

Data Safety Monitoring Board Information, Guidance and Procedures

UTGSM Institutional Review Board

Data Safety Monitoring Background & Overview

A clinical trial depends upon a relationship between research participants and investigators; each must fulfill certain obligations for the effort to succeed. A clinical trial also relies upon a partnership between investigator and institution/sponsor; together they must ensure proper monitoring and conduct of the clinical trial, in accordance with applicable regulations and Good Clinical Practice (GCP).

To ensure the safety of research participants, federal regulations require provisions to monitor data collected in the course of a research study, where appropriate (see 45 CFR 46.111(a)(6); 21 CFR 56.111(a)(6)). Data and safety monitoring aims both to protect participants and ensure the integrity and validity of research data. All studies involving human subjects require some level of data and safety monitoring. This includes physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); and efficacy, effectiveness, and comparative trials (phase III). The specific monitoring strategy will depend on the risk, size, and scope of the study, and may involve individuals or groups.

The method and level of monitoring should be commensurate with the degree of risk to subjects and the size and complexity of the study. Generally, minimal risk studies may only require a Data and Safety Monitoring Plan (DSMP) which outlines limited monitoring by the principal investigator (PI) at regular intervals. Higher-risk studies require more frequent monitoring, including outside monitoring. Outside monitors can include an independent safety officer, a sponsor-appointed monitoring committee or board, or an outside independent group of experts (often referred to as a Data Safety Monitoring Board (DSMB), or a Data Monitoring Committee (DMC)), which conducts interim monitoring, analysis, and oversight.

The PI must protect participants' health and safety, inform participants of information related to their continued participation, and pursue the research objectives with scientific diligence. The Food and Drug Administration (FDA) holds the PI responsible for the overall conduct of a research study, including the establishment of data and safety monitoring provisions (see regulation 21 CFR 312.60). The PI is responsible for developing DSMP before the study is initiated.

Data Safety Monitoring Board Definition

A DSMB is made up of members from a variety of disciplines who are knowledgeable about, and responsible for, the conduct of research. Membership must include representatives with backgrounds in biostatistics, experimental design, bioethics, and the medical field(s) of concern.

DSMBs are responsible for reviewing data and endpoints on a timeline set forth by the Data Safety Monitoring Plan in the IRB approved protocol. DSMBs are typically required for the following:

1. Studies that pose greater than minimal risk
2. Blinded studies
3. Studies involving a vulnerable population (e.g., pediatric, geriatric, cognitively impaired)
4. Studies involving new therapies or science
5. Studies involving highly toxic therapies or dangerous procedures
6. Studies involving high expected rates of morbidity or mortality in the study population
7. Studies involving a high chance of early termination
8. Multi-site studies—It is more difficult for an investigator to recognize a pattern of increased or unusual problems when he or she sees only a small fraction of study participants

DSMB RESPONSIBILITIES

- review the research protocol, informed consent documents and plans for data safety and monitoring to evaluate adequacy related to participant safety;
- develop a DSMB Charter from the DSMP
- evaluate the progress the study including, as applicable, periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- consider factors external to the study when relevant information, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review clinical center performance, make recommendations and assist in the resolution of problems
- protect the safety of the study participants;
- report on the safety and scientific progress of the study;
- make recommendations to the IRB, applicable Institutional Officials and the principal investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, conduct interim analysis of efficacy in accordance with stopping guidelines which are clearly defined in advance of data analysis and have been approved by the DSMB;
- ensure the confidentiality of the trial data and the results of monitoring; and,
- assist the UTGSM IRB by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

DSMB MEMBERS AND COMPOSITION

- The principal investigator may independently appoint members to the DSMB, and if requested, institutional leadership may appoint DSMB members at their institution;
- Board membership should be determined and described prior to submitting a project for human subjects review.
- Investigators are encouraged to consider appointment of individuals from different units or divisions from within their institution, and beyond, with a majority being external to the institution;
- The Board should include three to seven members in total (always an odd number);
- All members should have experience in the conduct of human subjects research;
- All members should have independence from the direct management of the research study, the absence of conflict of interest, financial, personal or professional.
- One member should have an extensive background in biostatistics;
- At least one member should have prior experience on a DSMB;
- One member should be appointed as chairperson and will be responsible for overseeing the meetings, developing the agenda, summarizing the meeting and being the DSMB contact person.

DSMB CHARTER GUIDANCE

A DSMB charter is a written policy that describes the roles, rules, and functioning of the DSMB. The charter is intended to be a living document that members may review at any time to determine whether changes in procedure are necessary.

Generally, a charter will include:

- The purpose of the DSMB;
- Responsibilities of the members;
- The operation and format of the DSMB meetings;
- Monitoring guidelines;
- Reporting processes (to and from the DSMB, as applicable);
- Research data to be monitored, and how data will be provided; and
- The responsibilities of the DSMB administrator.

DSMB MEETING PROCEDURAL GUIDANCE

1. Timing and Frequency of Meetings

DSMB meetings will take place at least annually. The board may choose to meet periodically (e.g., quarterly or semiannually) if the risk to the subject is high, the population is vulnerable, there is a large volume of data to review, and/or after a pre-determined number of subjects have accrued. The chair may also call ad hoc meetings depending on safety or efficacy concerns. Meetings may be conducted by teleconference at the request of the board members.

2. Meeting Agenda Outline

- The board will review required data (determined at the pre-enrollment meeting) provided by the investigator.
- As per the DSMP, The board will:
 - a. Determine if the study has adhered to the treatment plan
 - b. Review interim analysis, if applicable, and determine specific data to be analyzed
 - c. Evaluate end point/stop point rules
 - d. Review protocol violations and deviations to assess adequacy of the protocol
 - e. Ensure appropriate documentation of informed consent
 - f. Review current enrollment information to:
 - (1) Determine whether enrollment has followed eligibility criteria
 - (2) Ensure accrual is on target
 - (3) Assess visit compliance
 - (4) Review screening failure information
 - g. Review IND/IDE information
 - h. Discuss investigator or key personnel changes
 - i. Review completeness and quality of data collection forms
 - j. Evaluate the aggregate analysis of adverse events/serious adverse events
 - k. Review vital signs, clinical tests, etc.
 - l. Review confidentiality

3. Meeting Outcomes

The major outcomes following data review include:

- *Continuation* of the trial, unchanged

- *Modification* of the protocol and/or consent form (for example, it may be unethical to continue giving a placebo after a new treatment has been proven to be effective, or to continue a new treatment when there is no chance the trials will be positive)
- *Termination* of the trial

4. Minutes and Reporting

Minutes from each meeting will be maintained. The investigator should not be present for at least part of the meeting. Following the meeting, a report should be provided to the investigator, the IRB, the sponsor, and if necessary, study participants. The report should indicate whether the study should continue as originally designed, be modified to protect patient safety, or be terminated.

Adapted from “Harvard Catalyst-The Clinical and Translation Science Center, Regulatory Foundations, Ethics, and Law Program - Data Safety and Monitoring Guidance” updated March 15, 2018 and “Planning for Data and Safety Monitoring in Clinical Research Studies: Developing your Study-Specific DSMP,” in Boston University Medical Center’s *Clinical Research Times*, November 2006 issue.