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Dockets Management Branch (HFA-305)
Food and Drug Adminisration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 01D-0489
Draft Guidance for Clinical Trial Sponsors on the
Establishment of Clinical Trial Data Monitoring Committees

Eli Lilly and Company is dedicated to creating and delivering innovative pharmaceutical-based health care solutions to provide customers with optimal clinical outcomes. The comments that follow concerning the referenced draft guidance (the Guidance) as published in the Federal Register are intended to help the agency reach a final guidance for Clinical Trial Sponsors on the Establishment of Clinical trial Data Monitoring Committees.

Key Points

1. The guidance document is well written and thorough. We have no disagreements for large-scale confirmatory mortality or serious morbidity studies.
2. The guidance strongly recommends that the statistician who conducts the interim analysis and presents the data to the DMC (herein referred to as the analyzing statistician) be external to the sponsor in all cases where the study may be used as a registration study. We disagree with this position, and believe that the advantages of a sponsor statistician over an external statistician outweigh the disadvantages. We agree that for registration studies it is imperative that the analyzing statistician not be involved in the particular study, and probably not be someone involved with the compound in any way. But there are several distinct advantages to having the analyzing statistician be from the sponsor, but physically and organizationally removed from the team who is involved in research of the study drug. These reasons include:
    a. Statisticians within the sponsor have access to proprietary standard analysis systems which lead to greater accuracy, consistency, and efficiency (all of which lead to timely decision making)
    b. Sponsor statisticians typically will have greater knowledge of the specific protocol and previous clinical data.

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c. There is the potential for financial conflict of interest with external statisticians, as they are compensated a substantial sum of money (up to $100,000 or more) to conduct a single interim analysis.

3. As the guidance appropriately indicates, there are instances in earlier phases of research (e.g. Phase 2) where an internal group can comprise the DMC. We suggest that the guidance state explicitly that the FDA will not discount the data from such a study, potentially providing data which are supportive of the label indication, when the sponsor follows a well-defined and documented process to ensure the team involved in clinical research of the study compound remains blinded.

Detailed Additional Comments

Section 1.1
End of first paragraph: It is not clear whom "trial leadership" is referring to. Is this the same as "sponsor"? Or is it the principal investigator? We suggest that consistent terminology be used, and hence suggest that "trial leadership", both here and elsewhere in the document, by changed to "sponsor" (or whatever group it is intended to be).

Section 4.2
Regarding the following text

> "Therefore, interim data and the results of interim analyses should generally not be accessible by anyone other than DMC members."

This sentence should be expanded to acknowledge that there is an analyzing statistician (not a member of the DMC) who conducts the interim analysis and presents the data to the DMC, who necessarily must be unblinded.

Section 4.3
A suggestion for clarification of terminology is to refer to the DMC's SOPs as a DMC Charter instead. Sponsors should additionally have SOPs that describe the DMC process for all DMCs. However, each individual DMC should have their own charter, with content as the guidance describes.

Section 4.3.1.3
In addition to the list of topics for the initial meeting, this is an excellent time for the DMC to finalize and sign off the DMC Charter.

Section 4.3.1.4, first paragraph
Last sentence urges that the statistician conducting the interim analysis be independent of the sponsor and clinical investigators. We suggest that this is acceptable for large-scale confirmatory mortality and serious morbidity studies; however, for other studies this statistician should be independent from the team who is involved in research of the study drug, not necessarily independent from the sponsor.

Section 4.3.1.4, last paragraph

Although the masking of actual treatment assignments on analysis output is a viable option worthy of inclusion in the guidance, we suggest that the guidance document should also point out advantages of unmasking of treatments, the latter being our preference. Masking of treatments on the output can lead to confusion by the DMC members as they evaluate and interpret the data, constantly having to map "A", "B", "C", etc, to the respective actual treatment identifications. When treatments are identified on the analysis output, they can be ordered in logical ways (e.g., placebo, low dose, middle dose, and high dose), whereas when the treatment identification is masked the order that the treatments appear on the output is random. Steps can be taken to minimize the risk of someone not on the DMC seeing the interim data summaries, which address the issue that masking of treatments is attempting to satisfy. For example, interim data should be shipped overnight courier (not e-mail, not fax) in a sealed envelope clearly marked "confidential". DMC members should receive written instructions to return the contents to the envelope when they are finished looking at it. And, all materials should be collected at the DMC meeting.

Section 4.3.2, last paragraph

The last 2 sentences in this paragraph state

> "Stopping on the basis of futility does not raise concerns about Type I error in that trial, since the conclusions of the trial will not be positive. Nevertheless, protection of Type I error is important even when there is a stated intention to stop early only for futility reasons since interim review of outcome data always raises the possibility that the DMC may find early results so persuasive that it would recommend early termination of the trial."

We agree with this position for mortality or serious morbidity studies. In such studies where efficacy data are evaluated at an interim analysis, for ethical reasons at least, if the data are very positive the DMC likely will recommend stopping. Consequently for such studies, it is appropriate to spend some of the alpha. However, in many other studies, the DMC cannot recommend stopping for positive efficacy. Consequently, it is scientifically and statistically appropriate to not spend any alpha (i.e. not make any adjustment to the final nominal alpha level) in these cases. Section 4.4.1.5 of the FDA guidance document (middle of 1st paragraph) agrees with this position, and effectively contradicts the quote above, where in a discussion of studies of less serious outcomes it states

> "Early termination for effectiveness is rarely appropriate in such studies."

Section 4.4.1

It is not clear what is meant by the last sentence, which reads

> "In all studies, it is essential that the DMC carefully monitor the interim data throughout the duration of the study, regardless of the duration of treatment."

If this is intended for mortality and serious morbidity studies, then it should clearly state this. If it is intended for all studies, including non-mortality studies, then we suggest clarifying the language to allow some studies to have a single interim analysis (where

realistically the DMC will only look at that single snapshot, and even then only spend about a day monitoring the interim data).

Section 4.4.1.1
The discussion of the critical nature of a DMC recommendation to stop a mortality or serious morbidity study early for positive efficacy is very appropriate. We suggest expanding this section to suggest ways to minimize the possibility of having a DMC recommend stopping for positive efficacy only to have the FDA or an advisory committee decide to not accept the DMC recommendation. In such a serious disorder, when a DMC recommends stopping early for positive results, they are implicitly stating that no further placebo-controlled studies in the same patient population should be conducted. For such studies the FDA should be deeply engaged in the development of the protocol and DMC Charter to ensure that they agree with the data and analyses that the DMC will be evaluating, what constitutes sufficient evidence of efficacy (e.g. two-sided alpha=.05 from a single study), what subgroups need to be considered, etc.

Section 4.4.1.5
The last sentence states

> "Sponsors frequently constitute internal groups to monitor these types of studies, and these may be satisfactory in many cases; nevertheless, external advisors, who will be less committed to the existing development plan, may identify problems more readily than internal reviewers."

We have two points regarding this sentence. First, we suggest it also be pointed out here that because sponsor personnel have more time to commit to the project -- in fact the product, study, and disorder may be their fulltime jobs -- safety monitoring via routine interim analysis of safety data is likely to be more thorough when conducted by an internal group than when an external group conducts such monitoring. The external group would meet only periodically, only spending 1-2 days evaluating the data, would not give very much attention to the data in between meetings, and has many other daily responsibilities. The second point is regarding a comment made by Dr. Robert Temple during his presentation at the workshop for this draft guidance, held on November 27, 2001. In one of his slides, where he discussed "DMC Type II", he states

> "Need for independence of sponsor not as great (most descriptive) but should have strong element of external (needed expertise, needed freedom from obligations and assumptions)"

Does this point raised by Dr. Temple suggest that it may be beneficial to have an internal safety committee, along with external experts when necessary, to conduct interim analysis of safety data across several ongoing studies on a fairly frequent basis, rather than utilizing an independent DMC for such safety interim analyses? If so, we advise that this be addressed in the guidance document.

Section 4.4.3.1
We suggest that the 2nd paragraph be expanded to provide more guidance about what should occur after the DMC makes their recommendations to the sponsor, in order to

continue to maintain the data integrity. This is especially important when the DMC recommendation is to stop the study for positive results, since the interim data would then form a key basis of regulatory submissions. We generally advise that this recommendation initially come to a point-person within the sponsor (e.g., a member of senior management) who is not a member of the team responsible for clinical research of the study compound. They can then ensure that only a minimum number of sponsor personnel are unblinded to any of the data (rather than unblinding an entire DMC Steering Committee). In the event that other experts from the sponsor need to evaluate the DMC recommendation and associated data, the sponsor should control the extent to which further unblinding occurs.

Section 4.4.3.2

The 2nd sentence in the first paragraph states

> "After each meeting, the DMC should issue a written report to the sponsor based on the meeting minutes."

We suggest that the DMC appoint a DMC secretary who retains all meeting minutes confidentially, and shares them with the sponsor only after the study has completed (after final database lock). The only written communication from the DMC to the sponsor should be the DMC recommendation (which as the guidance appropriately indicates may state simply that the study should continue as planned).

Section 4.4.3.2, last paragraph

This paragraph states that all "non-confidential and confidential interim reports" be included in the clinical study report (CSR). We agree that this is important in mortality and serious morbidity studies, or any study where the protocol allows for early stopping for positive efficacy. However, in studies where safety interim analyses may be conducted monthly, for example, it would add a great deal of output to the CSR which is of dubious value. We advise that the FDA guidance indicate that all interim reports should be included in the CSR for mortality and serious morbidity studies, and in any case where the protocol stipulates an early stopping rule for positive results.

Section 5.2

The same comment made for Section 4.4.1.1 applies to this section. It would be ideal for such potentially important therapies that the DMC recommendation and relevant unblinded interim data be shared with the FDA, and possibly the FDA advisory committee, prior to implementing a DMC recommendation to stop the study for positive results.

Section 6.3

The points made in this section are very good and relevant. We suggest addition of a section to the guidance document that discusses and ranks, based on severity of bias, the various ways that bias can be introduced into a study from explicit knowledge of interim results down to a facial expression. Our contention is that knowledge of a subgroup for which the drug effect is greatest has a very significant potential for bias introduction.

However, at the other end of the spectrum is the communication regarding an interim analysis of a dose response study that indicates that future studies should include the high dose. What bias can be introduced with this knowledge if the dose response study is double-blind? And if any bias can be introduced from such information, it should be acknowledged that it is no different from bias that is introduced into a Phase 3 study that is started after results of a completed Phase 2 study have been published.

Section 6.4

Our input to this section was presented in the "Key Points" at the beginning. To summarize, we agree that for studies where the primary endpoint is mortality or serious morbidity and the study is a registration study, that the statistician preparing the unblinded summary reports be external to the sponsor. One possible exception to this requirement, however, is for an oncology study where enrollment and dosing have completed, and an interim analysis is conducted on time-to-progression, while the primary analysis at the end will be based on survival. In this special case, and for non-mortality and non-serious morbidity studies, we suggest that statisticians who are physically and organizationally removed from the team involved in clinical research of the study compound offer the safeguards that are desired.

Section 6.6

We suggest that submissions based on interim analyses are valid, so long as the protocol provides clear "stopping" rules, that in this case lead to a submission while the study continues to its pre-specified end. Alpha-spending issues here are equally relevant to the case where the study is terminated. Often the data collected after the interim analysis are primarily to provide additional safety data, and to evaluate what become secondary endpoints (that is, the primary endpoint becomes the point in time when the interim analysis stopping rule has been achieved, leading to the submission).

Section 7.2.1

The same comments made regarding Sections 4.4.1.1 and 5.2 apply to this section. One additional comment is for such a critical topic it might be best to consolidate the discussion into a single section of the guidance.

Sincerely,

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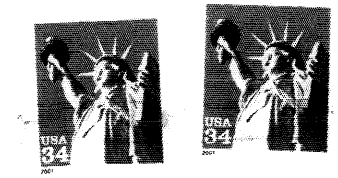
Eli Lilly and Company



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