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Corporate Regulatory & Quality Science

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-6091

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

<http://www.fda.gov/dockets/ecomments>

**Ref: DOCKET No.01D-0489 - Draft Guidance for Clinical Trial Sponsors
On the Establishment and Operation of Clinical Trial Data Monitoring
Committees**

Abbott Laboratories commend the Agency on the effort to provide guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees.

Abbott is very pleased to have the opportunity to provide comments on this draft guidance and we thank the Agency for your consideration of our comments.

Should you have any question, please contact Cheryl Spencer at 847-937-2609 or by FAX at 847-938-3186.

Sincerely,

D.L. Sporn (by APK)

Douglas L. Sporn,
Vice President
Corporate Regulatory Affairs

01D-0489

CIS



**COMMENTS ON
Draft Guidance for Clinical Trial Sponsors on the
Establishment and Operation of Clinical Trial Data Monitoring Committees**

DOCKET No. 01D-0489

COMMENTS

Section 4.3.1. Considerations for Standard Operating Procedures

4.3.1.2. Meeting Structure (page 8)

This section suggests that meetings between a sponsor and a Data Monitoring Committee (DMC) consist of a 2-step approach - an open session where representatives of the sponsor are present and general information on trial progress is discussed and a closed session where the sponsor's representatives are excluded and DMC members review unblinded trial data. The rationale for this format is that it ensures the independence of the DMC and, presumably, avoids biasing the sponsor's decisions on a trial.

We recommend that an additional alternative, such as a 3-step approach be considered for inclusion in the draft guidance. This approach would add the requirement that the DMC initially review trial data in a blinded fashion along with a limited number of a sponsor's representatives. Trial data would be aggregated by treatment arm, but the actual treatment would remain blinded. The DMC and senior, independent representatives of the sponsor would initially discuss the aggregate, blinded data. If, following its review of the blinded data, the DMC needs to make a decision on the risk/benefit of a trial, the sponsor's representatives could be asked to leave and the committee would deliberate in an executive session. At any time during the process the DMC could ask for a blind break at the group or individual patient level.

This 3-step approach offers several advantages over that proposed in the draft guidance document:

1. The sponsor's representatives can provide needed expertise and background on the product that is often critical in the DMC's evaluation of the study data.
2. The sponsor's representatives can provide insight into other studies being conducted with the product that may be relevant to the discussion.
3. Review of blinded, aggregate data can reduce bias on the part of the DMC.
4. Having senior representatives from the sponsor present avoids the DMC interacting with the sponsor's junior staff or outside contractors.



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4.3.1.4. *Format of Interim Reports to the DMC and Use of Treatment Codes* (page 9)

This section states “the statistician preparing the reports to the DMC should ideally be independent of the sponsor and clinical investigators (and a Steering Committee if there is one) to avoid inadvertent influence of data trends on the conduct of the trial (see Section 6.3 and 6.4)”.

We propose that the statistician who prepares the internal SAS codes for the analysis of trial data be an independent representative of the sponsor. This will ensure that the interim reports to the DMC and the final report on the study monitored by the DMC use consistent definitions. The use of an internal statistician to write the internal SAS codes and an independent contractor to perform the interim analyses for reports to the DMC also adds a quality control checkpoint in the process, as the independent contractor will serve as a second pair of eyes to evaluate the SAS codes. Additionally, this arrangement ensures the final report of the study is consistent with any future submissions of the sponsor that include the report.

4.3.2. Statistical Methods

Section 4.3.2 of the draft guidance (Statistical Methods) discusses statistical approaches a DMC might typically use to evaluate whether a trial is meeting its objectives including controlling type I error by pre-specifying boundaries that must be crossed in order for a DMC to recommend a trial be stopped prior to its planned completion, and a DMC recommending a trial be stopped based on futility.

We recommend the Agency to consider additional discussion with respect to data analysis and to include other statistical methods that may be used in making recommendations on trials, e.g., osculating p values is another statistical tool that might be used by a DMC and a sponsor in making a decision to stop a trial before a pre-specified threshold is reached.

5. DMCs AND REGULATORY REPORTING REQUIREMENTS

The Interaction and Roles of the DMC and IRBs

The role of the DMC may become clearer if the guidance includes further discussion of the roles and responsibilities of other groups involved in the patient’s safety (i.e. IRBs, Pharmacovigilance), and how these groups interrelate.

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Section 5.1. Safety Reporting

Paragraph 2 (page 18)

In the third sentence of this paragraph, the guidance states “Study investigators are generally responsible for reporting such findings to their IRBs, according to 21CFR 312.66 (drug trials) and 21CFR 812.150(a)(1)(device trials), although direct reporting from sponsors to responsible IRBs may be arranged and may be preferable in some situations, e.g., when a central IRB has been established.”

This is not defined in any other current FDA guidance document or compliance manual. The interactions and reporting relationships need to be addressed systematically in other guidance documents to accommodate for these changes e.g., the guidance appears to circumvent current regulation (i.e., investigator reporting the information to IRBs).

Paragraph 3

The guidance states “Sponsors should notify FDA and the responsible IRBs of any recommendations or requests made by a DMC to the sponsor that address safety of participants...”.

We recommend deleting this sentence regarding notification to IRB by sponsors of changes recommended by DMCs. The only information to be communicated ought to be if the trial is terminated. All other changes should go through investigators. The only current regulatory requirement for notification of IRB by sponsors is when the IND is terminated.

Additional COMMENTS:

Section 4.1 – Committee Composition

Paragraph 5 – last sentence (page 6)

The guidance states “Sponsors should have their own...DMC, and to provide disclosure to all DMC members of any minor conflicts that are thought to impede objectivity.”

We recommend deleting the statement “and to provide disclosure to all DMC members of any minor conflicts.” The difference between a "minor" and "important" conflict of interest is too subjective.

Section 4.4.1.5 Studies of Less Outcomes

Paragraph 2 (page 15)

The guidance states “DMCs have not commonly established for short-term studies...may identify problems more readily than internal reviewers.”



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We recommend deleting the entire paragraph, as it seems to promote DMCs for trials where they would provide no benefit.

Section 6 INDEPENDENCE OF THE DMC

Paragraph 1 (page 18)

The guidance states “An independent DMC is a committee ... DMC, and have no financial or other important connections to the study sponsor or other trial organizers.”

The last sentence indicating “no financial connections to the study sponsor” is inconsistent with CFR part 54, which requires only disclosure, not divestiture.

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