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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Data and Safety Monitoring Boards (DSMBs)

Monitoring means to watch, keep track of, or to check. Monitoring is part and parcel of trials. Obviously, James Lind in his trial involving twelve sailors "in the scurvy" on board the Salisbury in May 1747 monitored effects to observe *that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty*.[1]

There are two forms of monitoring; for compliance to the study protocol and for treatment effects. The two forms may be done together by the same person or as separate activities by different people.

Monitoring bodies go by various names, but DSMBs is the most common. The name has the advantage of covering both forms of monitoring; **data** for monitoring for compliance to the protocol and **safety** for monitoring for treatment effects.

Trials over time have been done by single investigators with them doing the monitoring. That changed with the advent of multicenter trials in the mid 1900s. The change meant monitoring was now a joint responsibility of the collective investigatorship represented in the trial.[2]

One of the first multicenter trials having documented formal treatment effects monitoring was the University Group Diabetes Program (UGDP); started in 1960 and finished in 1978. The UGDP had seven clinical centers (subsequently expanded to 12) and a coordinating center.

When started the trial involved four treatment groups, two insulin dosage schemes and tolbutamide (Orinase®) and a matching placebo. Expanded in 1962 to include phenformin (DBI-TD®) and a matching placebo.

The purpose was to determine if standard treatments for type-2 diabetes conferred benefit tested against control treatments in reducing morbidity associated with diabetes or mortality.

A few years into the trial it was obvious to investigators that they needed to monitor for treatment effects, but there were no guidelines or policy as to who should monitor, so they decided that the steering committee would do the monitoring. The steering committee was comprised of heads and deputy directors of the coordinating center and the 12 clinical centers for a total of 26 members.

In the summer of 1969 the steering committee voted to stop tolbutamide because of excess mortality and in 1971 voted to stop phenformin because of ineffectiveness and possible harm.[3,4,5,6]

The decision to entrust monitoring to the steering committee was criticized, principally by Tom Chalmers, then associate director of the National Institutes of Health (NIH) and Director of the NIH Clinical Center, because he regarded study investigators having conflicts of interest as monitors.

In 1967 the National Heart Institute (now the National Heart, Lung, and Blood Institute) commissioned Bernard Greenberg, then chair of biostatistics at University of North Carolina, to produce a document, ultimately entitled "Organization, Review, and Administration of Cooperative Studies" (1967; published 1988). The preamble read:

> *The National Heart Institute supports a number of complex cooperative studies, most of which have received initial review by the Heart Special Project Committee. The Committee believes that such studies can be an effective means, and in fact sometimes the only means, of resolving particularly pressing scientific problems. The costs in manpower and money are justified if, through a cooperative project, a definitive answer to a significant question can be obtained more expeditiously or accurately than through the traditional means of a solo investigator. The Heart Special Project Committee and the National Advisory Heart Council share a degree of concern regarding the impact of these long-term, usually costly projects on various segments of the scientific community. A discussion of their organization, review, and administration is all the more pertinent at the present time because of the increasing need for a sharper definition of research goals and opportunities in the cardiovascular field, and the present and possibly continuing shortage of funds coupled with a growing need to translate research progress into clinical practice. The Committee offers the comments that follow in the hope that they may be helpful in formulating guidelines for investigators, staff, and review panels, which can be used to attain maximal benefit from the coordinated utilization of talents and resources possible in a cooperative study.*[7]

The significance of the report is that it laid out a two tier system for review of monitoring reports. The first level involving combinations of study investigators and outsiders jointly appointed by the study chair and NIH. The second level review was done by a body appointed by the NIH and devoid of study investigators. Recommendations made in the first level of review may be rejected, accepted, or expanded in the second level review. The actions of the second review group were final, not subject to review.

The CDP (Coronary Drug Project; 1965-1985) had a two tier monitoring system akin to that outlined in the Greenberg report.[8] It was designed to assess several different treatments for coronary heart disease in men with previous myocardial infarctions. The trial had 53 clinical centers and the same coordinating center as in the UGDP.

In 1979 an NIH committee, chaired by Robert Gorden, recommended that:

1. *Every clinical trial should have provision for data and safety monitoring.*
2. *The mechanism(s) for data and safety monitoring should be presented to and approved by the Institutional Review Board as an integral part of its review of the project proposal. A variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the clinical trial. In many cases, the principal investigator would be expected to perform the monitoring function.*
3. *Large or multi-center trials, and trials in which the protocol requires blinding of the investigators, should have a data and safety monitoring unit. The unit should consist of clinicians expert in the disease under investigation, biostatisticians, and scientists from other pertinent disciplines. Physicians engaged in the care of study patients or directly responsible for evaluating clinical status are excluded.*[9]

In 1998 (June 10) in NIH Policy for Data and Safety Monitoring:
https://grants.nih.gov/grants/guide/notice-files/not98-084.html

> *It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).*[10]

From the outset, as seen with the UGDP, there has been concern of investigator bias influencing safety monitoring decisions. Though none of the policies cited, except the one by Gorden, do not

specifically exclude study investigator from safety monitoring, increasingly the trend is for data and safety monitoring to be done by persons having no connection to the study. The advantage is that the exclusion protects the study from criticisms of investigator bias influencing safety monitoring decisions. But the down side is that people who know the protocol and collection procedures best are excluded.

There is a communication process invoked for each DSMB monitoring session. The nodes in the communication chain involve sponsors, investigators, and IRBs.

IRBs expect to be informed after each DSMB monitoring session and of actions taken. That communication is typically done by the head of the coordinating center, by the chair of the study, or chair of the DSMB.

The other two nodes in the communication chair are usually addressed in letters to the sponsor and study investigators from the chair of the DSMB. If the recommendation is to continue as is, there may not be need for follow-on communication, but if the recommendation is to stop the trial or modify the protocol, there may be need for meetings with the sponsor and lead investigators to discuss the mechanics and logistics of the change.

Clearly, regardless who does safety monitoring, the norm is that it has to be done. So how does the clinical trials community stack up meeting its monitoring responsibility?

The closest we can get to an answer is by querying ClinicalTrials.gov by limiting the analysis to trials registered as multicenter and randomized and having a protocol posted. The good news is that the number of multicenter randomized trials has increased over time. The bad news is that only a fraction have protocols posted so no way to know about monitoring. (The drop in 2020 compared to 2015 may be due to the time difference needed for protocol development.)

In sum, the multicenter clinical trials community has a way to go in meeting its monitoring responsibilities.

Multicenter randomized trials registered on ClinicalTrials.gov

	Nos			%	
Yr registered	No. registered	Protocol posted	No posting	Protocol posted	No posting
2000	122	1	121	0.82%	99.18%
2005	696	4	692	0.57%	99.43%
2010	963	15	948	1.56%	98.44%
2015	1,227	279	948	22.74%	77.26%
2020	1,790	86	1,704	4.80%	95.20%

References

1 Lind J: *A Treatise of the Scurvy* (reprinted in *Lind's Treatise on Scurvy*, edited by CP Stewart, D Guthrie, Edinburgh University Press, Edinburgh, 1953). Sands, Murray, Cochran, Edinburgh, 1753.

2 Ellenberg S, Fleming TR, DeMetes DL: Data Monitoring Committee in Clinical Trials. John Wiley & Sons, 2002.

3 University Group Diabetes Program Research Group. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: I. Design, methods, and baseline characteristics. Diabetes 19, 1970 (suppl 2):747-783.

4 University Group Diabetes Program Research Group. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: II. Mortality results. Diabetes 19, 1970 (suppl 2):785-830.

5 University Group Diabetes Program Research Group (1975). A Study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: V. Evaluation of Phenformin therapy. Diabetes 24, 1975 (suppl 1):65-184.

6 Meinert C (2019). The trials and tribulations of the University Group Diabetes Program: lessons and reflections. JLL Bulletin: Commentaries on the history of treatment evaluation (https://www.jameslindlibrary.org/articles/the-trials-and-tribulations-of-the-university-group-diabetes-program-lessons-and-reflections)

7 Control Clin Trials. 1988 Jun;9(2):137-48. doi: 10.1016/0197-2456(88)90034-7. Organization, review, and administration of cooperative studies (Greenberg Report): A report from the Heart Special Project Committee to the National Advisory Heart Council, May 1967; PMID: 3396364 DOI: 10.1016/0197-2456(88)90034-7

8 Coronary Drug Project Research Group: The Coronary Drug Project: Design, methods, and baseline results. Circulation **1973**; 47(Suppl I):I-1-I-50.

9 National Institutes of Health: Clinical trials activity (NIH Clinical Trials Committee; RS Gordon Jr, Chair). NIH Guide Grants Contracts **5 June 1979**; 8 (# 8):29.

10 https://grants.nih.gov/grants/guide/notice-files/not98-084.html