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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: DSMBs

A number of us were treated to a rich discussion of issues in data monitoring on Easter Sunday, triggered by Marc Buyes and his email: Sun 4/12/2020; 8:27 AM:

> **One year ago I asked your opinion about an IDMC that I was a member of, as the IDMC wanted to get efficacy data against the Sponsor's will. At the time, you responded unanimously that IDMCs should indeed see efficacy data if they so wished, regardless of formal interim analysis plans. Your advice was greatly reassuring, and the IDMC fought to get complete efficacy data at their next meeting, which took place last week. I am happy to report that the trial will be unblinded as a result, as announced by the company the following day: https://www.astrazeneca.com/media-centre/press-releases/2020/tagrisso-phase-iii-adaura-trial-will-be-unblinded-early-after-overwhelming-efficacy-in-the-adjuvant-treatment-of-patients-with-egfr-mutated-lung-cancer.html.**

The note generated multiple responses and several DSMB "war stories".

The discussion caused me to review and revise a manifesto I wrote on DSMBs and posted to my website 13 February 2019.

The reality is that the function of DSMBs is not well understood by investigators or IRBs. If it was they would pay more attention to how monitoring committees are formed and rules under which they operate.

Data and Safety Monitoring Board Manifesto

Preamble

Data and Safety Monitoring Boards (DSMBs) go by various names, with board or committee as the base term and with or without "Safety" and the modifier, I, for Independent, e.g., as in IDSMB or IDMC. But regardless, their function is the same: To review accumulating data during a trial to advise sponsors and investigators as to whether to continue the trial unaltered.

DSMBs were born of concern that investigators in the University Group Diabetes Program (1960 - 1978) did safety monitoring; seen by some as constituting a conflict of interest; notably Tom Chalmers, then associate director of the National Institutes of Health and Director of the NIH Clinical Center. Those concerns led to the first standalone monitoring committee (Coronary Drug Project; 1965 - 1975) comprised of study investigators, representatives from the NIH sponsoring agency, and outsiders.

Early on data monitoring and whether or how done was left largely to study investigators but that changed for NIH-funded trials with the announcement (10 June 1998):

> *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).

Now DSMBs are standard fixtures in *multi-site clinical trials involving interventions that entail potential risk to the participants* and generally required by IRBs regardless of how trials are funded. Increasingly, they are created having watertight separation from investigators and with sponsors in control with rights to dictate what and how they monitor, creating their own conflicts of interest.

The reality is that DSMBs are jointly responsible to the study investigators and sponsoring agency. The manifesto that fellows is written to help ensure equity in the balance of responsibilities investigators have doing trials and those of agencies funding trials.

For a full discussion of data monitoring committees see *Data Monitoring Committees in Clinical Trials: A Practical Perspective*, 2nd ed. (2019; John Wiley and Sons), Susan S. Ellenberg, Thomas R. Fleming, and David L. DeMets.

Manifesto

Rule 1 Whereas DSMBs serve both investigator groups and sponsors, it behooves sponsors and investigator groups to appoint members of DSMBs with advice and consent of both parties
Comment: Investigators and sponsors have to have confidence in the DSMB; best achieved by a fair, open, and balanced process involving both shareholders jointly selecting and appointing members.

Rule 2 Once appointed DSMB members may not be individually or en masse dismissed without mutual consent of sponsor and study leaders
Comment: Purpose to prevent unilateral action by DSMB appointing authorities.

Rule 3 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 or on issues of design and protocol
Comment: The charter should indicate that the DSMB is simultaneously advisory to the investigator group and sponsor, should indicate how recommendations will be passed to both, and the processes to be followed when the investigator group or sponsor disagree with a DSMB recommendation.

Rule 4 The DSMB should not be constrained in what it may look at in performing its monitoring function
Comment: Monitoring is not an exact science. The DSMB has to be able to look at what they deem necessary to meet their responsibilities, whether it be for safety or efficacy. Sponsors, especially those with proprietary interests in products being tested, tend to distinguish between looks focused on safety versus those for efficacy, but they are on the same continuum. A stop for safety is no different then a stop for benefit in terms of benefits to people studied.

Rule 5 When the DSMB is formed, the sponsor, investigator leadership, and DSMB membership should agree on when looks are done and on what looks will entail
Comment: There should be dialog before the start of monitoring to agree on voting and nonvoting membership on the DSMB, who will present analyses to the DSMB, on the frequency of looks, and on how communications to the sponsor and study chair will proceed following reviews.

Rule 6 Voting members of the DSMB should be selected so as to not have affiliation with the study or sponsor and should be vetted to be free of conflicts of interest
Comment: The rule is essential for avoiding real or perceived conflicts of interest.

Rule 7 Statements presented to members of the DSMB by either the investigator group or sponsor for signature intended to constrain or instruct members as to how they exercise their duty should be subject to review and approval by the other party and the IRB of the study chair before execution
Comment: IRBs have duties to ensure that the monitoring process is not constrained or encumbered by agreements DSMB members sign before or after being seated.

Rule 8 The chair of the DSMB should be appointed with the mutual consent of the investigator group and sponsor

Rule 9 DSMB members should be appointed for the duration of the trial
Comment: 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 10 Nonvoting members seated on the DSMB should be identified when the DSMB is established
Comment: Operationally, DSMBs are comprised of voting and nonvoting members. Nonvoting members associated with the sponsor or investigator group should be specified when the DSMB is created.

A key issue is whether to seat the chair of the study. The advantage in doing so is in what the chair brings in understanding the treatment protocol and data collection procedures in the trial. Inclusion generally means a more informed and competent monitoring process. If seated, usually without vote.

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

The sponsor, if represented, is generally represented by a single person without vote.

Rule 11 Nonvoting members representing the sponsor and investigator group should be seated at par one to the other
Comment: 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 12 Recommendations of the DSMB regarding the trial should be passed simultaneously to the study chair and sponsor by the chair of the DSMB
Comment: Processes in which recommendations are passed to the sponsor and then to the investigator group via the sponsor leaves 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 13 The parent IRB of the trial should be informed of monitoring meetings of the DSMB within 30 days of happening and of their recommendations regarding the trial
Comment: Essential for completing the link between investigators and IRBs. Absent reporting there is no way for IRBs to know the nature and extent of monitoring or even if changes to the protocol have been recommended.

Rule 14 Recommendation for major protocol changes or early stops should be passed by the chair of the DSMB simultaneously to the sponsor and study chair with indication of underlying rationale and number of votes for and against the recommendation
Comment: Recommendations should be passed with indication of the nature and extent of deliberations underlying 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 recommendations.

Rule 15 DSMB members should not be masked to treatment assignment
Comment: 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 and approval of the chair's IRB.