

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

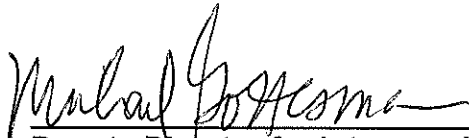
OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 17

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

TABLE OF CONTENTS

17.1 PURPOSE.....	1
17.2 POLICY.....	1
17.3 DEFINITIONS.....	1
17.4 DATA AND SAFETY MONITORING PLAN	3
17.5 RESPONSIBILITIES OF PIs, IRBs, MONITORING ENTITIES, AND INSTITUTE OFFICIALS	6
REFERENCES.....	9

SOP 17 - 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. The IC, the FDA or an IRB can require that a DSMP identify an independent data and safety monitoring entity (e.g. a medical monitor or a Data and Safety and Monitoring Board). When DSMPs involve monitoring of research by an NIH Data and 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** - a formalized process for reviewing accumulated outcome data from an ongoing research study to ensure the continuing safety and welfare of current research subjects and those yet to be enrolled, as well as the continuing validity and scientific merit of the study
- B. **Data and Safety Monitoring Plan (DSMP)** - A written description of the procedures for reviewing outcome data, reportable event data (including adverse reactions and unanticipated problems) and overall compliance with the protocol. It is intended to assure of the safety and welfare of research subjects during the course of the study.
- C. **Data and Safety Monitoring Entity** - The identified individual or group (e.g., the investigators, a coordinating or statistical center, a medical monitor, an IC- or other sponsor-designated Data and Safety Monitoring Board (DSMB), Data and

Safety Monitoring Committee, Data Monitoring Committee, or some other entity) who is assigned to conduct interim monitoring of data from research activities

- D. Data and Safety Monitoring Board (DSMB)** - For purposes of this Policy, the terms DSMB, Data and Safety Monitoring Committee (DSMC), Data Monitoring Committee (DMC), and an independent Data and Safety Monitoring Committee will be considered synonymous and will be referred to herein as “DSMB”. A formal committee, made up of independent experts, i.e. not the trial organizers or investigators, which reviews accumulating data and critical efficacy endpoints from one or more ongoing clinical trials (or multisite research). The DSMB reviews the data on a pre-set schedule throughout the life of the study. A DSMB is the only trial oversight group that has on-going access to un-blinded safety and efficacy data. Its role is to make recommendations to continue, modify, or stop the research based on an assessment of risks and benefits. At NIH, the recommendations are sent to the PI and IC leadership and/or other IC contacts based on the DSMB Charter and IC policy. It has the authority to request additional analyses and may schedule ad hoc meetings to review data.
- E. Medical Monitor** (also known as Safety Monitor) - a health care professional capable of overseeing the progress of the research protocol, especially issues of individual subject/patient management and safety. The medical monitor must be independent of the investigative team. He or she must possess sufficient educational and professional experience to serve as the subject/patient advocate. Depending on the nature of the study, the medical monitor may be assigned to assess one or more phases of a research project.
- F. Non-Medical or ‘Data’ Monitor** (also known as a Clinical Monitor or Clinical Research Associate) - a qualified and objective individual who reviews the research records and processes to look at the timeliness of accrual and ensure that the trial is being conducted as planned. The ‘data’ monitor is someone with no direct involvement in the design and conduct of a study. ‘Data’ monitors inspect regulatory binders (including informed consents and eligibility criteria) and study data (including source documents and case report forms (CRFs)). He or she is responsible for making certain the data is of high quality and validity. In the case of a protocol with an IND, if the data are not valid, the sponsor cannot use it to support a marketing application to the FDA. When NIH is the sponsor, the IC may require that a ‘data’ monitor review data on a pre-determined basis or randomly.
- G. Sponsor:** A person (or other entity) “who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or

dispensed to or used involving, a subject under the immediate direction of another individual. A[n] [entity] other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct a clinical investigation that it has initiated is considered to be a sponsor, and the employees are considered to be investigators” (21 CFR 50.3(e); 21 CFR 56.102(j)).

- H. **Stopping rules:** identify specific triggers (i.e. events) that require some action. These are predetermined guidelines as to when enrollment, administration of study products or one or more study arms should be altered or stopped.

17.4 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 **expected** risk involved in participation, the **nature**, size and complexity of the study, **and the populations involved in the study**. The DSMP **should** include the following elements, **as applicable**:

- A. **Data and Safety Monitoring Entity:** Depending on study needs and sponsor resources, one study may have a ‘data’ monitor, a medical monitor, a DSMB, or some combination of these. If a ‘data’ monitor(s) is being assigned specifically to verify data accuracy and compliance with the protocol, along with the inclusion of a medical monitor or DSMB, that individual/entity should be described in the plan. Examples of data and safety monitoring entities include the following:
1. **The PI, AI or another designated individual** may be appropriate for protocols involving no more than minimal risk or a minor increase over minimal risk that are conducted at a single site. **This type of monitoring is appropriate when the range of possible study events that could have an impact on the risks and benefits to research subjects is narrow. In such cases, continuous monitoring of events by the principal investigator, and prompt reporting of toxicity to the sponsor and others, and when applicable, to the FDA, may be adequate.**
 2. **A medical monitor** may be appropriate for certain protocols that pose more than minimal risk to the research subjects **or that enroll certain vulnerable populations. It is most appropriate for protocols that involve:**
 - a. **Endpoints that are not serious irreversible events;**

- b. An intervention (e.g. to relieve symptoms) that is not high risk, and the effects of which would not generally be so compelling as to ethically warrant early termination for effectiveness;
- c. A short term treatment where effects are evaluated over periods of a few days to a few months; and
- d. A smaller number of research subjects, a short time period and risk that can be adequately assessed through simple comparisons.

At NIH, the medical monitor may or may not be an employee of NIH or an external sponsor. For FDA-regulated research, the sponsor is responsible for ensuring proper monitoring of the investigation, including selecting monitors qualified by training and experience (see SOP 15 - Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications).

3. A group of experts, such as a DSMB, may be appropriate or required for protocols that involve:

- a. A large number of research subjects. Here, risk may better be assessed through statistical comparisons of treatment groups;
- b. A Phase III clinical trial (Having a DSMB for Phase III clinical trials is an NIH policy requirement.);
- c. A blinded study treatment group in which the validity and integrity of the trial may be adversely affected by having an individual (or group) associated with the design and conduct of the trial break the blind;
- d. A multicenter clinical trial (multisite trial) in which there is a need for investigators to submit reports of adverse events to a central reporting entity, such as a coordinating center or statistical center. In this case, the coordinating center is responsible for preparing timely summary reports of adverse events for distribution among the sites and to the sponsor (Having a DSMB for multicenter clinical trials is an NIH policy requirement.);
- e. A high risk intervention (e.g. gene transfer or gene therapy, a drug with significant toxicities) where death or severe disability is a major risk of research participation, or testing a new intervention where limited safety data is available;

- f. A controlled trial in which mortality or major morbidity is a primary or secondary endpoint. In this case, increased morbidity or mortality may better be assessed through statistical comparisons among treatment groups; and
- g. A research trial in emergency settings in which there is an exception from the requirement of informed consent (This is a requirement under FDA regulations (21 CFR 50.24(a)(7)(iv)).

The FDA has issued a guidance document called “The Establishment and Operations of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors (2006)” which addresses the types of trials that may warrant use of a DSMB (see **References**). This document is intended to assist clinical trial sponsors in determining when a DSMB is needed and how such boards should operate. It addresses the roles, responsibilities and operating procedures of DSMBs and describes reporting and recordkeeping responsibilities including: sponsor notification of DSMBs regarding waivers of expedited reporting; DSMB delivery of meeting minutes and other reports to sponsors; sponsor reporting to the FDA on DSMB safety-related recommendations; standard operating procedures for DSMBs; and DSMB meeting records.

At NIH, members of the DSMB may or may not be employees of NIH or an external sponsor. The DSMB should include experts in the relevant field of study, the conduct of clinical trials, statistics and/or research design. DSMBs meet at least annually or more often depending on the nature of the trial.

- B. **Type of data or events** that must be captured as part of monitoring. In describing what information will be monitored, consideration should be given to the following, as applicable:
 1. **An evaluation of the progress of the research study**, including assessments of data quality and timeliness, and whether participant recruitment, accrual and retention are consistent with plans for diversity and generalizability;
 2. **A review of unanticipated problem, adverse event and outcome data** to determine whether there is any change to the risk/benefit ratio of the study. In addition, the DSMP should address whether the study should continue as

originally designed, be changed, or be stopped if a stopping rule has been invoked or a study endpoint has been reached; and

3. **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 research subjects or on the ethics of the study

C. Reporting schedule for notifying the sponsor and, as applicable, the data and safety monitoring entity about adverse events and unanticipated problems

D. Frequency of assessments of data or events. This can be points in time (3 months, 6 months etc.) or after a specific number of research subjects are enrolled depending on the level of risk and the schedule for study visits, i.e. according to the planned accumulation of new data.

E. Stopping rules should be specific in terms of the endpoints that will be used and the decisions that will be made. Studies may be stopped, e.g. when there is a greater than expected rate of morbidity or mortality or when the experimental arm is shown to be better or worse statistically than the standard of care arm.

F. Plans for interim and/or futility analyses, designed and timed so as not to adversely impact the power of the study

G. Procedures for communication between the PI, research team members, the study sponsor, the coordinating or statistical center, the medical monitor, the DSMB, the IRB, the FDA, other study sites, and others at NIH, as applicable. This includes procedures for communicating the data and safety monitoring entity's recommendations and reports to the PI, sponsor and/or the NIH Institute Clinical Director/designee, and the IRB (see SOP 15 - Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications).

17.5 RESPONSIBILITIES OF PIs, IRBs, MONITORING ENTITIES, AND INSTITUTE OFFICIALS

A. PI Responsibilities:

1. **Establishing a DSMP:** The PI is responsible for including a DSMP in the protocol that is consistent with the requirements in this SOP.

2. **Implementing the IRB-approved DSMP:** The PI is responsible for ensuring that the requirements of the IRB-approved DSMP are implemented. This includes (a) providing the data and safety monitoring entity with all the data and information needed to monitor the study and (b) promptly notifying the data and safety monitoring entity of any IRB-approved protocol amendments. Regardless of the DSMP, the PI is ultimately responsible for protecting the rights, safety, and welfare of research subjects under his/her care and for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.
3. **Promptly submitting all data and safety monitoring entity's reports and recommendations to the IRB**
4. **Addressing the data and safety monitoring entity's recommendations:** The PI should take appropriate action, such as initiating protocol amendments and administrative holds or conferring internally, based on the data and safety monitoring entity's recommendations.
5. **Responding to the data and safety monitoring entity's reports: A response may be made to correct errors in fact or to respond to recommendations or requests for corrective actions and may be provided to the Clinical Director, and/or to the IRB.**
6. **For FDA-Regulated Studies:** NIH investigators are expected to ensure that all FDA-required data and safety monitoring requirements are met (21 CFR 50.24(a)(7)(iv)) (see SOP 15 - Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications).

B. IRB Responsibilities:

1. **Reviewing and approving the DSMP:** The IRB reviews the DSMP in the protocol to determine whether it makes adequate provisions to ensure, to the extent possible, the safety of research subjects and the integrity of the data. As applicable, the IRB will include in its review, the criteria set forth in **17.4.B.-G**. An IRB-approved DSMP is required before research begins.
2. **Reviewing data and safety monitoring entity's 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.

The IRB should review all monitoring reports since the date of the last IRB review and approval of the project at the time of continuing review:

- a. Information regarding any unanticipated problems that have occurred since the previous IRB review will be pertinent to the IRB's determinations regarding the risk/benefit ratio of the study.
 - b. It also may be appropriate for the IRB to confirm that any provisions for monitoring the data to ensure safety of research subjects, contained in the previously approved protocol, have been implemented and are working as intended (45 CFR 46.111(a)(6)).
3. **Reviewing the PI's proposed actions, based on monitoring report findings:** The IRB will review actions proposed by the PI, e.g. protocol amendments, an administrative hold or closure, that are based on the data and safety monitoring entity's recommendations.

C. Responsibilities of Monitoring Entities:

1. **Providing oversight of the study consistent with the IRB-approved DSMP**
2. **Generating reports for review by PIs, sponsors, IRBs, etc. that include the following items:**
 - a. A statement indicating what information (e.g., project-wide adverse events, research subject withdrawals, complaints about the research, interim findings, and any recent literature that may be relevant to the research) was reviewed;
 - b. The date of the review; and
 - c. The assessment of the information reviewed.
3. **Recommending the continuation, modification, or closure of a study based on review of the data**

D. Responsibilities of IC Officials:

1. **Ensuring a system for appropriate monitoring of the conduct of clinical trials** to assure the safety of research subjects and the validity and integrity of the data
2. **When NIH is the sponsor, establishment of a monitoring entity:** When IRB-approved DSMPs involve a data and safety monitoring entity, e.g. a medical monitor or DSMB, ICs are responsible for providing adequate resources and staff support to the data and safety monitoring entity and for appointing **a medical monitor** or members to the DSMB. Establishment of formal DSMBs **must** be consistent with written IC procedures and NIH policies, **e.g. the NIH Policy for Data and Safety Monitoring (see References)**. For example, if the monitoring mechanism is a DSMB that includes non-Federal members, consideration will be given to the application of the Federal Advisory Committee Act, 5 U.S.C. **(see References)**.
3. **When NIH is convening the DSMB, ensuring that conflict of interest requirements are addressed for DSMB members, as applicable** (see SOP 21 - Conflict of Interest Requirements for Researchers and Research Staff)
4. **Addressing the data and safety monitoring entity recommendations:** IC officials, will work with PIs, to address the data and safety monitoring entity's recommendations, as applicable.

REFERENCES

- A. The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm>
- B. NIH Policy for Data and Safety Monitoring:
<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>
- C. The Federal Advisory Committee Act: <http://www.gsa.gov/portal/content/100916>