Data and Safety Monitoring Plan Requirements

Every study requires a plan with some level of data and safety monitoring.

Contents:

What do we mean by Monitoring?

- Monitoring is an ongoing process of overseeing the progress of a study from start to finish
- It 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 study conduct, 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 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.

NOTE: If a study evaluates or directs the use of a device (For example: use of a TMS device, wearable devices that collect medical data, etc.), regardless of the overall study risk, a

monitoring plan is required. The IRB would generally expect this type of study to fall under "medium complexity".

Studies That Involve More Than Minimal Risk[1]

Complexity and Risk Categories

The IRB will consider the level of risk and burden a participant may experience in a study when determining additional requirements for studies involving more than minimal risk. We refer to these combined attributes as "complexity."

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

Medium-complexity Examples:

- Protocol directs invasive sampling collection (e.g., bone marrow, CSF, or biopsy collections)
- Protocol directs imaging with contrast (e.g., CTs or MRIs with contrast)
- Protocol directs procedures that introduce energy into the body (e.g., X-Rays, PET scans, microwaves, TMS, other electrode-based tools)

Includes use of a wearable device that collects medical data

High-complexity:

- Phase I –III clinical interventional studies (toxicity/safety/dose finding/effectiveness); and
- 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.

  We define *risk-based categories* for **High-Complexity** studies. These determine the minimum requirements for the DSMP.

  - **Category A**:
    - Phase I/II/III trial (toxicity/safety/dose finding/effectiveness), under an IND or IDE.
    - Clinical study without an IND or IDE that the IRB determines is high risk due to the procedures involved.

  - **Category B**:

[1] The following requirements apply to studies that are: 1) Investigator-initiated, or Emory-led, or 2) Multi-site studies where Emory is not the lead site and the study is not monitored by a CRO.

- Clinical trial using a drug or device under its FDA-approved indication. For example, a comparative effectiveness trial of two standard-of-care interventions.
- Studies that are IND exempt, IDE exempt or under an abbreviated IDE without other interventions that elevate the study to Category A.
- Studies under an IND or IDE where the intervention does not pose significant risk to the participants. These studies may use a drug or device (approved or not) that does not significantly increase morbidity or mortality. For example, a radiotracer study where the risk is limited to a single scan.
- Using software or an algorithm that may potentially inform clinical care without other interventions that elevate the study to Category A.
- **Application of other novel clinical techniques or intervention** (e.g., nonstandard surgical step)

Data Monitoring Requirements Assessment:

The Data Monitoring Requirements Assessment available in the Biomedical Protocol template directs the team which chart to insert from the [DSMP charts] for the protocol..

Basic DSMP plan requirements

(Special considerations for FDA-regulated and high-complexity trials follow)

After reviewing the complexity of a study, the IRB will require the following for **all medium and high-complexity studies**:

- Must include a plan for both:

  (1) **Real-time review** of participant data for safety, welfare, and to ensure data integrity during initial data collection.

  - Information obtained directly from participants should be reviewed in real-time by the person(s) collecting the data. 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.

  (2) **Site Monitoring** at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.

  - There should be a standard operating procedure to review data at pre-determined intervals to ensure that they have adequate documentation of critical elements such as eligibility criteria. At a minimum, a review is required **annually,** but additional monitoring may be needed for a higher study complexity.

- For example, the plan may include study-team review of participant data after the first two participants are enrolled and then at specified intervals based on enrollment.

- For **medium-complexity** studies, as well as **high-complexity "Category B"** studies, the IRB may approve a monitoring plan that relies on "self-monitoring."
  - *Self-assessment*: a process for self-assessment of protocol compliance and data integrity which can be part of an overall DSMP.
  - Click here for a Self-Assessment Tool.
- For Category A **high-complexity** studies, monitoring should be conducted by a designated study monitor: an experienced, knowledgeable person *who is independent of the study team*. The responsibility for site monitoring may be delegated by the study sponsor to a Contract Research Organization (CRO).

Medium Complexity Site Monitoring

- The **Site Monitoring Plan** should include:

  - 100% review of consent forms
  - Review of credentials, training records, the delegation of responsibility logs (if applicable)
  - Comparison of case report forms (CRF) to source documentation for accuracy and completion
  - Review of documentation of all adverse events
  - Monitoring of critical data points (eligibility, study endpoints, etc.)
  - A monitoring schedule that includes monitoring at the following timepoints:
    - study initiation
    - at least yearly while participants are receiving intervention and are in follow-up

Additional requirements for high-complexity studies

The **Site Monitoring** plan should include the requirements specified above, for medium complexity studies, AND:

- *Reminder*: Monitoring should be conducted by a designated study monitor - an experienced, knowledgeable person *who is independent of the study team*. The responsibility for site monitoring may be delegated by the study sponsor to a Contract Research Organization (CRO).
  - Consult the IRB Office regarding acceptable qualifications for the independent monitor, if not using an outside expert such as a CRO.
- 100% review of investigator regulatory files, reviewed at first and close-out visits
- Laboratory review of processing and storage of specimens at first and close-out visits and at least biannually
- Assessment of laboratory specimens stored locally, annually, at a minimum

- Test article accountability review at first and close-out visits and at least biannually
- Biannual review of accountability logs, dispensing records, and participant records.
- Based on participants' risk, the IRB may require interim monitoring once every 12-24 weeks when subjects are being actively enrolled and undergoing study intervention. Interim monitoring may include the possibility of remote monitoring.
    - Based on risk, the IRB may consider a longer frequency for studies under category B. The protocol should include justification for the frequency of interim monitoring.

Specific considerations for FDA regulated trials[ii]

For an FDA-regulated clinical trial, depending on the procedures affecting risks to participants, the **Site Monitoring** plan should include:

- Monitoring methods (may include centralized, on-site, and self-monitoring)
- Timing, frequency, and intensity of 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

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

High-complexity clinical trials with international sites

Besides 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.

Data and Safety Monitoring Boards (DSMBs)

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

- Are there plans for any predetermined actions outlined, for example for 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 usually should be implemented if answers to two or more of the above questions are 'yes'.

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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] FDA guidance-Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring Additional requirements for *medium* complexity studies and FDA Guidance-A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry

[iii] http://irb.emory.edu/documents/DSMB-DSMPGuidance.pdf

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.