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University of Pennsylvania
Human Research Protections Program

Data Safety Monitoring Plan (DSMP) Guidance

The IRB is responsible for determining if a study needs formal monitoring to ensure that research participants will be protected. A criterion for study approval outlined in federal regulations is that "when appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects" (45 CFR 46.111[a][6]).

Monitoring is an ongoing process of overseeing the progress of a study to determine whether study activities are being carried out as planned and whether there are any unexpected safety concerns. Monitoring enables study teams to identify and correct any deficiencies in the conduct of the study, record keeping, or reporting. It also helps to ensure the safety of participants.

When is a DSMP Required?

Research that is determined by the IRB to be greater than minimal risk should have a Data Safety Monitoring Plan (DSMP). Monitoring activities and roles are typically outlined in the study protocol and/or a stand-alone monitoring plan. A DSMP should be risk-based with a focus on safety and scientific integrity. The degree of monitoring varies based on the risk level, size and complexity* of the study, the nature of the investigation, the regulatory requirements, and the study sponsor. These factors help determine the appropriate level of monitoring, including who should be involved in the monitoring (identifying key people), what should be monitored (scope) and how often the monitoring should occur (frequency/timing).

Based on NIH guidance, complexity can be broken down from low to high complexity. Levels of complexity are based on participant overall risk and duration of risk, trial size, number of sites, intricacy of study design, use of an investigational product, etc. Examples are given in the figure below.

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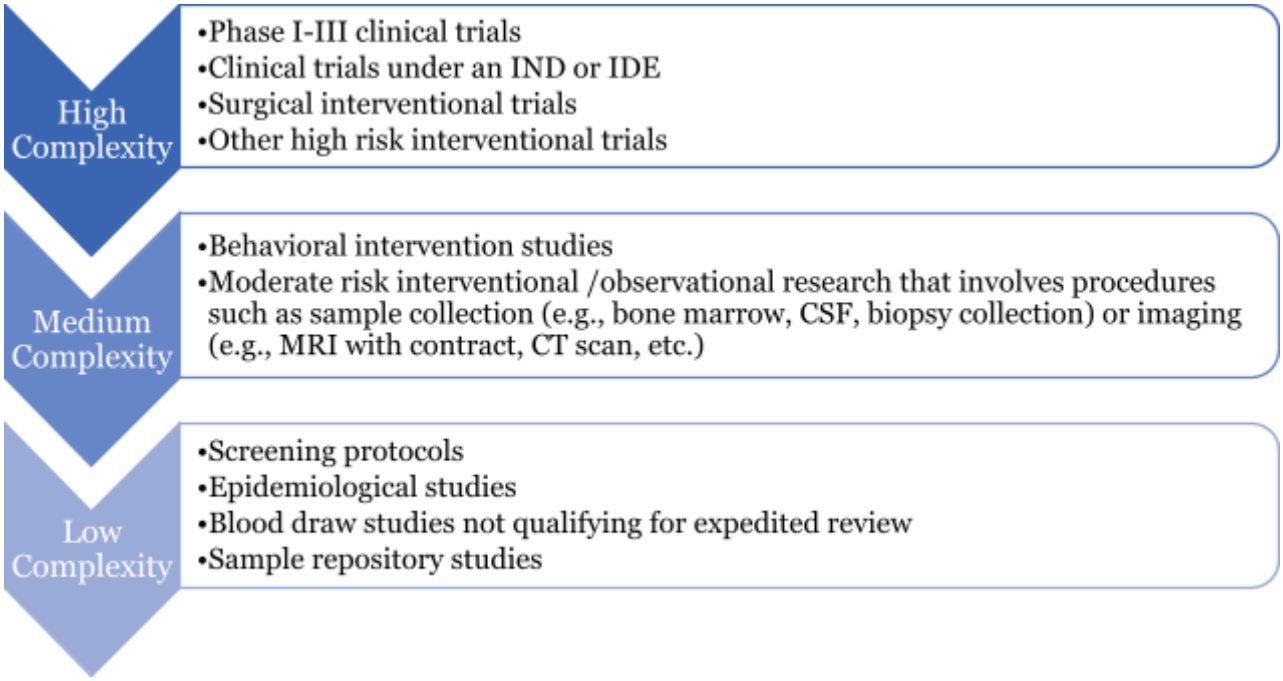

Elements of a DSMP

For medium and high-complexity studies, a DSMP should include a review of participant files and site files.

Review of Participant Files

Participant files should be reviewed for safety, welfare, and data integrity. Data should be reviewed in real time, such as consent forms, eligibility, adverse events, and (if applicable) product accountability, etc. The study team should have a documented standard operating procedure to review data at pre-determined intervals to ensure there is adequate documentation of critical elements such as eligibility criteria.

Review of Site Files

Site monitoring is a process to ensure that the protocol is being followed. For Low – Medium Complexity studies self-monitoring is usually acceptable unless otherwise directed by the IRB. Self-monitoring should be done through completion of the Principal Investigator Compliance Assessment (PICA)).

For High Complexity studies, an independent study monitor should be identified. Monitoring should be more frequent and more comprehensive as study complexity increases.

The following elements should be considered within a DSMP:

- **Data Integrity**: ensure that data is accurate and complete as well as adherence to the approved study.
- **Subject Privacy**: ensure individual's rights are protected.

- **Data Confidentiality**: ensure data is secured.
- **Study Documentation**: ensure that required documentation and reports are on filed, accurate, and complete.
- **Participant Safety**: avoid or minimize risks (i.e., physical, psychological, or social).
- **Study Coordination**: ensure that investigator delegation and communication with the research team is planned and systematic.
- **Product Accountability**: when applicable, ensure drug(s) or device(s) are tracked and accounted for.

Protection Element	DSMP Component	Examples of monitoring activities
Subject safety	Specific subject safety parameters	Vital signs, weight, safety blood tests, cardiac status, anxiety, depression scores, etc.
	Frequency of subject safety observations	Weekly telephone follow-up, monthly appointments, observations of participants while in the clinical setting, etc.
	Individual responsible for safety monitoring	Principal investigator, safety monitor, site monitor, or Data/Safety Monitoring Board, etc.
	Subject stopping rules - under what conditions will a subject be removed from study participation and who will make the decision?	• Adverse response to study procedures, pregnancy, stroke, cardiac irregularity, non-compliance with medication, etc. • Decision made by sponsor, investigator, medical monitor • Include procedures for analysis and interpretation of data, etc.
	Study stopping rules - under what conditions will the study be modified or stopped and who will make the decision?	• Potential unanticipated problems (UPs) involving risks to subjects or others, unexplained adverse outcomes, life threatening adverse event, etc., futility • Decision made by DSMB, sponsor
	Reporting mechanisms (i.e., deviations, adverse events, UPs)	Plans for reporting to IRB, FDA, Sponsor, participating sites, or Data/Safety Monitoring Board, etc.
Data integrity	Specific data elements to be reviewed	Participants inclusion criteria being met, transcription of data is accurate and complete, units of measure are recorded appropriately, calculations are standardized and performed accurately, etc.
	Frequency of monitoring data, points in time, or	First 3 participants and every 10th participant, monthly, quarterly, or annually, according to study complexity.

	after specific number of participants	
	Individual responsible for data monitoring	Principal investigator, study coordinator, safety monitor, independent monitor, etc. Ideally, someone external to the study team should be named responsible.
Subject privacy	Conditions (time and place) under which a subject will be consented, interviewed, or telephoned	Observations of consenting process, interviewing, or clinical visit performed quarterly on 3 participants.
Data confidentiality	Conditions that will protect the confidentiality of the data	Locked file cabinets, encrypted electronic records, secure location where protected health information is stored, etc.
Product accountability	Responsibility for obtaining, storing, preparing, administering, or disposing of the study drug or study device. Responsibility for overseeing product accountability	Research Pharmacy, Principal Investigator, Central Pharmacy, Research Laboratory, Nursing, etc.
Study documentation	Study file management	Study File Management guidelines and checklists for monitoring (sampling of study files annually), etc.

Clinical Trial Data Safety Monitoring Requirements

This IRB follows guidelines set out by the National Cancer Institute (NCI), as they are the most comprehensive of the NIH guidelines. The NIH (NCI model) says: "All clinical trials supported or performed by NCI require some form of monitoring."

- **Early studies (non-therapeutic, Phase I, Phase II**): These studies are allowed flexibility in monitoring. It is permissible for the PI to conduct self-monitoring. However, the policy requires written policies and procedures, and also requires that "regardless of the method used, monitoring must be performed on a regular basis."
- **Phase-III studies:** These require a formal DSMP, which may mean the establishment of a Data Safety Monitoring Board (DSMB) at the sponsoring institute, the study site, or at the lead institution of a multi-center trial.

Data Safety Monitoring Boards (DSMB)

A DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. A Data and Safety Monitoring Board / Committee (DSMB/C) is a component of a Data Safety Monitoring Plan. Establishing a DSMB is not always required.

Factors Suggesting a DSMB may be Necessary

The following types of studies are generally required to have a DSMB appointed:

- NIH-sponsored Phase 3 clinical trials (as well as some Phase 1 and 2)
- FDA-sponsored planned emergency research (EFIC)
- Multi-site randomized studies evaluating treatments intended to prolong life or reduce risk of a major adverse health outcome. *It is more difficult to recognize a pattern of increased or unusual problems when investigators treat small fractions of the population separately.*
- A large study population
- Highly toxic therapies or dangerous procedures.
- Controlled trials comparing rates of mortality or major morbidity

Additionally, the FDA recommends the use of a DSMB when a sponsored study includes:

- An endpoint which might ethically require termination of the study at interim analysis
- A particular safety concern, such as administration of treatment by an invasive method
- A subject group that includes a fragile, vulnerable population
- A subject group at elevated risk of death or other serious consequences

Board Composition and Functioning with the IRB

The NCI guidelines set forth requirements for DSMB composition and function. Note that it is required that a majority of the members be drawn from outside the institution (or institute) conducting the study. Membership is usually comprised of:

- experts in the fields of medicine and science that are applicable to the study,
- statistical experts,
- lay representatives, and
- other who can offer an unbiased assessment of the study progress

The DSMB is not specifically required to communicate with the IRB, but the intent is clear that the important information get to the IRB: "The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators, to be shared with their IRBs." It is the responsibility of Penn study teams to promptly submit DSMB Reports to the IRB in a timely manner.

References and Resources

National Cancer Institute (NCI)

- NCI Data and Safety Monitoring Guidelines

FDA Guidance

- FDA Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006
- FDA Guidance Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, August 2013

National Institutes of Health

- NIH Data and Safety Monitoring Center-specific Guidance
- NIH Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials, June 5, 2000
- NIH Policy for Data and Safety Monitoring, June 10, 1998