Data and Safety Monitoring Plan Requirements

Every study requires a plan with some level of data and safety monitoring. Monitoring, an ongoing process of overseeing the progress of a study from start to finish, is a quality control tool for determining 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. The Data and Safety Monitoring Plan (DSMP) should be based on a risk assessment of critical data and processes that are necessary for human participant protection and integrity of the investigation.

Studies That Involve No More than Minimal Risk

The protocol should include a DSMP to protect data and ensure the safety and confidentiality of research participants. Paper forms should be secured. Digital data should be encrypted and password-protected and should only be collected and stored using encrypted devices. Participant protections should be appropriate for the population and research procedures and typically focus on ensuring participant privacy and the confidentiality of any data, as physical harms are not reasonably foreseeable.

Studies That Involve More Than Minimal Risk

Complexity and Risk

Besides the requirements described above to protect data confidentiality and participants 'privacy, additional requirements apply to all studies involving more than minimal risk. The IRB will consider the level of risk and burden a participant may experience in a study when determining additional requirements for a plan. An inadequate monitoring plan may result in a study deferral.

Based on NIH guidance[i], the Emory IRB defines study complexity as follows:

- Medium-complexity: This includes behavioral interventions and studies involving sample collection or imaging done during a single interaction with a study participant or when the probability of harm is limited to the immediate circumstances of the research encounter. For example, studies involving an MRI with contrast, bone marrow sample collection for research purposes, or CSF or biopsy material collection in the context of a clinical encounter or when the remainder of the study-related activities are considered to be no more than minimal risk.
- High-complexity: (1) Phase I – III interventional studies, and all studies under an Investigational New Drug [IND] or Investigational Device Exemption [IDE] with the FDA. (2) Other studies that may not be under an IND or IDE, where a participant is exposed to risk for an extended period or for which the risk might change with time.

Data and Safety Monitoring Plan (DSMP)

For medium and high-complexity studies the IRB will require a plan for both (1) review of participant safety, welfare, and data integrity; and (2) site monitoring conducted to ensure data accuracy and protocol compliance.

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(1) Review of participant's data for safety, welfare, and data integrity: Study teams should have a process to review data during data collection.

- Information obtained directly from participants should be reviewed in real time. For example, when obtaining consent from a participant, the person obtaining consent should check the consent document to ensure the participant has signed in the right place(s) and the documentation of the consent process is adequate.
- The study team should have a standard operating procedure to review other data at pre-determined intervals to ensure there is adequate documentation of critical elements such as eligibility criteria.

(2) Site Monitoring: study teams should have a process to ensure that the study is following the protocol, including review of study procedures, study intervention, and data collection processes.

- For medium-complexity studies, the IRB may approve a monitoring plan relying on self-monitoring
  - Site Monitoring conducted via self-monitoring: a process for self-assessment of protocol compliance and data integrity which can be part of an overall DSMP. Click here for a Self-Monitoring Tool
- For high-complexity studies, the monitoring plan in the protocol should specify who will serve as study monitor and should specify the frequency and percentage of the files to be reviewed.
  - The site monitoring should be more frequent and more comprehensive as study complexity increases. The monitoring schedule should include study initiation, early in enrollment, and interim monitoring, based on the site activity and study complexity.
  - Monitoring should be conducted by a designated study monitor, who is experienced and knowledgeable about the regulations and the subject matter being studied. This person should not be collecting study data themselves. Ideally, this person should be independent of the study team. The responsibility for site monitoring may be delegated by the study sponsor to a Contract Research Organization (CRO).

Monitoring Plan Minimum Requirements

Review of the following items:

- Consent forms (for example, a high-complexity study should plan to review 100% of consent forms)
- Credentials, training records, the delegation of responsibility logs (if applicable)
- Critical data review that compares case report forms (CRF) to source documentation for accuracy and completion for critical data points (eligibility, study endpoints, etc.)
- Documentation of adverse events
- Regulatory documents including IRB correspondence, sponsor correspondence, FDA correspondence, etc. High-complexity studies should plan to do a 100% review of this information at site initiation, first participant visit, and end of study.
- Review of laboratory processing and storage of specimens at first and close-out visits and at least biannually
- Assessment of laboratory specimens stored locally

- Drug and Device accountability procedures. For most studies using drugs or biologics, test article accountability is managed by IDS per Emory policy 7.14. See this decision tree for more information.

See appendix 1 for more examples.[ii]

Additional considerations for FDA regulated trials[iii]

Depending on the procedures affecting risks to participants, the site monitoring plan should specify:

- Monitoring methods (may include centralized/remote, on-site, and self-monitoring)
- Reference to any tools used (i.e. checklists)
- Identification of events that may trigger changes
- Identification of deviations or failures that would be critical to study integrity
- Categorization of activities done centrally and those on-site if applicable

Please ensure you read the FDA documents referenced at the end of the document for more detailed information.

Data and Safety Monitoring Board (DSMB)

Not all studies require a DSMB. The following questions are designed to help determine whether a DSMB may be needed.

- Are there plans for any predetermined actions outlined, for example stopping rules?
- Is there a large study population, or are there multiple study sites?
- Is this a study where investigators are blinded to the treatment arm?
- Is the trial intended to provide definitive information about the effectiveness and/or safety of 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 should usually be implemented if answers to two or more of the above questions are 'yes'.

High-complexity clinical trials with international sites

In addition to all the above, as applicable, these studies are required to engage a CRO working in the study country, and/or to consult with legal counsel regarding compliance with the country's clinical research regulations.

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[i] NIDC Guidelines for Level of Clinical Site Monitoring, https://www.nidcr.nih.gov/sites/default/files/2017-12/level-of-monitoring.docx

[ii] Mayo Clinic DSMP Guidelines: https://www.mayo.edu/research/documents/43-data-and-safety-monitoring-guidelinespdf/doc-10026780

[iii] FDA guidance-Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring Additional requirements for *medium* complexity studies; FDA Guidance-A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry; NIH guidance: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html (release date June 5, 2000) and

http://grants.nih.gov/grants/guide/notice-files/not98-084.html (release date June 10, 1998); OHRP guidance: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

Appendix 1

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?	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 after specific number of participants	First 3 participants and every 10th participant, monthly, quarterly, or annually, according to study complexity.
	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.