The George Washington University
WASHINGTON DC

THE BIOSTATISTICS CENTER
A RESEARCH FACILITY OF THE DEPARTMENT OF STATISTICS

December 3, 2001

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

RE: Docket No. 01D-0489, CBER 200130. *Federal Register*, Vol. 66 (November 20, 2001).

Dear FDA:

I am writing to strongly object to elements of, and to suggest clarifications to, the proposed "Guidance for Clinical Trial Sponsors On the Establishment of Clinical Trial Data Monitoring Committees," while generally supporting the effort to provide overall guidance.

Application to Publicly Sponsored Research:

Section 1.2 states:

> *The FDA believes that the issues discussed in this document arise in both industry- and government-sponsored trials, and therefore has not distinguished between them. We recognize that the potential conflicts of interest faced by government sponsors are somewhat different from those of industry sponsors, so that the implications for the approach to monitoring, particularly with regard to confidentiality and independence issues (see Section 4.2 and Section 6) may also differ to some extent. Nevertheless, we believe that the discussion of advantages and disadvantages of various approaches to DMC operation is relevant to all trials, regardless of the sector of the sponsor.*

I strongly disagree with the suggestion by implication that the standard approach to the conduct of data monitoring in clinical trials sponsored by the NIH and other government agencies, which is at variance with the FDA recommendations, should be changed. **I suggest that these sentences be deleted.**

The fundamental distinction between NIH and industry sponsored trials is that in the former those who organize and conduct the trial have no hidden financial interests, whereas in the latter the sponsor has inherent financial interests. Further, these financial conflicts of interest pose severe threats to the scientific validity of an industry-sponsored study in which interim data monitoring is conducted.

01D-0489 C1

6110 EXECUTIVE BOULEVARD • SUITE 750 • ROCKVILLE, MD 20852 • (301) 881-9260 • FAX (301) 881-3742

I am aware of situations in which alleged improprieties in the conduct of interim analyses in an industry-sponsored trial have lead FDA reviewers to questions of the validity of the study. Thus I agree with the need for safeguards in such analyses and with the general recommendation of the guidance for industry-sponsored trials. Over the past 6 years I have presented the following lectures at scientific meetings on this issue:

Lachin JM. "Interim analysis and Data-safety Monitoring Boards." *FDA/Industry Statistical Workshop: Statistical Issues for the New Millennium*, Crystal City, Virginia, 1999.

Lachin JM. "Design and interim monitoring of clinical trials." *Drug Information Association: Models for Launching and Coordinating Multi-Center Trials.* New Orleans, 1988.

Lachin JM. "Discussion: The Role of DSMBs and the Accumulating Evidence in the Conduct of Clinical Trials". *International Biometric Society, Eastern North American Region*, 1998.

Lachin JM. "Role of data and safety monitoring boards in phase 3 clinical trials." *Drug Information Association: Clinical Trials and Drug Development in Biotechnology*, Dana Point, CA, 1998. **(Complete text available from http://www.bsc.gwu.edu/bsc/staff/jlachin.html)**.

Lachin JM. "Experience and perspectives of the monitoring committee in NIH and industry sponsored trials." *Harvard University Shering-Plough workshop on "Flexible Strategies for Clinical Trials"*. Boston, 1996.

Lachin JM. "Some considerations in monitoring pharmaceutical trials." *International Biometric Society,* Eastern North American Region, 1995.

In each of the above presentations I have argued strongly for an independent statistician to conduct analyses for industry-sponsored Data Monitoring Committees, one of the principal recommendations in the FDA Guidance document.

However, I strongly disagree with the implication that this strategy should also be applied to NIH-sponsored studies. In an NIH-sponsored study the investigators are selected from among the academic community. Individuals who may hold a financial interest in the therapies under study are required to disclose such interests in any discussions. Usually individuals selected as members of a Data Monitoring Committee have no such financial interests. Further, the statistician and the coordinating center are selected from academic institutions. It is customary that the statistician participate both in the management of the study and in the conduct of the interim analyses for review by the DMC. This model for interim monitoring by a Data Monitoring Committee has been employed for every multi-center clinical trial conducted by the NIH over the past 40-50 years. *I am not aware of a single instance in which the participation of the academic statistician for the study in the conduct of interim monitoring has compromised the validity of a study.* Thus there is no

compelling justification for the FDA to generalize these recommendations to trials conducted by government, trials over which the FDA generally has no purview.

Many NIH-sponsored trials are studies of non-proprietary therapies, such as a lifestyle intervention. Others involve use of established agents, such as the study of ACE inhibition using captopril in diabetic nephropathy (Lewis, et al., *NEJM*, 1993), or the use of metformin as one of the therapies evaluated in the Diabetes Prevention Program (DPP Research Group, *NEJM*, 2001, to appear). In both instances, the compound had already been approved by the FDA for other primary indications, captopril as an anti-hypertensive, metformin as an anti-hyperglycemic agent. Our academic biostatistics center served as the coordinating center (statistical center) for these and other studies with funding from the NIH. Neither I nor other members of our staff held a financial interest in the sponsor of either compound and we did not have other substantial conflicts of interest. While such studies are conducted under an IND, and with some financial support from the manufacturer, the official *government* sponsor, and its *academic* partners, have no vested financial interests and have no vested interest in the outcome of the trial, whether it be positive or negative. **Thus I see no need to apply the proposed Guidance in such situations.**

Monitoring for Effectiveness:

The draft Guidance in general proposes that a Data Monitoring Committee be appointed to monitor both *effectiveness* and safety, whereas from my experience with industry the major need is to monitor for safety. While the two are the same in some instances, such as a study with total mortality, or cause-specific mortality, as a the primary outcome, in most trials they are not. Further, in most trials of a non-fatal morbidity, far more patients and patient-years of exposure are required to establish the profile of adverse events, than are required to establish effectiveness.

While the "ethical justification" for early disclosure of effectiveness applies to trials of unregulated therapies, such as a lifestyle modification, this does not apply to regulated therapies, such as pharmaceuticals. Most would agree with the statement (p. 14) "*all would wish that any major treatment advance be identified and made available as soon as possible.*" The problem, however, is that early closure of a study due to demonstration of effectiveness may preclude the ability to obtain an adequate *controlled* assessment of adverse events. If placebo double-masked controls are deemed justifiable for the assessment of effectiveness, they are no less justifiable for the assessment of adverse events.

I also question whether it is necessary for a DMC to monitor effectiveness and safety so as to assess a benefit-to-risk ratio. I feel that the principal role for a DMC in industry-sponsored trials is to monitor for safety, and that monitoring for effectiveness should be performed only when there is a clear intent to stop early for effectiveness considerations alone.

Later, in Section 4.4.1.5 for "Studies of Less Serious Outcomes," it is stated that the desirability "*of early stopping for efficacy or protocol modification is certainly less compelling...*" (p. 15). However, I would recommend a more definitive statement either in the

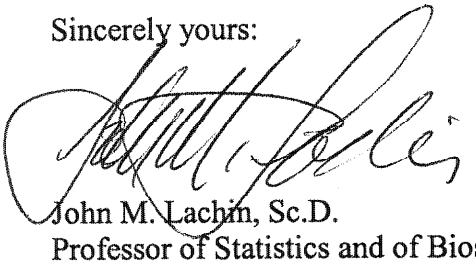
introduction to Section 4.4, or in Section 4.4.4.1 to the effect that in any trial, **interim monitoring for effectiveness should only be conducted when termination of the trial for effectiveness would be acceptable, at the expense of obtaining more definitive controlled assessments of adverse events and other outcomes.**

Some might argue that it is just as important to monitor for lack of effectiveness, or *futility*, as for the early demonstration of effectiveness. In some cases, sponsors have specified that a futility analysis be conducted when 50% of the information has been obtained, with no further interim examinations if the study is continued. However, established statistical procedures, such as stochastic curtailing based on conditional power, will in general require that at least 75% of the original planned study information be obtained before one could stop without substantial inflation of the probability of a type II error. Whether at 50% or 75%, to monitor for futility does not require regular interim monitoring for effectiveness at every meeting of the DMC. Thus in these cases I would recommend that **interim monitoring for futility should be conducted at a predefined landmark of information percent with explicit rules for continuation or termination.**

My overall recommendation is that in industry sponsored trials, it is preferable that monitoring for effectiveness should be kept to a minimum and should be implemented only in those instances where early termination for effectiveness (or futility) would not jeopardize the assessment of the other trial objectives.

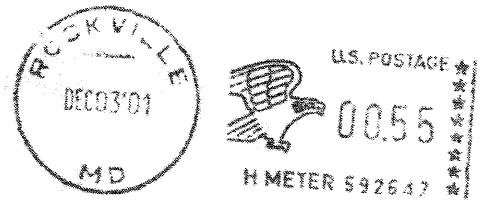
I applaud your effort to provide guidance on this important topic. Please feel free to contact me if I can provide any further comments.

Sincerely yours:



John M. Lachin, Sc.D.
Professor of Statistics and of Biostatistics
Graduate Program Director for Biostatistics
Former Director, the Biostatistics Center
Principal Investigator, Coordinating Center, Type 1 Diabetes TrialNet
Principal Investigator, Coordinating Center, Diabetes Control and Complications Trial and study of the Epidemiology of Diabetes Interventions and Complications
Co-Principal Investigator, Coordinating Center, Diabetes Prevention Program
The Biostatistics Center
The George Washington University
6110 Executive Blvd.
Rockville MD 20852

e-mail: jml@biostat.bsc.gwu.edu, home page:http://www.bsc.gwu.edu
Voice: (301)-816-8081
Fax: (301)-881-3742



THE GEORGE WASHINGTON UNIVERSITY
BIOSTATISTICS CENTER
6110 EXECUTIVE BLVD. SUITE 750
ROCKVILLE, MD 20852

TO: Docket Management Branch (HFA-305)
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, MD 20852