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Client Alert

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FDA Issues Draft Guidance on Use of Data Monitoring Committees in Clinical Trials

The U.S. Food and Drug Administration (FDA or Agency) has issued draft guidance, *Use of Data Monitoring Committees in Clinical Trials*,[1] that applies to sponsors of clinical trials of investigational drugs, biologics, and devices. In the draft guidance, FDA addresses the well-known concept that a data monitoring committee (DMC)[2] is an independent body convened by the sponsor to monitor data in an ongoing clinical trial and advises, as it has previously, that the primary responsibility of a DMC is to recommend to the sponsor whether to continue, modify, or stop a trial or trials. As set forth in the draft guidance, however, the breadth of FDA's expectations for the scope of oversight, conduct, and practices of a DMC is broader and more complex than was expressed in the Agency's prior guidance on the subject, *Establishment and Operation of Clinical Trial Data Monitoring Committees*, which was issued in March 2006.[3]

A major shift in FDA's current thinking, in comparison with the 2006 guidance, is heightened emphasis in the Agency's view that DMC assessment of interim safety data alone is not sufficient. FDA advises that a "DMC should evaluate safety data within the context of the intervention's efficacy, such that the DMC should have access to safety results as well as comparative efficacy results," including consideration of whether interim effectiveness analyses support benefit or futility. Thus, from FDA's perspective, the DMC monitoring a trial has a unique and powerful role because it is generally the only group of individuals with access to both unblinded safety and efficacy data while a trial is ongoing. FDA observes that revised guidance on the use of DMCs is needed because DMCs are being used in a broader range of trials beyond those that involve serious morbidity or mortality. Indeed, a single DMC may oversee a program of multiple trials, which themselves have become more complex, with adaptive components in the trial design that require

interim analyses of efficacy that may trigger recommendations for modification of enrollment or other major changes in trial conduct.

Here we highlight the major new recommendations and considerations on DMC conduct outlined in the draft guidance.

DETERMINING WHETHER TO USE A DMC

Per FDA regulations, the use of a DMC is only mandated when an Institutional Review Board (IRB) approves a clinical trial for emergency research without requiring informed consent from all research subjects.[4] In the 2006 guidance, FDA emphasized use of a DMC in trials in which subjects are at risk of serious morbidity or mortality. In the new draft guidance, FDA also calls attention to trials where it may be difficult to distinguish the relationship of a safety event to the investigational treatment due to a frequent rate of occurrence in the patient population to be enrolled, trials where there is limited experience in a therapeutic area or where subjects will be drawn from a vulnerable population, and single-arm trials with adaptive elements and historical controls. FDA cautions that if a DMC is to be used for safety monitoring in a very short-term trial, specific mechanisms should be in place to permit DMC assessment in a timely and expedient manner.

RELATIONSHIP OF THE DMC TO OTHER OVERSIGHT GROUPS

- **Interface with IRBs**. A heightened focus of the draft guidance is the interaction between DMCs and IRBs. FDA stresses that in trials where serious morbidity or the enrollment of vulnerable populations is a possibility, "an IRB should inquire as to whether a DMC has been established, and if so, seek information about its scope and composition as part of its oversight." This emphasis may increase the likelihood of an IRB refusing to approve the conduct of a clinical investigation unless a DMC is in place.
- **Steering and endpoint adjudication committees**. FDA acknowledges the expanding role of clinical trial steering committees but cautions that such committees, unlike a DMC, "should always be blinded to outcomes by study arm," and any direct interactions between the steering committee and the DMC should occur during open sessions of the DMC, when recommendations are communicated to the sponsor. FDA also warns that a DMC should not adjudicate clinical trial endpoints because it may have access to unblinded comparative data; per FDA, such activity should be conducted by a separate endpoint adjudication committee blinded to the assigned intervention.
- **Sponsor's regulatory safety monitors.** FDA clarifies that compliance with regulatory safety requirements, including reporting to FDA, is the responsibility of the sponsor's monitors and safety reporting personnel, not the DMC. FDA emphasizes that "the threshold that a DMC would use for reporting safety concerns to the sponsor and recommending termination or significant modification to the trial may be higher than the threshold for reporting serious risks obtained from aggregate data in an IND or IDE."
- **Trials with an adaptive design.** Many contemporary trials now utilize an adaptive design that allows for pre-specified modifications to the trial design to be implemented while the trial is ongoing based on accumulating data. FDA advises that sponsors may establish a dedicated independent "adaptation committee" or assign this role to a DMC (in addition to its primary responsibilities). In either case, the assigned committee should include one or more statisticians who are highly knowledgeable about adaptive design methodology and decision rules, with pre-specified criteria for communication of recommendations to the sponsor.

DMC ESTABLISHMENT AND OPERATION

FDA continues to endorse its longstanding recommendations regarding DMC membership, including inclusion of an independent biostatistician, screening of potential members for both *financial* and *intellectual* conflicts of interest, and ensuring that the DMC is supported by a separate independent statistician to provide data and reports to the DMC. The Agency also continues to recommend that an initial open session be held between DMC members and the sponsor, discussion and generation of recommendations be carried out in closed session of the DMC and independent biostatistician, and succinct presentation of recommendations to the sponsor in a follow-up, open session and via a written communication. FDA, however, takes the position that if the clinical trial involves "unusually high risks to subject safety" or "broad public health implications," then the sponsor should consider including a medical ethicist in the DMC. FDA provides extensive recommendations regarding the establishment of a charter describing DMC composition, obligations, responsibilities, and operating procedures that do not substantially differ from recommendations in the 2006 guidance. However, the draft guidance pays new attention to specifying in the charter the "rules" for implementing a predefined adaptive feature, including the determination of (i) efficacy such that enrollment should be stopped, (ii) futility such that enrollment or continued participation of subjects should be stopped, and (iii) other adaptations, such as changing sample size, modifying the randomization ratio, or restricting enrollment to a pre-specified subgroup ("adaptive enrichment").

- **Monitoring for safety**. Although interim assessments of safety have always been a primary role of a DMC, FDA emphasizes that statistical considerations (thresholds) for the recommendation of early termination for harm are usually lower than the threshold for early stopping due to an emerging signal for benefit. If a trial may be terminated due to safety concerns raised by the DMC, FDA advises that the sponsor should take immediate action and initiate discussions with FDA before suspending or terminating the trial in question or any other use of the investigational product. The Agency also emphasizes that adverse events of particular concern should be identified by the sponsor such that the DMC compares rates of these events in each treatment arm. It clarifies that it is acceptable for a DMC to elect to review all or only specific serious adverse events. FDA also advises that if concerns about patterns of specific adverse events arise, the DMC can consider measures short of termination, including recommendations for changing eligibility or screening procedures, modifying the product dosage and/or schedule, and/or informing current and future trial subjects through modification of the consent form and reconsenting current subjects. In determining whether trial termination or modification for safety risks is warranted, the DMC should also evaluate emerging data regarding potential for benefit.
- **Monitoring for effectiveness**. For trials where the investigational treatment would have major implications for treating a serious condition, FDA emphasizes that clear evidence of effectiveness should be identified as soon as possible. The Agency warns, however, that it is important to use appropriate statistical methods to avoid "inflating the chance" of obtaining an erroneous result by conducting repeated reviews of comparative data in the treatment and control arms of the trial. FDA stresses that a DMC should have a pre-specified statistical monitoring plan in place to make sure that a recommendation for early termination based on efficacy ensures that "the risk of a false positive conclusion (Type 1 Error) is acceptably low."
- **Monitoring for futility**. Similarly, FDA advises that if interim data suggest that the investigational product is of no benefit, then early termination should only be recommended if statistical procedures are used to reduce the risk of false negative conclusions regarding benefit.

- **Monitoring for other adaptions**. FDA stresses the importance of identifying adaptations that do not threaten data integrity due to unblinding of comparative data, such as increasing sample size or modification of the randomization ratio. If the recommended adaptations are based on unblinded data, the potential adaptation should be pre-specified.
- **Consideration of external data**. FDA provides extensive considerations regarding DMC consideration of the impact of new external information on an ongoing clinical trial, such as unexpected adverse safety results in another trial of the investigational product. The draft guidance says, "When FDA has critical safety information regarding another trial of the investigational product or a trial of a related product from the same sponsor that is relevant and important for a DMC to consider," then FDA may ask the sponsor to confirm that the DMC is aware of the data and/or may request that the sponsor arrange for FDA to communicate with the DMC directly.
- **Recommendations and documentation**. FDA's views in the draft guidance regarding the processes for DMC interaction with the sponsor, making recommendations, and maintaining meeting records/minutes of both open sessions with the sponsor and closed sessions of DMC deliberations do not differ substantially from the 2006 guidance. The Agency continues to emphasize that unblinded interim data and the results of comparative interim analyses "should generally not be accessible by anyone other than DMC members or the statisticians performing these analyses and presenting them to the DMC."

INDEPENDENCE OF THE DMC

FDA stresses that independence of the DMC from the sponsor, as well as the trial investigators, is critical (1) to ensure that sponsor interests do not influence the DMC, (2) to enhance the objectivity of the DMC and reduce the possibility of bias in its deliberations and recommendations, (3) to maintain the ability of the sponsor to make appropriate modifications to a trial without introducing bias, and (4) to protect the sponsor and the trial from conflicts of interest by maintaining the sponsor in a fully blinded state regarding accumulating findings in the treatment and control arms.

FDA RECOMMENDATIONS AND REGULATORY REPORTING REQUIREMENTS

In comparison with the 2006 guidance, FDA places increased emphasis on the potential linkage between DMC recommendations regarding safety and disclosures to FDA. For drugs and biological products, FDA stresses that a sponsor **must** investigate a DMC's recommendation related to specific safety events identified by a comparison of rates between the two arms of a controlled trial as potentially reportable to FDA under 21 C.F.R. § 312.32. Similarly, FDA emphasizes that a sponsor of a trial of an investigational medical device **must** consider whether an increased rate of specific adverse events constitutes an unanticipated adverse device effect under 21 C.F.R. §§ 812.46(b) and 812.150(b)(1). FDA goes a step further and recommends that sponsors "inform FDA about all DMC recommendations related to the safety of the investigational product, whether or not the adverse events that led to the recommendation meet the definition of *serious*." FDA also recommends that a sponsor should discuss with FDA any DMC recommendation for early termination of the trial because of the observation of a substantial favorable effect on efficacy.

SUMMARY

In this new draft guidance, FDA addresses a broad expansion of the conduct and roles of contemporary DMCs in FDA-regulated drug, biologic, and medical device clinical trials in comparison with the 2006 guidance. An overarching theme is that the DMC should have access to safety results as well as comparative efficacy results. Sponsors should review their policies and procedures for convening DMCs, including consideration of the impact of increasingly complex adaptive trial designs in which the DMC may make major recommendations regarding changes to the conduct of the trial

based on emerging evidence of futility or substantive benefit. Further, sponsors should ensure that DMC recommendations pertaining to comparative interim assessments of safety signals between the treatment and control arms are evaluated for potential reportability to FDA.

If you have questions regarding the new draft guidance or would like assistance in preparing revised policies and procedures for the conduct of DMCs, we are glad to help. Please contact Beverly Lorell, Chris Markus, Kyle Sampson, or Elaine Tseng for more information.

[1] See FDA, Draft Guidance, *Use of Data Monitoring Committees in Clinical Trials* (Feb. 2024), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-data-monitoring-committees-clinical-trials.
[2] A data monitoring committee (DMC) may also be known as a data and safety monitoring board (DSMB), a data and safety monitoring committee (DSMC) or an independent data monitoring committee (IDMC).
[3] See FDA, Guidance for Clinical Trial Sponsors, *Establishment and Operation of Clinical Trial Data Monitoring Committees* (Mar. 2006), https://www.fda.gov/media/75398/download.
[4] *See* 21 C.F.R. § 50.24(a)(7)(iv).