

Data Safety Monitoring Plans and Data Safety Monitoring Boards

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What is a DSMP?

A Data Safety Monitoring Plan (DSMP) describes how the Principal Investigator (PI) plans to oversee the human subject's safety and welfare. The Emory Policies and Procedures require a DSMP for all research that is not exempt under Federal regulations applicable to Human Subjects Research. The level of detail in the plan should be based upon the degree of risk to the subjects. The intensity and frequency of monitoring should be tailored to fit the expected risk level, complexity, and size of the particular study. Review of safety reports and trial data by a Data Safety Monitoring Board (DSMB) or medical monitor may be part of a DSMP, but it is not the entire DSMP.

What are the essential elements of the DSMP?

The plan should describe processes for dealing with the following, as applicable:

1. Monitoring the Progress and Safety of the Trial
 - a. Assessment of potential risks for study participants, including the screening process and how it will be used to protect participants
 - b. Measures to protect participants against risk
 - c. Site monitoring plan for data quality, including the type of information that will be reviewed, the parameters for defining abnormal values, and review periods
 - d. Stopping rules for the study, as appropriate
 - e. Any specific procedures that are in place for activities such as monitoring and reporting in multi-site trials
 - f. Plan to manage potential Conflicts of Interest
2. Reporting of Unanticipated Problems (UPs)
 - a. Define what events will constitute a UP (include a definition, grading scale, and "study relatedness" criteria).

- b. Define the process for assessing and timeline for reporting of potential UPs.
3. Reporting of Suspensions or Terminations
 - a. Define the actions (FDA, Sponsor, IRB, etc.) that will be reported and who will bear the responsibility for reporting.
4. Assuring Data Accuracy and Protocol Compliance
 - a. Define how data accuracy and protocol compliance will be assured. (i.e., protocol compliance checks, external data-audits, regular data verification, etc.).
 - b. Define reporting obligations for protocol deviations/violations and noncompliance.

Examples of DSMP elements:

The monitoring plan should describe the monitoring methods, responsibilities, and requirements for the trial and should specify the following elements:

- Frequency of reviews.
 - Example: Review after the first three subjects are enrolled. At a minimum, review is required annually.
- Identity of site monitor.
 - Example: Specify position of person who will monitor or name CRO to which monitoring has been delegated.
- Scope of site monitoring.
 - Example: Informed consent process, eligibility, CRFs, AE reporting
- Number of records reviewed.
 - Example: 10% or 2 of the first 5 subjects enrolled
- Plan for evaluating and documenting findings/observations.
 - Example: a monitoring report will be provided to the S-I within 5 days of review.
- Follow-up process.
 - Example: PI will document receipt & review of the monitoring report, resolutions and/or corrective actions to findings on the Site Monitoring Log; PI will notify IRB according to P&P

The monitoring plan for a minimal risk study should address the following elements:

- Oversight
 - Example: Oversight of the progress and safety of the trial will be provided by the PI. Adverse events are not anticipated, but any occurring will be documented and reported according to Emory IRB policies and procedures. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review
- Confidentiality
 - Example: Confidentiality will be protected by utilizing a code number as the only identifier for each subject and the master list will be kept under lock and key with access limited to the PI.

- Data accuracy
- Example: The PI will be responsible for reviewing protocol compliance, data collection and verification

Multi-Site Investigations

An Emory investigator may conduct a multi-site study which includes non-Emory sites. The DSMP requirements are based on the role of the Emory investigator.

1. Multi-Site Trials where Emory investigator is the sponsor (IND/IDE is held by the Emory investigator): The DSMP must include:
 - a) Prompt review of safety information received from sites and analysis of reports for significance.
 - b) Plan for keeping all investigators informed of new observations re. drug or device, including information on safe use.
 - c) Plan for notifying FDA and investigators of reportable events.
 - d) Plan for reporting to IRB of UPs, terminations of the IND/IDE or termination of participation in the trial by a specific investigator.
 - e) Robust monitoring plan that should include the following elements:
 - Centralized monitoring:
 - Example: study sites send source documents for comparison with CRFs.
 - On-site monitoring:
 - Example: Emory sponsor or designated person visits site. Per FDA inspectors, a site visit must occur at least once a year or once during course of study if study duration is less than 12 months. CRO or independent monitor is a good option.
 - Self-monitoring:
 - Example: The Emory sponsor should provide a monitoring tool to be completed by site at prescribed frequency, with results reported to Emory sponsor.
 - Self-monitoring by site investigator alone is unlikely to pass FDA muster for adequate monitoring by Emory sponsor of multi-site investigation involving non-Emory sites.
2. Multisite Trials where Emory investigator is 'Coordinating Investigator' (study is not under an IND/IDE): The DSMP should specify:
 - a) Emory as coordinating site is only providing information to all investigators who each determine if event should be reported to their IRB.
 - b) Participating sites (or CRO) will promptly provide the coordinating site with copies of adverse event reports that require expedited reporting to their local IRBs
 - c) Coordinating site (or CRO) will forward adverse events reports requiring expedited reporting to participating sites
 - d) Coordinating/Lead investigator will review data summary reports of adverse events on a regular basis, at least annually
 - e) Coordinating/ Lead investigator will submit data summary reports to the Data Safety Monitoring Committee for review as per their guidelines.

What is a DSMB?

A Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the sponsor and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. Other names for committees that monitor accumulating data are Data Monitoring Committee (DMC) and Data Safety Monitoring Committee (DSMC). In a 2006 guidance document, the FDA defined a DMC as “a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial”. <http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf>

What is the Purpose of a DSMB?

The DSMB evaluates research data on an ongoing basis to assure participant safety and study integrity. The DSMB periodically reviews study data and unanticipated problems and makes recommendations based on their reviews along with assessing the performance of overall study operations and any other relevant issues, as necessary.

Independence of the DSMB

It is essential that the judgment of members of the DSMB not be influenced by factors other than those necessary to maintain subject safety and to preserve the integrity of the study. Persons who have an apparent financial, intellectual, or other interests with a drug, device, or procedure should not be a DSMB participant for the evaluation of that product. Independence is essential to ensure that DSMB members are objective and capable of an unbiased assessment of the study's safety and efficacy data. The following will ensure the independence of the DSMB:

- Members of the DSMB will not participate as investigators in this study and are not supervised by study investigators.
- Members of the DSMB must not have a direct interest in knowing or influencing trial outcome or have a financial or intellectual interest in the outcome of this study.
- DSMB members must disclose all pharmaceutical companies, biotechnology companies, and CROs in which they hold financial interest. Members must disclose all consultancies (direct or indirect) with pharmaceutical companies, biotechnology companies, and CROs.
 - Members of the DSMB will be responsible for notifying the DSMB Chair and the Sponsor/Sponsor-Investigator of any changes of interest in pharmaceutical companies, biotechnology companies, or CROs, including consultancies. Members will be polled at the beginning of each DSMB meeting to disclose whether status has changed and this will be reflected in meeting minutes.

Do the regulations require DSMBs?

The regulations provide minimal insight on DSMBs. The Code of Federal Regulations indirectly address data safety monitoring in [45 CFR 46.111 \(a\)\(6\)](#) which states “When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.”

The 2006 [FDA guidance document](#) discusses the roles, responsibilities, and operating procedures of DMCs. This document is helpful in determining whether a DMC is needed and how it should function. Some government agencies that sponsor clinical research have required the use of DMCs in certain clinical trials. Current FDA regulations, however, impose no requirements for the use of DMCs in trials except under 21 CFR 50.24(a)(7)(iv) for research studies in emergency settings in which the informed consent requirement is excepted. Though it is not required, the FDA generally expects the use of a DMC for randomized trials with mortality or major morbidity as primary endpoints.

Do I need a DSMB?

While it is important to remember that all studies require a DSMP and careful monitoring, it is also important to know that not all studies require DSMBs. Some studies have too few subjects to support statistical analysis by a DSMB, but must have a clinical safety monitoring mechanism. Some trials do not require a DSMB for other reasons; for example, early phase non-randomized trials with limited safety concerns. Additionally, studies with rapid recruitment and short-term endpoints may not be long enough for a DSMB to be of any use.

The following questions are designed to help make a determination as to whether or not a DSMB may be needed.

- Is there a large study population, or are there multiple study sites?
- Is the trial intended to provide definitive information about effectiveness and/or safety of a medical intervention?
- Do prior data suggest that the intervention being studied has the potential to induce unacceptable toxicity?
- Does the trial evaluate mortality or another major endpoint, such that inferiority of one treatment arm has safety and effectiveness implications?
- Would it be ethically important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed?

A DSMB usually should be implemented if two or more answers to the above questions are yes.

Who should be on the DSMB?

The PI or trial sponsor generally appoints the DSMB and should have multidisciplinary representation, including physicians from relevant medical specialties and biostatisticians. When appointing individuals to a DSMB, the following should be considered: relevant expertise, experience in clinical trials, experience as a member of other DSMBs, and a lack of apparent significant Conflicts of Interest, whether they are financial, intellectual, professional, or regulatory in nature. The appropriate size of a DSMB will depend upon the particular study and types of expertise needed. A DSMB may consist of as few as three members, but this number should be large enough to include a representation of all needed skills and experience.

Who is typically included in a DSMB?

- Clinicians with expertise in relevant clinical specialties

- At least one biostatistician knowledgeable about analysis of trial data

Who might also be included in a DSMB?

- Medical ethicist
- Other types of scientists (i.e., clinical pharmacologist, toxicologist, epidemiologist, laboratory scientist, etc.)

Best practice is to include an appropriate representation of gender and ethnic groups.

What are the responsibilities of the DSMB?

The primary responsibility of the DSMB is to safeguard the interest of study participants. Therefore, the DSMB must approve the safety measures in the protocol to preserve the study credibility and facilitate the availability of timely and reliable findings to the broader clinical community.

In addition, the DSMB should:

- Provide written documentation confirming review of the protocol and agreement with the study design and the data safety monitoring plan (DSMP).
- Review the progress of the study carefully and diligently. The DMC or DSMB should assure that all significant Adverse Events are reported to the IRB according to policies and procedures
- Be available to the Investigator for consultation concerning any adverse study events.
- Consider the impact of newly published findings bearing on the safety profile of the study.
- Provide a written report to the IRB which summarizes oversight activities and recommendations, and any concerns regarding subject safety.

DSMB Charter Template:

http://niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.asp

What is the role of the IRB with regard to DSMBs and DSMPs?

Reviewing the DSMP and all DSMB reports is a part of the IRB initial approval and subsequent reapproval. The IRB does not typically have access to the interim data, but the IRB may take action based on recommendations from the DSMB. The IRB must still review internal AEs and UPs involving risks to subjects or other and any information to ensure that the review is meaningful.

IRB review includes:

Initial Assessment of the Overall Monitoring Plan:

The IRB should assess the overall Monitoring Plan for adequacy in detecting and addressing safety issues AND ensuring protocol compliance and data quality.

Monitoring Plan Components:

- Data Safety Monitoring Plan – How is safety information collected from sites and from other sources (e.g., other studies, other countries where drug is approved, etc.); evaluated; and results disseminated to investigators?
- Data Safety Monitoring Board (DSMB) – Who will review safety data, consider stopping rules, etc.?
- Site Monitoring Plan – How is information being collected about protocol compliance at each site and the quality of the data being collected?
- Review of Monitoring Plan Results: Ensure that Site Monitoring results are being reviewed by investigator and events that impact subject safety or data integrity are reported per IRB requirements.
- At continuing review, IRB should review and assess DSMB reports and overall DSMP.

Where can I find more information about DSMBs and DSMPs?

- [Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees](#) March (2006)
- [The Emory IRB Policies and Procedures: Section 50 Data and Safety Monitoring Plans](#)
- [NIH/NIAMS Policies, Guidelines and Sample Documents for Clinical Trials](#)
- [NIH Policies and IC Guidance for Data and Safety Monitoring of Clinical Trials](#)
- [NIAID Decision Tree for Data and Safety Monitoring Plan](#)
- Ellenberg, Susan S., Thomas R. Fleming, and David L. DeMets. [Data Monitoring Committees in Clinical Trials: A Practical Perspective](#). Chichester, England: John Wiley, 2003.