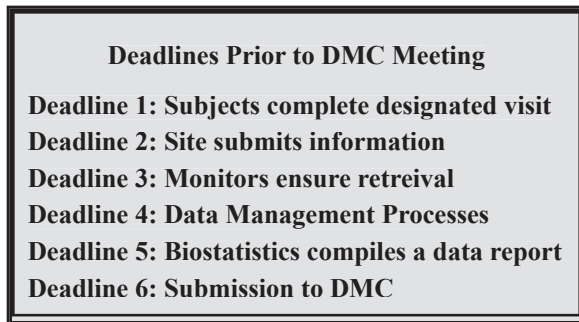


Figure 1. The above represents a possible scenario of chronological deadlines in a trial with a DMC in place.

Monitors may need to accelerate data retrieval so that it can be processed in time for the DMC. Often, the DMC will conduct its assessment based on a specific point in the trial, such as the data for all subjects completing a designated visit or all data up until "x" date. Scheduled and designated timelines mean that monitors will potentially have more issues to manage within a limited time. Monitors may need to plan visits according to these deadlines, assure query resolution, complete source document verification, and request that the site fax the most current information on forms that track cumulative information, such as adverse events or concomitant medications (knowing that these will still require future source document verification) (C. Tyner, personal communication, February 18, 2002).

Monitors will need to determine which sites require more of their attention and prioritize follow-up activities. These sites may include those with less experience, those historically delinquent in meeting deadlines, those with a significant amount of queries, or those with high enrollment (C. Tyner, personal communication, February 18, 2002; A. Hosfeld, personal communication, February 20, 2002).

Conclusion:

The FDA estimates that there are currently 740 trials with DMCs regulated by various branches of the FDA and that DMCs will continue to be used at about the same rate for the next few years (DHHS, 2001). Comprehending the role and functions of DMCs and how the use of DMCs impacts monitoring at the site level will help CRAs understand the purposes of the work-related tasks they need to perform in trials with DMCs: planning visits for accelerated data retrieval to meet designated deadlines, requesting that sites fax the forms that track cumulative information, 100% source document verification for all protocol endpoints, query resolution, and management of sites where difficulties in meeting deadlines is anticipated.

Abbreviations

- CEC – Clinical Event Committee
- CEVA – Clinical Event Validation and Adjudication
- CFR – Code of Federal Regulations
- CRA – Clinical Research Associate
- DHHS – Department of Health and Human Services
- DMC – Data Monitoring Committee
- DSMB – Data Safety Monitoring Board
- ICH – International Committee on Harmonization
- IRB – Institutional Review Board
- FDA – Food and Drug Administration

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