

Mathias Hukkelhoven, Ph.D. Novartis Pharmaceuticals Corp.
Vice President, Global Head Drug Regulatory Affairs
1 Health Plaza
East Hanover, NJ 07936-1080

Tel 973-781-6035
Fax 973-781-5544

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February 19, 2002

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

Re: Docket # 01D-0489

Comments on the document *"Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees"*

We feel that this document is a well-written, well-organized presentation of the issues surrounding the implementation and usage of DMCs. It addresses many of the complex and subtle issues which arise in this context, and it will be very useful to have such a guidance document in place.

Our main comment involves the discussion of the potential use of a sponsor employee as the statistician who performs interim analyses and provides results to the DMC. At Novartis, we have experience both using sponsor statisticians in this role, and using external parties contracted out to perform this function. In either scenario, the statistician is kept independent of all trial activities and decision-making, for reasons which are well described in the draft guidance document.

Generally, the tone of the document discourages use of sponsor personnel in this role. Among the reasons presented for this is knowledge by FDA of cases in which a sponsor statistician performing interim analyses has been present for other meetings or discussions where trial conduct was considered. When a sponsor statistician is used to perform interim analyses, we agree that that individual should be strictly prohibited from involvement in those other types of activities.

Experienced external DMC personnel have expressed to us that they at times find it preferable for the independent statistician to be a sponsor employee, with appropriate documentation of safeguards in place to ensure confidentiality of the interim results and to insulate that individual from other trial activities to the extent possible. They feel that this individual can serve a useful role in facilitating their obtaining of more information or results if needed. At times, issues arise unexpectedly in trials which require unanticipated analyses or other

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information to be requested by a DMC. A concern of a DMC in such cases can be that this information should be supplied to them in such a way that a minimum number of persons even know that the request has taken place, in order not to set off “alerts” or speculation by trial personnel regarding what this might mean. Often, this can take place more quickly and confidentially when a sponsor employee is serving in the role of independent interim analysis statistician (for example, confidential authorizations of additional programming activities might more easily be facilitated by an internal statistician than by an external party). Also, at various points of the trial a DMC may find it helpful to raise questions about the trial, project, test substance, company strategy, etc., for which a sponsor statistician may know the answers, or be able to obtain them quickly and confidentially – for a DMC to have to explicitly ask such questions of trial personnel might cause undesired speculation. Potential benefits to a DMC of interacting with a sponsor statistician are not addressed in the draft guidance document.

We concur with the authors of this document that an independent sponsor statistician should generally not be accorded membership status on an otherwise-independent DMC, nor be present during formal DMC deliberations. As alluded to above, we agree entirely with the concerns of the authors regarding the potential involvement of an independent sponsor statistician in other trial activities. When a sponsor statistician performs interim analyses, that person should no longer be permitted to attend or participate in discussions in which trial personnel consider modifications to the protocol, analysis plan, etc. That individual should not be permitted to attend meetings of the trial team, Steering Committee, Operations Committee, etc., other than minimally as needed to discuss logistics of providing information to the DMC. These limitations of activities should be fully documented in SOPs and in DMC charters, and we do this at Novartis. We believe that the concerns expressed by the authors can be minimized to an acceptable extent. The sponsor must always remain sensitive and vigilant to the possibility that any activities of the independent statistician which could convey to others the nature of interim results could jeopardize the interpretability of the trial.

Therefore, our opinion on this issue, and on how it is addressed in Section 6.4 of this document, can be summarized as follows: as presented in that section, a major justification against the use of a sponsor statistician is that FDA is aware of cases where that individual has had involvement in other trial activities; rather, we feel that a general approach along the following lines might be considered: “when the statistician performing the interim analysis is a sponsor employee, the sponsor must understand the risk that inappropriate contact by that person with trial personnel may jeopardize the integrity of trial; that individual should be prohibited from all other trial activities and decision-making; his/her interaction with trial personnel should be minimal, and only involve facilitating the supplying of information to the DMC.” We feel that the possibility that use of a sponsor statistician might facilitate providing additional information to a DMC can also be a legitimate factor in a decision, and might be acknowledged within Section 6 of the document.

Minor specific comment: Section 4.4.1.4, paragraph 3, line 1: “access to the blinded data”; should this not be “access to the *unblinded* data”?

Sincerely yours,

A handwritten signature in black ink, appearing to read "M. Hukkelhoven". The signature is fluid and cursive, with a long horizontal stroke at the end.

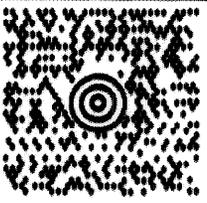
Mathias Hukkelhoven, Ph.D.
Vice President, Global Head
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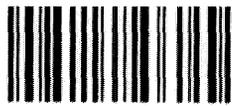
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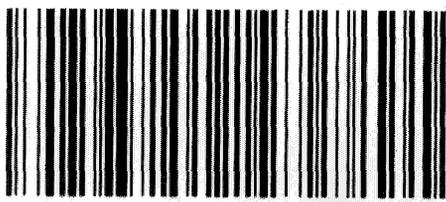
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