Published on *The National Law Review* https://natlawreview.com

FDA Proposes Rule to Update Clinical Trial Data Monitoring

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On February 13, 2024, the US Food and Drug Administration (FDA) issued draft guidance entitled Use of Data Monitoring Committees in Clinical Trials (Draft Guidance). It provides sponsors and others involved in clinical trial management with recommendations for determining when to engage a data monitoring committee (DMC) for trial monitoring. It also provides recommended procedures and other considerations for DMCs. Once the Draft Guidance is finalized, it will supersede FDA's March 2006 guidance entitled Establishment and Operation of Clinical Trial Data Monitoring Committees.

IN DEPTH

BACKGROUND ON DMCs

A DMC (often referred to as a data safety monitoring committee) is a group of individuals with relevant clinical, scientific, statistical or other expertise. This group regularly reviews human-subject data accumulating from a clinical trial and provides recommendations to the sponsor on whether to

continue, modify or suspend the clinical trial. In certain circumstances, a DMC may also provide recommendations regarding operational matters based on noncomparative safety and efficacy data.

Even though sponsors are required to use DMCs only for certain emergency research, the use of DMCs has increased in many areas beyond the historic norm of diseases involving serious morbidity or mortality. (21 CFR 50.24(a)(7)(iv) sets forth the exception for the requirement to obtain informed consent for a clinical trial in an emergency setting. One condition for such exception is the establishment of an independent DMC to oversee the clinical trial.) FDA notes that DMCs are now being used for modest-sized trials, to implement certain adaptive clinical trial designs, and to oversee entire clinical development programs (as opposed to single clinical trials). In part, the Draft Guidance appears to be an effort by FDA to update its recommendations for DMCs given the significant changes in the use of DMCs that have occurred since FDA released its 2006 guidance.

Relationship Between DMCs and Other Oversight Groups

The Draft Guidance addresses the specific relationships DMCs have with other groups that may be involved in a clinical trial, including an institutional review board, a clinical trial steering committee, an endpoint assessment/adjudication committee, clinical site monitors, entities reviewing safety reporting, and an adaptation committee. DMCs are often the only group with access to the accumulating unblinded safety and efficacy data of a clinical trial. (FDA considers data to be unblinded when it is reviewed by treatment group (*e.g.*, A versus B), even when the groups are identifiable.) Generally, access to such data is not granted to other groups involved in a clinical trial to avoid biasing the outcome of the trial by inappropriately influencing trial conduct or the approach to analyses. DMCs, in contrast, have access to this data in order to:

- Monitor the safety data
- Advise the sponsor on the safety of the interventions in trial subjects
- Monitor interim effectiveness results to determine if they support a benefit or futility
- Help ensure scientific merit and integrity of the clinical trial

DMCs should remain independent of sponsors and therefore should not have a significant financial connection to a sponsor. Additionally, DMCs should not be involved in the design or conduct of the trial. A DMC’s independence is important because it:

- Ensures the sponsor’s interests do not inappropriately influence the DMC
- Enhances the DMC’s objectivity and limits the possibility of bias
- Preserves the sponsor’s ability to make modifications to a clinical trial without introducing bias
- May help prevent a conflict of interest for the sponsor by keeping them in a fully blinded state

How independence is defined is important. Too narrow a definition may prohibit knowledgeable researchers from being DMC members.

OVERVIEW OF THE DRAFT GUIDANCE

Use of DMCs

In the Draft Guidance, FDA provides sponsors with considerations for determining whether to use a DMC for any given clinical trial. Such considerations include:

- Whether the use of a DMC is practical for a particular clinical trial
- The extent of investigator, study site or other experience in a therapeutic area
- The participation of subjects from a vulnerable population

However, FDA states that it strongly recommends using a DMC whenever trial subjects are at risk of serious morbidity or mortality, even if one of these factors is not relevant.

Considerations for Establishing and Operating DMCs

While sponsors are responsible for establishing DMCs, the DMC should remain independent of the sponsor and the trial conduct. The Draft Guidance describes how to successfully achieve this independence, makes suggestions for DMC composition and outlines training considerations for DMC members.

FDA recommends that DMCs include:

- Individuals with expertise in conducting clinical trials
- Clinicians with relevant clinical specialty expertise
- A biostatistician
- Members with experience serving on DMCs
- Members with FDA regulatory expertise

The agency also recommends considering the inclusion of an individual with expertise in informatics and technology. As clinical trials proliferate in the field of artificial intelligence (AI), it will increasingly be wise to include a member with computational or other relevant experience in keeping with the spirit of the Draft Guidance, although the Draft Guidance does not address this point.

Importantly, DMC members should be screened for both financial and intellectual conflicts of interest or bias. For example, DMC members should not have any ongoing financial relationship with the commercial sponsor of the clinical trial (or such sponsor's direct competitors). Additionally, individuals should not have intellectual conflicts of interest that may render them unable to evaluate the clinical trial data objectively because they have strong views on the relative merits of the investigational product or intervention.

FDA also recommends establishing a DMC charter that states the DMC's obligations, responsibilities and standard operating procedures. Either the DMC itself or the sponsor (with the DMC's input) may prepare the charter. The charter should address:

- Specific information about the composition of the DMC
- Meeting information, schedule and format
- Planned analyses by the DMC
- The protection of data, where applicable
- How the confidentiality of the data will be maintained

ADDRESSING DMC RECOMMENDATIONS

The Draft Guidance states that a sponsor must investigate if the DMC makes a recommendation to the sponsor about a clinical trial based on a potential relationship between an increased rate of serious unanticipated adverse events and the investigational product. If the investigation leads the sponsor to conclude that there is a reasonable possibility that the event is associated with the

product, the sponsor must inform FDA of these findings. FDA also recommends that sponsors notify the agency of all DMC recommendations that are related to an investigational product's safety, irrespective of whether any adverse events underlying the recommendation meet the definition of "serious."

While DMCs may make recommendations to sponsors regarding whether to continue, modify or stop a clinical trial, the final decision as to whether to terminate any clinical trial belongs to the sponsor.

NEXT STEPS

You should evaluate the potential impact of the Draft Guidance and submit comments by April 15, 2024.

National Law Review, Volume XIV, Number 61