

Implementation Approval

HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

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SOP Title: DATA AND SAFETY MONITORING

Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB
Chairs, IRB Administrators, Protocol Navigators

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SOP 17. DATA AND SAFETY MONITORING

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SOP17 DATA AND SAFETY MONITORING

17.1 PURPOSE

The purpose of this policy is to define requirements for inclusion of data and safety monitoring plans in research protocols submitted to NIH IRBs. This is to ensure, to the extent possible, the safety of research subjects and the integrity of research data consistent with regulatory and NIH requirements.

17.2 POLICY

In accordance with regulatory requirements (45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6) (Criteria for IRB approval of research) and 21 CFR 50.24(a)(7)(iv) (Exception from informed consent requirements for emergency research), the NIH Human Research Protection Program (HRPP) requires inclusion of data and safety monitoring plans (DSMPs) in all research protocols submitted to NIH IRBs. When IRB-approved DSMPs involve monitoring of research by an NIH Data Safety and Monitoring Board (DSMB), Institute officials are responsible for DSMB organization consistent with their Institutes' written procedures.

17.3 DEFINITIONS

- A. **Data and Safety Monitoring Plan (DSMP)** - A written description of the procedures for reviewing accumulated data in an ongoing research protocol to ensure the safety of research participants and the continuing validity and scientific merit of the protocol.

- B. **Data and Safety Monitoring Board (DSMB)** (also known as a Data and Safety Monitoring Committee {DSMC} or Data Monitoring Committee {DMC}) - A formal committee made up of experts, who are not the trial organizers or investigators, that reviews on a regular basis accumulating data from one or more ongoing clinical trials.

- C. **Independent** - For the purpose of this policy, this refers to individual(s) not engaged in the research, not in supervisory or subordinate positions and unrelated to the investigators and sponsor.

17.4 PROTOCOL DATA AND SAFETY MONITORING PLAN

All protocols submitted to an NIH IRB must include a DSMP. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. In general, the DSMP will include the following elements:

- A. Selection of a Data and Safety Monitoring Mechanism: Appropriate mechanisms for data and safety monitoring range from monitoring by the PI to monitoring by an independent DSMB. For example:
 1. Monitoring by the PI or AI or other designated individual may be appropriate for protocols involving no more than minimal risk or a minor increase over minimal risk and that are conducted at a single site.
 2. Monitoring by an individual who is independent of the protocol may be appropriate for protocols that pose more than minimal risk to the subjects, for multi-site protocols, for studies where an investigator has a potential conflict of interest, or for some FDA-regulated research, (for more information see SOP 21, "Conflict of Interest Requirements for Researchers and Research Staff, Appendix A: A Guide to Avoiding Financial and Non-financial Conflicts or Perceived Conflicts of Interest in Clinical Research as NIH.")
 3. Monitoring by a group of experts, which may be a DSMB, is usually appropriate for phase III blinded randomized clinical trials; high risk multicenter protocols; protocols using gene transfer or gene therapy methodology, and for some FDA-regulated research.
- B. Elements of the Data and Safety Monitoring Plan: Data and Safety Monitoring Plans will address the following as appropriate:
 1. **Monitoring mechanism (see 17.4.A.):** Identify who will be responsible for the data and safety monitoring. When a DSMB is the monitor, the PI will provide the DSMB name and establishing entity within the DSMP.
 2. **Frequency of the monitoring:** Monitoring should be done on a regular basis at intervals determined before the study begins.
 3. **Stop or change rules:** Provide specific criteria to be used for interrupting enrollment or administration of study products or procedures and formal guidelines to be used for stopping one or more study arms.

4. **Advanced plans for any interim analyses and/or futility analyses.**
5. **Information to be monitored:** In describing what information will be monitored, consideration will be given to the following, as appropriate:
 - a. An evaluation of the progress of the research study, including assessments of data quality and timeliness and participant recruitment, accrual and retention consistent with plans for diversity and generalizability.
 - b. A review of outcome and adverse event data to determine whether there is any change to the risk/benefit ratio of the study, if a stop rule has been invoked, or a study endpoint has been reached, whether the study, should continue as originally designed, be changed, or be stopped.
 - c. An assessment of external factors or relevant information (e.g., developments in the literature, results of related studies, etc.) that may have an impact on the safety of participants or on the ethics of the research study.
6. **Communication:** Identify the lines of communication between the PI, the study sites, research teams, the data and safety monitor/committee, the IRB, the FDA, and other individuals at the NIH. This includes responsibilities for providing the recommendations and reports of the monitor to the sponsor (see SOP 15, "Research Regulated by the Food and Drug Administration. General Procedures for Both IND and IDE Applications") and/or the Institute Director/designee, to the PI and the IRB.

17.5 RESPONSIBILITIES OF PIs, IRBs, MONITORS AND INSTITUTE OFFICIALS

A. PI Responsibilities:

1. **Establishing a DSMP:** The PI is responsible for including in the protocol a proposed DSMP consistent with the requirements of this SOP.
2. **Implementing the IRB-approved DSMP:** The PI is responsible for assuring that the requirements of the IRB-approved DSMP are implemented. This includes (a) providing monitors with all the data and information needed to monitor the study and (b) notifying the monitor promptly of any IRB-approved protocol amendments.

3. **Implementing monitor recommendations:** The PI will submit protocol amendments, as appropriate, to the IRB for review and approval of monitor recommendations.
4. **For FDA-regulated studies:** NIH investigators are expected to assure that all FDA-required data and safety monitoring requirements are met. For example, FDA regulations require the use of DSMCs for research studies in emergency settings in which there is an exception from the requirement of informed consent (21 CFR 50.24(a)(7)(iv)). See SOP 15 for more information on investigator and sponsor-investigator responsibilities for FDA-regulated research.

B. IRB Responsibilities:

1. **Review and approval of the DSMP:** The IRB reviews the DSMP to determine whether it makes adequate provisions to ensure, to the extent possible, the safety of research subjects and the integrity of research data. As appropriate, the IRB will include in its review the criteria set forth in 17.4.B. An IRB-approved DSMP is required before research begins.
2. **Review of monitor reports:** The IRB Chair reviews data and safety monitoring reports as they are received. The Chair has the discretion to recommend review by the convened IRB at any time.
3. **Review of monitor recommendations:** The IRB will review and approve protocol amendments that address monitor recommendations.

C. Responsibilities of Monitors:

1. Monitors are responsible for providing oversight of the study consistent with IRB-approved DSMPs.

D. Responsibilities of Institute Officials:

1. **Establishment of monitoring groups:** When IRB-approved DSMPs involve monitoring of the research by a group of experts or a DSMB, ICs are responsible for providing adequate resources and staff support to any group or DSMB established by the IC and for appointing members of expert groups or DSMBs organized by the intramural program.
 - a. Establishment of expert monitoring groups or formal DSMBs will be consistent with written IC procedures and NIH requirements. For example, if the monitoring mechanism is a group of experts or a DSMB that includes

non-Federal members, consideration will be given to the application of the Federal Advisory Committee Act, 5 U.S.C.

2. **Implementing monitor recommendations:** Institute officials, PIs and IRBs will work together as appropriate to address and implement monitor recommendations.