

Submitted April 15, 2024

Re: Docket No. FDA-2001-D-0219
Use of Data Monitoring Committees in Clinical Trials

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the Food and Drug Administration's ("FDA's" or "the Agency's") Draft Guidance for industry entitled, "*Use of Data Monitoring Committees in Clinical Trials*," published at [89 Fed. Reg. 10084-87 \(Feb. 13, 2024\)](#) (the "Draft Guidance"). Guidance on this topic is timely, welcome, and important to stakeholders across the entire enterprise as clinical research continues to evolve.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.¹

The MRCT Center appreciates the Agency's efforts to compile this guidance, and we are eager to contribute to its development. We offer first a few overriding comments on issues that we believe would benefit from inclusion in the Guidance and that are not currently evident and follow with specific comments on the Guidance itself. Additional comments of areas that are not apparently addressed in the Guidance currently are also included in the applicable sections specific to the topic (below).

General Comments

In our experience, there are a few situations that are difficult or troublesome and that we hope FDA could consider including in the guidance with recommendations for their resolution.

- Central to our concern is the fact that DMCs are constituted and report to sponsors (and sponsor-investigators). The situation is easy when recommendations by the DMC are considered and accepted by the sponsor and then communicated by the sponsor to the IRB, investigator(s), and others. However, when the sponsor does not accept the recommendations of the DMC, the other entities with direct (PI, sub-investigators) or oversight (e.g., IRB) responsibilities are left without recourse. DMC members have

¹ Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, and Harvard University.

confidentiality constraints, and access to information is not forthcoming. What actions does FDA recommend?

- Direct communications between the IRB of record and DMC do not occur, but there are situations when that communication would be beneficial for the safety of participants and data integrity. We believe that the Guidance could allow for the possibility of direct communication as a possible element to be included in the Charter.
- Similarly, it would be helpful for the Guidance to address whether and when direct communication by the DMC with FDA is permissible. The lines of communication and transparency of that communication are not described, and they are currently dependent on the actions of the sponsor. Are there checks and balances if problems arise?
- When a trial involves both a safety monitoring committee and a DMC, what is the axis of communication, if any. Should the safety monitoring committee report its assessment and findings to the DMC? Should there be an exchange of the charters for each committee in advance and discussion of potential overlap or conflict?
- In many places in the Guidance, there is a lack of clarity regarding whether data are blinded, coded (A, B), or unblinded and in what settings. In our opinion, the DMC should have access to the data by treatment arm, and the DMC should know what treatment is assigned and the specifics of that intervention. Complete transparency is necessary for the DMC to provide for participant safety. If we are incorrect in this assessment, it would be very helpful for FDA to provide clear examples.
- The Guidance should clarify when data, either at the study or individual level, may need to be unblinded and how and by whom that should occur. For instance, if a participant's safety considerations require that their treatment assignment be unblinded, how is that information communicated, and to whom?
- Many DMC meetings are conducted virtually. The Guidance should specify that data, meeting recordings, and all communications should be collected, stored, transferred, and accessed through secure channels that are auditable.
- As the Guidance mentions, the number of DMCs has increased over time. It would be helpful for FDA to elucidate when DMCs are not generally required. Treatments for rare genetic disorders, for instance, even though there is a significant risk of morbidity and/or mortality, may not require a DMC. Open-label trials can often be monitored appropriately without a DMC in place. These and other examples would be helpful.
- The number of people with the necessary experience to impanel a DMC is decreasing. Clinical investigators and statisticians need training and experience in serving on a DMC. It would be beneficial to include the necessity of workforce development and capacity building in the Guidance.

Specific comments on Guidance Sections:

III. Background

We commend the inclusion in the introduction of Section III of the Draft Guidance that “Different designs for DMCs may be appropriate in different situations, and experience has shown that no single design is optimal for all settings.” (lines 78-79). We fully support the acknowledgment of the need for careful consideration of the interplay between trial design and the appropriateness of incorporating a DMC into a particular design – and, if so, how that DMC may operate under the circumstances. We do, however, suggest the inclusion of language explicitly advising sponsors to interact with CDER, CBER, or CDRH as appropriate when threshold questions arise regarding whether the establishment of a DMC is necessary or advisable. Fostering communication between sponsors and the offices of the FDA can save time, eliminate waste, and ensure that all stakeholders remain aligned throughout the clinical research life cycle.

IV. Determining Whether to Use a DMC

The guidance on determining whether the use of a DMC is appropriate includes the caveat that “not all trials call for involvement or monitoring by a DMC” and then proceeds to direct readers to “see section V of this guidance.” (lines 125-26). Section V of the Guidance offers descriptions of various types of oversight groups for clinical trials, including DMCs, but does not appear to resolve the question of which trials may indeed “call for involvement or monitoring by a DMC.” It would be helpful to direct the reader’s focus to the specific lines in section V that are responsive to the parenthetical reference (line 126).

Later in Section IV, the Guidance indicates, “FDA strongly recommends establishing a DMC if trial subjects are at risk of serious morbidity or mortality (e.g., hospitalization, heart attack stroke, death).” (lines 146-47). Implicit in this language is the understanding that DMCs in such circumstances would usually be advised, *but not always*. It would be helpful for the Guidance to provide examples of clinical trial settings in which participants are at risk of serious morbidity/mortality but for which a DMC is not indicated.

V. DMCs and Other Oversight Groups

We commend the clear and direct language employed at the beginning of Section V.C, “Given that DMCs have access to unblinded data...they should not adjudicate trial endpoints.” (lines 231-32). We agree that a bright line exists between endpoint evaluation and unblinded data, and we appreciate the forthright guidance. Similarly, the clarity of Section V.D.2 – at lines 269-71 (“If the entity that reviews safety data is unblinded to information regarding the subjects experiencing the adverse event, it should be blinded to efficacy data.”), at lines 277-78 (“...there

should be separation between individuals reviewing unblinded safety data and those involved in the conduct of a trial.”), and in Section V.E at lines 318-321, is helpful.

We do, however, feel that Section V.D.2 would benefit from more granularity in a few key areas. First, the Guidance distinguishes the “threshold that a DMC would use for reporting safety concerns...may be higher than the threshold for reporting potential serious risks...in an IND or IDE report to FDA.” (lines 292-95). Footnote 21 directs the reader to a guidance document on IND safety reporting that may offer guidance on the threshold for reporting safety concerns to the FDA, but there is no further exploration of what distinguishes the threshold for reporting safety concerns by a DMC when it comes to recommending trial modifications relative to the threshold for reporting safety concerns in an IND/IDE report. Second, the Guidance clearly indicates that the role of a DMC is “distinct” from the role of an entity reviewing safety data, but it then proceeds to signal that “it may be possible” for DMCs to perform both functions. (lines 295-99). We believe the Guidance would benefit from further explanation regarding the circumstances in which such dual functions “may be possible” and what factors sponsors and/or DMC members should consider when determining whether they are currently in such a circumstance.

VI. DMC Establishment and Operation

A. Committee Composition

We echo the suggestion to include a medical ethicist on DMCs for trials with “unusually high risks to subject safety or with broad public health implications” (lines 348-50) in Section VI.A.1. We recommend that the language “the DMC should consider...” be replaced with “FDA recommends...,” similar to lines 146-47 of the Guidance.

Section VI.A.2 includes brief guidance on potential intellectual conflicts of interest, described as existing when an individual is “known to have strong views on the relative merits of the intervention(s) under evaluation.” (lines 370-71). The Guidance explains that such individuals are “usually not appropriate DMC members.” (lines 372-73). In light of preceding guidance from Section VI.A.1 that DMC members should be composed of “clinicians with expertise in relevant clinical specialties” (lines 334-35), we expect that some tension will arise between finding clinicians of such expertise *without* strong views on the relative merits of the intervention the DMC will evaluate. This tension appears to be contemplated elsewhere in the Guidance in Section VII. (lines 859-64). Section VI.A.2 offers little to guide sponsors in navigating that tension, offering only a very general warning that individuals with strong views on the intervention “may not be able to review the data in a fully objective manner.” (lines 371-72). Readers might benefit from a hypothetical or historical anecdote (cf. lines 544-46) and/or methods to mitigate such tension.

We recommend deleting the word “typically” at line 341: it would be helpful for the Guidance to specify that the Chair has prior DMC experience and appropriate expertise in regulatory requirements.

The section on DMC composition does not address the inclusion of a number of important members:

- Patient/patient advocates and/or community members.
- Members with an understanding of the sites of performance, particularly when a trial will be conducted in low- and middle-income countries.
- Individuals (e.g., clinicians, investigators, statisticians) developing DMC skills and experience who would benefit from participating as a learning exercise.

We recommend that the Guidance specifically state whether and under what conditions ad hoc advice from content experts can be provided to the DMC.

Establishing a Charter Describing DMC Obligations, Responsibilities, and Standard Operating Procedures

The Guidance explicitly advises that the DMC charter and corresponding documentation of concurrence by all DMC members “should be in place in advance or performing any interim analyses” and, likewise, may be requested by the FDA “well in advance of the performance of any interim analyses.” (lines 405-409). In both cases – the establishment of the charter and its submission to the FDA – the Guidance includes the language “ideally before the initiation of the trial,” at lines 406-07 and 408-09, respectively. Use of this language implies that there may be times when a sponsor may initiate a trial whose design incorporates a DMC prior to the establishment of that DMC’s charter, documentation of the members’ concurrence with that charter, and/or submission of the charter to the FDA. Under what circumstances would this be permissible?

As mentioned above, there are additional elements of the Charter that we believe should be included (please see General Comments).

C. DMC Responsibilities

We recommend that the Guidance specifically address the role and responsibilities of the Chair of the DMC as we believe that the function of the Chair does differ from that of the members (e.g., the Chair is the person empowered to speak externally for the Committee).

Section VI.C.2.a offers clear and well-constructed guidance on the role DMCs play in monitoring for safety, describing safety monitoring as “the most common and most recognized purpose of a DMC.” (line 515). However, Section V.D.2 explicitly distinguishes the role of “an entity that reviews safety data” from “how a traditional DMC operates.” (lines 275-76). This distinction also appears in Section VI.D.1. (lines 771-74) and Section VI.D.3 (lines 840-841). Section V.D.2 later creates space for a DMC to perform both roles: “Although DMCs and entities that review accumulating safety data have distinct roles in characterizing safety, it may be possible in some settings to have the DMC conduct these safety evaluations...” (lines 295-

97). It would be helpful to reconcile the safety monitoring guidance of Section VI.C.2.a and the guidance from Section V.D.2. Moreover, the Guidance in Section VI.C.2.a may further benefit from a subsection to expound on those circumstances when a DMC takes on safety monitoring duties alluded to in Section V.D.2 that are beyond the scope of “how a traditional DMC operates.”

Guidance in Section VI.C.3 on “program-wide DMCs” (lines 660-68) should be clarified. Is the program-wide DMC contemplated in this guidance a single entity? The sentence beginning, “These are DMCs of separate...” (lines 660-63) seems to indicate that a program-wide DMC is not a single entity so much as an opportunity for separate DMCs to communicate where appropriate. By contrast, the following sentence beginning, “Sharing the results...” (line 663-666) invokes a single DMC charter. Some clarification of this section may be needed.

The subsection on “Maintaining Meeting Records,” Section VI.C.4.b, relies on the distinction between open and closed sessions of DMC meetings. Reference to Section VI.2.D.1 in this section, in addition to the footnote (line 716), would be helpful.

A minor note: Footnote 28 for section VI.C.2 should be reviewed, given the context of where the reference to the footnote appears. (line 498). A reference to Footnote 29 appears on p 14 at line 501, but no Footnote 29 exists.

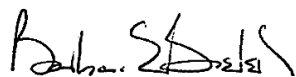
D. Interim Data and Analyses

The introduction to section VI.D makes frequent use of non-absolute statements (e.g., “...unblinded interim comparisons from a clinical trial is rarely critical...” at lines 742-43, “Unblinded interim data...should generally not be accessible...” at lines 745-46, “...summary evaluations...would usually *not* be available to anyone other than the DMC...” at lines 760-62, emphasis in original). Elaborating on circumstances on those rare-but-not-prohibited circumstances would be helpful.

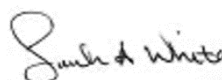
Conclusion

The MRCT Center appreciates the opportunity to comment. We reiterate our support for the development of this guidance amid an ever-evolving clinical research landscape, and we would welcome the opportunity to contribute further if we can be helpful. Please feel free to contact the MRCT Center (bbierer@bwh.harvard.edu or sawhite@bwh.harvard.edu) if we can be helpful or if you wish to discuss.

Respectfully submitted,



Barbara E Bierer, MD
Faculty Director, MRCT Center



Sarah A White, MPH
Executive Director



HARVARD
MEDICAL SCHOOL



**MULTI-REGIONAL
CLINICAL TRIALS**
THE MRCT CENTER of
BRIGHAM AND WOMEN'S HOSPITAL
and HARVARD

Professor of Medicine, Harvard Medical School