

# UNIVERSITY OF MINNESOTA

Twin Cities Campus

Coordinating Centers for Biometric Research  
Division of Biostatistics  
School of Public Health

Suite 200  
2221 University Avenue S.E.  
Minneapolis, MN 55414-3080  
612-626-8887  
Fax: 612-626-9054

2862 '02 FEB 13 P1:25

February 7, 2002

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

Dear Sir or Madam:

I have six comments on the draft guidance document concerning clinical trial data monitoring committees. Four of the comments concern language on pages 3, 7, 9, 13, 18, and 21.

1. Page 3. As written, this document pertains more to industry-sponsored than NIH-sponsored trials. I think you should say that some of the guidance in this document may pertain to NIH-sponsored trials, that much of it was developed based on NIH trial experience, but that many of the recommendations do not reflect current practice for NIH-sponsored trials (e.g., sponsor presence during closed sessions and a statistician responsible for the interim analyses who is independent of the protocol team and Steering Committee). NIH may be doing it wrong, but you do not provide any convincing arguments based on experience that this is the case. Furthermore, while advantages and disadvantages to various approaches to DMC operation are discussed, that is not the case for the recommendations on who performs the interim analysis (see point # 2 below).
2. Pages 7, 9 and 21. I disagree that it is always ideal for the statistician preparing reports to be independent of the sponsor and clinical investigators. Of utmost importance is that the statistician be familiar with the protocol. You do not want a statistician preparing interim analyses who is simply running computer programs or who has not been an integral part of the thinking and planning of the study. Such an individual cannot do the job required. On a more practical note, I wonder if there are sufficient numbers of statisticians to afford the luxury of having one work with the Steering Committee of investigators and another work with the DSMB. I have no objection to the model you propose as long as the statistician preparing the DSMB interim analyses is very familiar with the protocol, the methods for data collection, and more generally the overall conduct of the trial. However, we have much more experience with the model in which the statistician works both with the

01D-0489

C9



investigative team and DSMB. We know that works and you should not discourage it. In fact, it might be considered the established control, based on NIH experience, to which other models should be compared.

Independence of the statistician performing interim analyses for the DSMB from the sponsor and independence of that statistician from the investigative team are two very different issues and they should be separated. I also disagree that independence of the sponsor is the desired approach. Some of my worst experiences as a DSMB member were receiving reports from "independent" groups on contract with the sponsor. I think that is a reasonable way to proceed for some trials where the contracted group has been intimately involved with the planning of the study and is responsible for its implementation and conduct. An equally good approach is for an informed and experienced statistician working for the sponsor to carry out the interim analyses. If the statistician working for the sponsor helped design the trial and worked with the investigative team to plan its implementation, this is the way I would want to do it because I would be more confident that the statistician working with the DSMB was informed and could do the job.

Related to the above, some guidance on internal blinding to sponsors who choose to have a statistician employee carry out the interim analyses would be helpful. These standard procedures will probably have to be different for blind and non-blind studies. More generally, what are your expectations with respect to standard internal operating procedures when the sponsor statistician carries out the interim analyses?

3. Page 13. A minor point, but many DSMBs do review individual adverse events. This can often be helpful in addition to the review of summary data. I think that both the review of individual cases and the review of summary data by treatment group are important components of ensuring patient safety in a trial. The DSMB has the advantage of reviewing the individual cases unblinded. In this section, I think you should say that this review of individual cases does not replace the regulatory responsibilities of the sponsor, which include filing safety reports in a timely way and submitting annual IND reports (both frequently blinded to treatment).
4. Page 18. I agree that, for industry sponsored trials, DSMBs should operate independent of those sponsoring, organizing, and conducting the trial. They should also operate independent of regulatory authorities and IRBs. Thus, it should be explicitly stated that it is generally inappropriate for regulatory agencies and IRBs to see confidential interim analyses until the trial has been completed.
5. An item missing from the document concerns interaction of DSMBs with IRBs. We have found it useful to prepare a brief letter following each scheduled DSMB review for investigators to share with their IRBs. For example, a statement that there were no differences in efficacy or safety outcomes that would lead the DSMB to recommend stopping or modifying the trial is helpful. In some studies we post a meeting summary with such a statement to a study web site for investigators to

download and send to their IRBs. Some recommendations along these lines might be useful in the guidance document. Also, some advice on how to respond to an IRB that request interim data might be helpful.

6. Another item missing is what constitutes open data (e.g., baseline data only, total number of events for all treatment groups combined, overall adherence or adherence to test treatment). This will necessarily differ for non-blind and blinded studies (i.e., in non-blind studies the sponsor can count how many patients assigned test treatment have died or experienced a serious adverse event). It may also vary depending on the outcome. For example, in a cardiovascular disease prevention trial of a lipid-lowering intervention with established efficacy for lowering cholesterol, the investigative team might be unblinded to the cholesterol lowering effects of the intervention in order to monitor adherence. In an earlier trial to establish the efficacy of the intervention for cholesterol lowering this would not be a good idea. I suspect some guidance on this point for sponsors would be helpful.

Thank you for the opportunity to provide comments on this important document. I believe it is generally well written and timely. My comments reflect the general view that you should be flexible on matters for which we do not have convincing data that one model is preferred (e.g., whether the statistician performing the interim analyses works for the sponsor and is independent of the investigative team), and you should be firm on matters that are more likely to threaten the integrity of the trial and the independence of the DSMB (e.g., sponsors, except statistician performing interim analyses, and regulatory oversight groups should remain blind to interim analyses until the trial is complete).

I hope you find the comments above helpful as you prepare the final document

Sincerely,

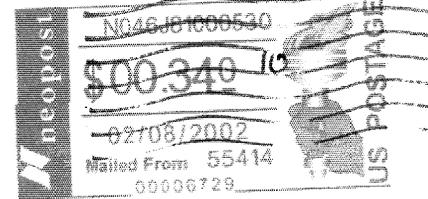
A handwritten signature in black ink, appearing to read 'J. Neaton', with a long horizontal flourish extending to the right.

James D. Neaton, Ph.D  
Professor of Biostatistics

**UNIVERSITY OF MINNESOTA**

*Twin Cities Campus*

**Community Programs for Clinical Research on AIDS**  
*Coordinating Centers for Biometric Research*  
*Division of Biostatistics*  
*School of Public Health*  
*Suite #200*  
*2221 University Avenue S.E.*  
*Minneapolis, MN 55414-3080*



DOCKETS MANAGEMENT BRANCH (HFA-305)  
FOOD AND DRUG ADMINISTRATION  
5630 FISHERS LANE  
ROOM 1061  
ROCKVILLE, MD 20852

20857+0001

