



Center for Clinical Trials

Department of Biostatistics
Department of Epidemiology
Department of International Health

Department of Medicine
Department of Ophthalmology
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Friday, 18 January 2002

Memorandum

To: Mary Foulkes (CBER), Robert Temple (CDER), Joanne Lee^{SS} (CDRH)

Fr: Curtis Meinert

Re: Comments on Draft guidance for clinical trial sponsors on establishment and operation of clinical trial data monitoring committees

I am writing to comment on the above cited document (fr www.fda.gov/cber/gdlns/clindatmon.htm; 6 Dec 2001).

On the name, DMC

The name, *Data Monitoring Committee*, is not as informative as *Treatment Effects Monitoring Committee* or *Data and Safety Monitoring Committee*. In any case, the document should include a list of common synonyms including:

- Data and Safety Monitoring Committee (DSMC) or Board (DSMB)
- Safety Monitoring Committee (SMC) or Board (SMB)
- Treatment Effects Monitoring Committee (TEMC) or Board (TEMB)

Definition of sponsor

Largely, the implication is that the sponsoring agency is also the holder of the IND and that the agency has a proprietary interest in the drug. In reality, however, there are a fair number of large-scale phase 3 and phase 4 trials that are funded by the NIH and where the holder of the IND is a study investigator. The guidance should include a definition of sponsor.

On history of DMCs

The list in Section 1.1 should include a bullet citing awareness of investigators of the need for monitoring and demands by IRBs as impetus for DMCs.

On risks to study participants

The discussion in Section 2.1 (*Risk to trial participants*) should be refocused to indicate that the purpose of monitoring is to minimize the risk of harm and the risk of "unnecessary study" (from continuing a trial when results are sufficient to answer the question or when it cannot be answered by the trial).

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The focus is on safety and the possibility of direct harm accruing from use of a given study treatment. The concept of harm should be expanded to include the form that comes from continuing to assign persons to treatment when results are sufficient to show that it is inferior to another of the study treatments in the trial.

On determining need for a DMC

The discussion in the opening paragraph of Chapter 2 is noncommittal. The operative mind set should be that sponsors and investigators should assume the need for monitoring and that IRBs should require monitoring unless they are satisfied that the absence of monitoring does not place persons at increased risk of harm or of "unnecessary study".

On the relationship of the DMC to study investigators

The language in the guidance should be rewritten to ensure linkage of the DMC to investigators. The linkage is ensured when the monitoring body is commissioned to report to study investigators. When the body is commissioned to report to the sponsor, the sponsor should be required to provide written assurance that recommendations for change will be passed to study investigators in a timely and forthright manner regardless of whether or not the change is endorsed by the sponsor.

On appointment of the DMC chair

The statement that "the study sponsor usually appoints the DMC chair" (Section 4.1) is not correct across the expanse of trials. It is not evident that it is even true for the subset of trials funded by drug companies. In the 25 industry-sponsored trials with DMCs (work of Antariksha Kiri in a doctoral dissertation entitled *Treatment effects monitoring committees in clinical trials*; March 2000) only 3 reported appointment of members by the sponsor (10 with appointment by study investigators and 12 with appointment being the joint responsibility of the sponsor and investigators).

On coded DMC reports

The message of Section 4.3.1.4 (*Format of interim reports to the DMC and use of treatment codes*) is mixed. The 2nd paragraph gives arguments as to why masked monitoring is not rational and the 3rd paragraph suggests that reports should be masked.

There are reasons to question the wisdom of masked monitoring (*NEJM* 338:1,381-82, 1998). The guidance should be written to be less proscriptive with regard to masking.

On stopping rules and guidelines

The guidance is written from a frequentist perspective with emphasis on the desirability of preserving type I error by restricting looks. The revised guidance should recognize that there are other perspectives and that such restriction may not be in the best interests of patients.

On use of external data from other studies

One can argue that DMCs have a duty to consider all relevant data pertinent to a trial, hence, the *may* in the first sentence of Section 4.4.1.4 (*Consideration of external data*) should be changed to *should*. DMCs should have access to the results of ongoing sister trials being done by

the sponsor – especially when the trial in question is small and when results are suggestive of harm. The guidance should be more explicit in encouraging real-time meta-analyses of sister trials.

On who should prepare DMC reports

The guidance should be rewritten to recognize the need for wider input in preparation of monitoring reports than represented in the current draft. The notion conveyed is that monitoring reports are prepared by a single person ("the statistician"; Section 4.3.1.4) and suggests that the "ideal" is for that person to be isolated from the investigators and management of the trial. The admonishment (Section 6.4) that "the statistician should have no responsibility for the management of the trial and should have minimal contact with those who have such involvement" is unwise because it conveys the erroneous impression that the task is simply statistical in nature and that it can be done reliably and competently by people disconnected from the trial. The isolation has the potential of degrading the protective value of monitoring.

In any case, the notion that those preparing the report "should ideally be independent of the sponsor and clinical investigators (and a Steering Committee if there is one)" is predicated on the presumption that such persons do not have investigator status in the trial. That presumption is false in most multicenter trials with independent coordinating centers.

On linkage of the DMC to study investigators

The emphasis in the opening sentence in Section 4.4.3.1 (*Making recommendations*) is misplaced. DMCs exist for the protection of persons from harm and, hence, are first and foremost advisory to investigators and secondarily to sponsors. The present version of the guidance makes communication with investigators appear to be an afterthought. It should be revised to make it clear that the monitoring has to be inviolately linked to study investigators.

On objectivity vs competence

The discussion in Chapter 4 should include a caution that objectivity constructs such as masking, constraints on what may be looked at or on the number of looks can reduce competency and that they should not be imposed at the expense of competency.

On isolation of the DMC from the sponsor and on independence of the DMC

The guidance should present a more balanced view of the pros and cons of isolation of the sponsor from the DMC. Chapter 6 (*Independence of the DMC*) conveys the impression that independence and isolation are synonymous. Congress is an independent branch of government but it does not conduct its business in isolation from the other branches of government. It is by no means obvious why such isolation adds to the protective value of monitoring.

The revised document should include some of the major disadvantages of isolation including the prospect of reduced competency in interpretation and analysis of data and clumsy logistics in implementing recommendations for change.

On independence of the funding agency and the data center

There are various allusions to the desirability of separation of those who prepare monitoring reports from the sponsor. One can argue that responsibilities for receiving and processing data in trials should be vested in centers that are independent of sponsors, public or

private. The revised guidance should include a discussion of the virtues of independent data centers.

On balance of interests

The focus in the guidance is on achieving iron-clad objectivity by exclusion of investigators and sponsors because of their "conflicts of interest" without any regard for other conflicts, including those of the FDA in its desire for unassailable objectivity. The guidance should be less proscriptive, especially in regard to representatives of sponsors as nonvoting members of the DMCs. The proscription on such representation is at odds with constructs for monitoring many of the NIH-sponsored trials.

Distribution

Curtis Meinert
FDA draft on DMCs
Chronologic file