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STATISTICAL DATA ANALYSIS CENTER  
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**Docket 01D-0489** Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

**General**

We congratulate you on the quality and comprehensiveness of the Draft Guidance. We commend the integration of expertise from CBER, CDER, and CDRH. A common view by the FDA is extremely helpful.

We are in agreement with the principles of the Draft Guidance and nearly all of the specifics. Most of our comments below reflect requests for clarification. In some cases, we are specifically pointing out places of agreement where we suspect there may be differences of opinion.

**Comments by Section**

*Section 2 Determining Need for a DMC*

We recommend it be clear there are *three* separate issues to be addressed - whether a data monitoring plan needs to formally become a DMC, whether the DMC should be independent of the sponsor and Steering Committee, and whether the statistical support group for the DMC should be independent of the sponsor and Steering Committee.

*Section 2.2 Practicality of DMC Review*

We suggest sentence two be reworded as follows "If a trial is likely to be completed quickly and the sponsor has decided it is important to have a DMC, then the sponsor needs to implement mechanisms to permit the DMC to be informed and convened quickly in the event of unexpected results that raise concerns." Editorial suggestions are to eliminate this as a subsection heading as it is not of equal importance with Section 2.1 and Section 2.3 and to incorporate this into Section 2.1.

*Section 3 DMCs and Other Oversight Groups*

We recommend citing and/or incorporating some or all of ICH E9 Section 4 Trial Conduct Considerations. This would reinforce the two types of monitoring - one concerning the oversight of the quality of the trial and the other involving breaking the blind to make treatment comparisons (i.e. interim analysis).

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### *Section 3.1 IRBs*

We suggest adding the phrase "nor is it constituted to have all the relevant expertise or a statistical support group."

It would be helpful to comment on what information a DMC should convey to an IRB. Some IRBs, reacting to recent federal review, have asked for a great deal of information that traditionally would only be given to the trial DMC, assuming there is one. If a trial has a DMC, properly appointed and chartered, an IRB should not be responsible for the efficacy and safety monitoring but should expect a brief letter from the DMC stating that they met and recommended continuation or whatever was decided. Sometimes the frequency of DMC meetings is an indication of evolving concerns so it may be helpful also to comment on the frequency of DMC contact with an IRB.

### *Section 4.1 Committee Composition*

We take the point of view that clinical trial leadership should be shared between the sponsor and the steering committee in order to be successful and to have credible results and suggest this partnership be cited as often as possible. One such place is the appointment of DMC members and of the DMC chair. We believe there should be mutual consent between the sponsor and steering committee in these appointments; both have substantial stakes in the ability of the DMC to protect not only the patients' interest but also their scientific and economic investments.

The list of factors to consider in the selection of individuals to serve on a DMC includes relevant expertise, experience in clinical trials and in serving on other DMCs, and a lack of serious conflicts of interest (further described in the section). At this point, experience has been the primary teacher for education concerning DMCs. It would be helpful to indicate that ideally experience is not the only teacher. We recommend a range of educational tools - case studies, simulated examples, peer-reviewed articles, books, short courses, etc. - supplement experience. These educational tools would encourage best DMC practices similar to best regulatory review practices, increase the pool of potential DMC members, further educate past and present DMC members, and provide background for the public, medical writers, etc. DMC members should also have quantitative literacy, i.e. be comfortable reviewing and understanding figures and tables.

The last paragraph has a parenthetical sentence that, if the DMC includes only one statistician, it is desirable for the statistician to have had prior DMC experience. We recommend, in this case, that it is critical that the statistician understand the fundamentals of interim monitoring.

We commend the recognition that the chair should have administrative skills as well as facilitate discussion.

#### *Section 4.2 Confidentiality of Interim Data and Analyses*

We suggest that there be more discussion in the guidance concerning the multiple statistical roles possible and the potential for introducing bias and comprising confidentiality. These statistical roles include statistical contributor to strategic development for a sponsor, statistical collaborator in a clinical trial or in a research program (e.g. steering committee), statistician member of a DMC, statistical support group member for a DMC, statistical leader for a data management team, statistician member of a regulatory advisory committee, and statistical collaborator for peer-reviewed publications, presentations, and/or regulatory submissions. For each clinical trial with a DMC, it is crucial to recognize the simultaneous roles a statistician may play. We commend the Draft Guidance for raising awareness concerning potential bias and need for confidentiality while not prohibiting any model. Indeed, perhaps there should be even more emphasis there is no single model that may be optimal for all settings and there is not necessarily consensus about the optimal model in any given setting (citing Section 1.2).

#### *Section 4.3.1.2 Meeting Structure*

We commend the section on meeting structure, particularly the open session that helps to ensure that those with the most intimate knowledge of the study share their insights with the DMC and raise issues for DMC consideration. We suggest that this meeting structure should be used whether the DMC is or is not independent of the sponsor and whether the statistical support for the DMC is or is not independent of the sponsor. The significant advantages of sponsor involvement with the DMC are also noted in Section 6.2 and perhaps can be cross-referenced. We recommend noting the content of the open session report often provides an additional mechanism for improving ongoing trial management and for ongoing quality assessment of the statistical support group for the DMC.

#### *Section 4.3.1.4 Format of Interim Reports to the DMC and Use of Treatment Codes*

In our experience, there are many misconceptions about the need for coded reports and a DMC masked to treatment assignment. This Draft Guidance should help and the more explicit it is the better. We commend the formal statement that a DMC should generally have access to the actual treatment assignments for each study group. What we have found especially problematic is masking the treatment assignments differently between efficacy and safety within the same report. We strongly agree that the most critical DMC responsibility is balancing risks and benefits of the active intervention and that knowledge of treatment assignment is necessary to provide the best advice possible.

We recommend stating explicitly that it is essential to provide the DMC with clear, comprehensive, and carefully constructed reports on the accumulating data in order to have the DMC fulfill its responsibilities. These report characteristics should be present whether the statistical support group for the DMC is or is not independent of the sponsor.

The Draft Guidance states that the sponsor should ensure that the general format and content of reports to the DMC are acceptable to the DMC. We agree analysis of the primary endpoint and interim monitoring guidelines should be specified by the sponsor and steering committee and acceptable to the DMC. We recommend stating that the DMC should have access to the entire data file without having to negotiate with the sponsor during the study to access some data item. Our experience has been that the sponsor and steering committee sometimes try to limit what the DMC should evaluate by pre-specifying the DMC report contents. The structure and content of interim analysis reports need not be fixed and may change during the course of the trial. Many factors (e.g. the stage of the trial, the nature of accumulating data, the focus of a DMC meeting, and requests by DMC members) will influence report content or how specific data items are analyzed and presented.

Occasionally sponsors propose that the independent statistician member of an independent DMC also prepare the interim DMC reports by executing sponsor-prepared programs after merging them with treatment assignment. We recommend stating that this is not a solution since the sponsor programming necessary to address evolving issues in DMC reports may potentially introduce bias and compromise confidentiality.

The Draft Guidance often references "the statistician" preparing unblinded data for the DMC; we recommend it be changed to the statistical support group. Parallel to the concept that a DMC should consist of more than one person is the recognition that the statistical support for the DMC should consist of more than one person. There are benefits to the depth and breadth of DMC report contents from a statistical support group as well as minimization of the delay between data closure for analysis and report distribution for DMC review.

#### *Section 4.3.2 Statistical Methods*

In the last paragraph concerning statistical assessment for futility, the guidance considers the Type I error but omits the Type II error. We suggest that there be some statement that the a DMC, before recommending a trial is futile, consider the false negative or Type II error.

#### *Section 4.4.1.1 Monitoring for Effectiveness*

We found the fifth sentence beginning "estimates of ..." to be already covered by the following sentence concerning a pre-specified monitoring plan and make the editorial suggestion that it be deleted as redundant and potentially confusing.

#### *Section 4.4.1.2 Monitoring for Safety*

The draft guidance states that the sponsor should provide the DMC with summaries of the adverse events observed. We recommend that the statistical support group for the DMC provide the DMC with the results of analyses of safety data by assigned treatment group and the DMC not receive pages of listings of adverse events or serious adverse events without treatment assignment and without consideration for efficient and effective summarization.

We personally maintain that a DMC cannot monitor safety without also monitoring efficacy. The views of the sponsor and/or steering committee concerning early termination need to be made very clear to the DMC, prior to any review of data by the DMC. During the open session, aggregate information on treatment safety and benefit can be presented and discussed. It is educational for the DMC to have the steering committee consider the range of possibilities for the accumulating aggregate results, e.g. if all are in one treatment group and none in the other treatment group.

*Section 4.4.3.1 Making Recommendations*

We believe that this is another section where the emphasis should be on the clinical trial leadership consisting of both the sponsor and the steering committee. The DMC recommendation should send its recommendations to the sponsor and to the steering committee. If there is a controversy, the steering committee will share in the criticism as much as the sponsor and the DMC.

*Section 6 Independence of the DMC*

We suggest that this section be retitled Relationship between Sponsor and DMC. The text and its current title are not consistent.

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Sincerely,



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