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Memorandum

To: Trialists
Fr: Curtis Meinert
Re: A DSMB manifesto

I wrote previously on rules of conduct in trials (distributed 6 Feb 2019). This memo focuses on data and safety monitoring boards (DSMBs) in trials.

The birth of DSMBs traces to the University Group Diabetes Program (UGDP). The UGDP was a multicenter long-term secondary prevention trial; started in 1960 and ended in 1981. (See Ellenberg, Fleming, and DeMets, *Data Monitoring Committees in Clinical Trials: A Practical Perspective*, John Wiley & Sons, 2019, for an extensive work on DSMBs and the web for template charters for DSMBs.)

It was a given that someone in the trial had to monitor results for quality control and for treatment differences. It was clear that responsibility for monitoring fell to the coordinating center, but it was not clear who in the investigator group should see interim treatment results. Ultimately it was decided that the entire steering committee (comprised of the director and deputy director of each of the 12 clinics and the director and deputy director of the coordinating center) should see them. The practice was well established when a mortality trend against a study treatment, tolbutamide, began to emerge. At first the trend was just a matter of curiosity, but eventually led investigators to stop the treatment in mid 1969.

The fact that monitoring was done by the steering committee raised concerns of bias and conflicts of interest. Tom Chalmers, associate director of the NIH and Director of the NIH Clinical Center during the tolbutamide decision, was critical of the fact that investigators involved in the trial also monitored results to decide if treatments should continue. He regarded investigator involvement as constituting a conflict of interest.

The issue raised ultimately led the NIH to require separate monitoring bodies for multicenter trials it funds:

> *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 June 1998)*

The issue of who appoints DSMBs, who sits on them, and who they report to is left to the individual institutes and centers of the NIH and study investigators. Increasingly, the trend is for watertight separation of the board from study investigators and even for masking monitors to treatment assignment because of concerns of bias in the monitoring process.

If you look to published papers for answers to those questions, you will be disappointed. You will be hard pressed to even know the membership of the monitoring body, let alone who appointed it or to whom it reported.

The trend, at least for NIH, is for sponsors to own and operate DSMBs with a diminishing role for investigators. The trend is contrary to ethical obligations underlying trials and duties of investigators to the people they enroll and study in trials.

A **DSMB Manifesto**

Rule 1 Whereas DSMBs serve both the investigator group and sponsor, it behooves the sponsor and investigator group to create and appoint members of the DSMB with consent of both parties

Rule 2 The function of the DSMB is to serve in an advisory capacity to the investigator group and sponsor as to whether the trial should continue unaltered based on interim looks at treatment results and to provide advice, when requested by the investigator group or sponsor, on matters pertaining to performance of centers in the trial and on issues of design and protocol

Rule 3 Voting members of the DSMB should be selected so as to not have any affiliation with the study or sponsor and should be vetted so as to be free of conflicts of interest

Rule 4 The chair of the DSMB should be selected with the mutual consent of the investigator group and sponsor

Rule 5 DSMB members should be appointed for the duration of the trial

Rule 6 Nonvoting members representing the investigator group and sponsor should be designated when the DSMB is established

Rule 7 Nonvoting members representing the sponsor and investigator group should be seated at par one to the other

Rule 8 Recommendations of the DSMB regarding the trials are to be passed simultaneously to the study chair and director of the NIH center or institute by the chair of the DSMB

Rule 9 Recommendation for major protocol changes or early stops are to be passed with indication of the rationale underlying the recommendation and the number of votes for and against the recommendation

Rule 10 The study chair should be informed of any recommendation for changes to the treatment protocol

Rule 11 The chair of the study, study officers, and DSMB members should discuss logistics and procedures for implementing recommendations for stopping a trial or a treatment in the trial as a prelude to implementation

Rule 12 DSMB members should not be masked to treatment assignment

Comments

Rule 1 Investigators and sponsors have to have confidence in the DSMB. That is best achieved by a fair, open, and balanced process involving both shareholders for selecting and appointing members.

Rule 2 The charter should indicate that the DSMB is simultaneously advisory to the investigator group and sponsor, should indicate how recommendations will be passed, and the processes to be followed when the investigator group or sponsor disagreed with a recommendation.

Rule 3 The rule is essential for avoiding real or perceived conflicts of interest.

Rule 4 The chair should be acceptable to both parties and be vetted by both parties.

Rule 5 The rule is designed to maintain continuity in the monitoring process. There may be replacements due to deaths or resignations, but members are appointed for the life of the trial.

Rule 6 Operationally, DSMBs are comprised of voting and nonvoting members. Nonvoting members associated with the sponsor and investigator group should be specified when the DSMB is created.

A key issue is whether to seat the chair of the study. That is generally precluded if the chair is involved in treating people in the trial but not otherwise. The advantage in seating the chair is in what the chair brings in understanding of the treatment protocol and data collection procedures in the trial. Inclusion generally means a more informed and competent monitor process.

The board cannot function without people from the coordinating center responsible for producing monitoring reports; typically the director of the coordinating center and serveral support staff.

The sponsor is generally represented by a single person, typically the study project officer.

Rule 7 The point of the rule is to ensure equity of status among nonvoting members. For example, if nonvoting members are excluded from executive sessions of the board, all nonvoting members should be excluded, not just some.

Rule 8 Processes in which recommendations are passed to the sponsor and then to the investigator group leave open possibilities for delays in passage or withholding recommendations considered unwise or unwarranted by the sponsor. That possibility is precluded when the DSMB reports simultaneously to the sponsor and investigator group.

Rule 9 Recommendations should be passed with indication of the nature and extent of deliberations underlying the recommendations, whether the deliberations were face-to-face or via conference phone, the number of persons voting, and the number of votes for or against the recommendation.

Rule 10 The rule applies to any change including those involving changes mandated in Bayesian adaptative designs. The linkage to the principal study investigator is necessary because that person is accountable to persons enrolled and studied in the trial and to IRBs.

Rule 11 Any recommendation to stop a trial or a treatment in a trial requires extensive discussion before implementation. Issues that have to be discussed include:

How persons in the trial are to be informed of the stop;
What persons enrolled are told about results;
What persons are told about future care and treatment;
The cutoff date for data collection:
How results relating to the stop will be communicated to the public and scientific community;
Publication plan;

and

IRB review of closeout procedures prior to implementation.

The issue of communication of the decision is complicated if it involves a product of a publicly traded company. If not carefully controlled and orchestrated it can lead to insider trading and criminal charges.

Rule 12 Masking reduces competency in the monitoring process by virtue of denying DSMB members access to the most important variable in the monitoring process – treatment assignment. The masking reduces capability of members to explore, query, and understand treatment results. In no case should masking be imposed without knowledge of the study chair's IRB.