Chapter 21
Data Safety Monitoring (DSM)

The USC IRBs follow the Department of Health and Human Services (HHS) and the U.S. Food & Drug Administration (FDA) regulations regarding the monitoring of research for the safety of human subjects. This chapter describes situations in which a plan for the monitoring of research is required, the roles of Data Safety Monitoring Boards (DSMB) and the relationship between DSMBs and IRBs.

21.1 Data Safety Monitoring (DSM)

The IRB criteria for approval, as listed in the FDA and OHRP regulations, requires in part that "when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects" 45 CFR 46.111[a][6], 21 CFR 56.111[a][6]. The IRB is responsible for determining when a study needs ongoing monitoring by a data safety monitoring (DSM) plan or the establishment of a data safety monitoring board to ensure protection for research subjects. However, the USC IRBs do not act as data safety monitoring boards.

The regulations do not discuss data and safety monitoring committees or boards. However, in 1998, the NIH created a requirement for data and safety monitoring boards for some of the studies it funds. 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). The NIH Policy for Data and Safety Monitoring is available at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The FDA has created guidance for the establishment and operation of clinical trial data monitoring committees. This policy highlights the FDA guidance. To review the FDA guidance in its entirety, visit the website at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

Every clinical trial conducted at USC must include a plan for data and safety monitoring. Specific plans should be based on:

- The amount of risk involved for participating subjects
- The size and complexity of the clinical trial
- The nature of the investigational agent

- The study sponsor requirements
- The phase of the clinical trial

DSM plans may be required for non-clinical trials and for studies involving more than minimal risk as determined by the IRB.

During the initial IRB approval process and annual review, the IRB will review all proposed protocols for scientific relevance, protocol completeness, and the presence of an appropriate DSM plan.

Investigators will develop a DSM plan based upon the characteristics of the individual study. Investigators must describe how the study will be monitored for the safety of subjects and for the validity and integrity of the data. Sponsor-investigators who act as both the investigator and the study sponsor for drug/biologic/device studies must perform the sponsor data safety monitoring requirements from FDA, HHS, and the funding agency.

Appointment of a Research Monitor for Department of Defense (DOD) Sponsored Research

The following pertain to the appointment of a research monitor for DOD-sponsored research:

- Required for research involving greater than minimal risk, although IRBs can require a research monitor for a portion of the project or for studies involving no more than minimal risk studies if appropriate
- The independent research monitor must be appointed by name
- The research monitor has the authority to:
    - Stop a research study in progress
    - Remove individuals from study
    - Observe group recruitment
    - Take whatever steps are necessary to protect the safety and well-being of participants

21.2 Data Safety Monitoring Board (DSMB)

A DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if continuing the study is scientifically and ethically appropriate. DSMB's are also known as Data Monitoring Committees (DMCs) or Data and Safety Monitoring Committees (DSMCs).

Factors that Suggest a DSMB Is Needed

- A large study population
- Multiple study sites (it is more difficult to recognize a pattern of increased or unusual problems when one site enrolls only a small percentage of the study population)
- The study is blinded
- The study employs high-risk interventions that may include highly toxic therapies or dangerous procedures, expected high rates of morbidity or mortality in the study population, or high chance of early termination of the study
- The study includes vulnerable populations, such as minors, prisoners, and/or pregnant women

FDA Guidance on Data and Safety Monitoring Boards, Committees, and Plans

FDA regulations (21 CFR 56) specifically require a Data Monitoring Committee (DMC) only for research conducted in emergency settings with an exception from informed consent requirements (21 CFR 50.24). However, all clinical trials require safety monitoring, and sponsors of trials evaluating new drugs, biologics, and devices are required to ensure proper monitoring of the trial.

FDA guidance defines a DMC as a group of individuals with pertinent expertise that regularly reviews accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of study subjects as well as the continuing validity and scientific merit of the trial. The FDA recommends that sponsors establish a DMC in studies where safety concerns may be unusually high, such as when:

- There are *a priori* reasons for a particular safety concern; for example, the procedure for administering the treatment is particularly invasive
- There is prior information suggesting the possibility of serious toxicity with the study treatment
- The study is being performed in a potentially fragile population such as children, pregnant women, the elderly, or other vulnerable populations such as those who are terminally ill or of diminished mental capacity
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint
- The study is large, of long duration, and multi-center
- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion

Data Monitoring Committee for Investigator-Initiated Research

The FDA recommends that when the investigator is also the product manufacturer or IND/IDE sponsor and thereby subject to potentially strong influences related to financial and/or intellectual incentives, a DMC would provide additional, independent oversight that would enhance safety of study subjects and the credibility of the product development. DMCs should be considered in such settings.

IRBs and DMCs

In order to determine that risks are being minimized "by using procedures that are consistent with sound research design", the IRB may appropriately ask for information about the approach to trial monitoring, including the statistical basis for early termination (when relevant) and what steps the sponsor is taking to minimize risks to subjects.

Since multi-site clinical trials generally have many IRBs and only one DMC, the DMC often has more information about the data, including interim efficacy and safety data than any single IRB. IRBs may want to appropriately take advantage of this situation and request information about the latest meeting and recommendations from the DMCs, even when those reports and recommendations show that no problems have been identified.

DMC Charters

DMCs typically operate under a written charter that includes their operating procedures. These procedures generally include the schedule and format of meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DMC meetings, procedures for assessing conflicts of interest of the DMC members, the method of providing interim reports to the DMC, and other issues relevant to committee operations.

Frequency of DMC meetings may depend on the expected rate of accrual and event occurrence at the time the trial is designed as well as the perceived risk of the experimental or control interventions. Annual meetings maybe adequate for some studies; other trials will require more frequent review. The study protocol will generally describe the schedule of interim analyses or other considerations that will determine meetings.

The IRB may ask for the DMC charter during initial review of the study.

Independence of the DMC

Independence of the DMC will depend upon the relations of its members to those sponsoring, organizing, conducting, and regulating the trial. Independence is greatest when members have no involvement in the design and/or conduct of the trial except through their role on the DMC, and have no financial or other important connection to the sponsor (other than compensation for serving on the DMC). However, DMCs are rarely totally independent since the sponsor usually selects members, gives them their charge, and pays them for their services.

21.3 The Relationship between DSMBs and IRBs

The National Institutes of Health (NIH) explicitly identifies required communication that must occur between DSMBs and IRBs when multicenter trials are supported by the NIH (see policy at http://grants.nih.gov/grants/guide/notice-files/not99-107.html). Generally, the DSMB provides feedback at regular and defined intervals to IRBs. After each meeting of the DSMB, the DSMB Executive Secretary or Chair should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB members' review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform study investigators of

the DSMB members' conclusions with respect to progress or need for modification of the protocol. Investigators are required to transmit the report to their local IRBs.

For studies sponsored by National Cancer Institute (NCI) see safety monitoring guidelines, visit: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines.

Chapter 22:

Complaints Regarding Human Subjects Research

Chapter Contents

22.1 – Handling Complaints Regarding Human Subjects Research