

Alice E. Till, Ph.D.
VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS



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February 12, 2002

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

Re: Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees [Docket No. 01D-0489, 66 *Federal Register*, 58151, November 20, 2001]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier and more productive lives. Investing more than \$30 billion in 2001 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

The effective monitoring of clinical trial data is a very important aspect of conducting meaningful clinical trials for drug development. PhRMA, therefore, appreciates the opportunity to provide the attached comments on the Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial data Monitoring Committees.

We hope that you will give careful consideration to the attached comments as you work to finalize the guidance. Please contact me if there are any questions.

Sincerely,

A handwritten signature in cursive script that reads 'Alice E. Till'.

Alice E. Till, Ph.D.

Att.

01D-0489

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Pharmaceutical Research and Manufacturers of America

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Comments on “Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees” [Docket No. 01D-0489, 66 *Federal Register* 58151, November 20, 2001]

The guidance document is well written and thorough. It is clear that a great deal of work has gone into it and that the authors are to be commended. The document will be very useful and important to both pharmaceutical and government sponsors of clinical trials.

We have few or no disagreements with the guidance document for large-scale confirmatory mortality or serious morbidity studies. However, we do have a few key points to raise for the FDA’s consideration before the final guidance is published.

1. The guidance strongly recommends that the statistician who conducts the interim analysis and presents the data to the Data Monitoring Committee (DMC) be external to the sponsor in all cases where the study may be used as a registration study. Although there will be cases where this may be the most appropriate approach (e.g. mortality studies), the majority of clinical studies need not and should not go to this extreme. The analyzing statistician can be an employee of the sponsor and still be isolated from the study team, completely maintaining the blind for sponsor personnel who are involved in the study. There are some distinct advantages to having the analyzing statistician being a member of the sponsor’s staff, such as:
 - a. Statisticians employed by the sponsor have access to proprietary standard analysis systems, which lead to greater accuracy, consistency, and efficiency. In addition, if an unplanned analysis is requested by the DMC, internal statisticians often can respond in a more expedited manner.
 - b. Statistical and disease-specific expertise is usually greater among the sponsor’s scientific staff, including greater knowledge of the specific protocol and previous clinical data.
2. The guidance indicates that under certain circumstances an internal DMC may be appropriate (e.g. Phase 2 studies). The expressed preference for an external analyzing statistician should be clarified to apply only to the case where the DMC is independent of the sponsor.
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 more explicitly that the FDA will not discount the data from such a study when the sponsor follows a well-defined and documented process to ensure the study integrity remains intact.
4. Although it is not the intent of the guidance to limit sponsors to a specific process, the FDA should acknowledge that even the word “should” will be interpreted as “must” by sponsors of clinical trials. One solution is to soften the message by providing more balanced advantages and disadvantages to the suggestions presented in the guidance.
5. Although an independent DMC has the advantage of a perception of lack of bias, it can have an important disadvantage. Just as an advisory committee would

never be expected to replace the many hours of FDA review of an NDA, in some cases the safety of study subjects would be better protected by use of internal sponsor experts instead of an independent DMC. The reason why this would be the case in some situations is because the internal experts may spend full-time on the current and previous studies, and may have insight and knowledge that an external expert group cannot replicate in a series of one-day DMC meetings. Although this issue is discussed briefly at the very end of Section, 4.4.1.5 (bottom of page 15), we suggest that this drawback to independent DMCs be acknowledged in the guidance.

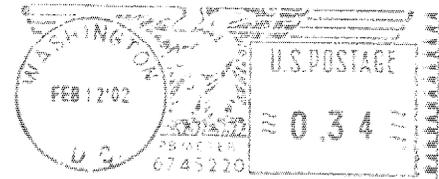
6. Some of the terminology requires further clarification and/or definition. In particular, "Steering Committee" should be defined in the guidance. We suggest something like "DMC Steering Committee," defined as the group to whom the DMC makes their recommendation. And, where the guidance refers to "SOPs" (section 4.3), it should instead refer to this document as a DMC Charter. That is, a charter needs to be created uniquely for each DMC, but each sponsor should have an SOP that describes the process relating to DMCs.
7. It would be very beneficial for the guidance to address issues posed by open-label or single-blind studies. In many cases oncology studies are not double-blind and since they usually have a mortality endpoint, it is especially important for sponsors to understand how best to approach such studies with respect to interim analyses and DMCs.
8. In section 4.4.1.4, 3rd paragraph, it states "In many cases, access to the blinded data..." We believe you mean to say "unblinded" here, as this paragraph addresses how the DMC may be able to utilize external data along with their knowledge of the unblinded interim data from the current study.
9. The last sentence in the last paragraph of Section 4.3.2 states
"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, where ethical reasons would dictate early stopping for strong positive efficacy results. However, in other studies, it often is not the case that the DMC can recommend stopping for positive efficacy; the interim analyses may be conducted to test for futility, or to evaluate safety. 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. In fact, Section 4.4.1.5 of the guidance document essentially agrees with this position (and contradicts the previous quote from the guidance), where it states

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

10. A DMC recommendation to stop a mortality or serious morbidity study for positive efficacy has important ramifications. It is critical that the sponsor and DMC be aware of ways to minimize the potential for subsequent disagreement with the recommendation (e.g., by FDA or an advisory committee) long after the trial has been curtailed. How to achieve this is discussed to some extent in

P/RMA



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