National Institute of Diabetes and Digestive and Kidney Diseases

Data and Safety Monitoring

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National Institute of Diabetes and Digestive and Kidney Diseases

Learning Objectives

- History of Data and Safety Monitoring
- Why Data and Safety Monitoring is Important
- The Data and Safety Monitoring Plan
- Applying Risk-Based Monitoring

The Beginning of the External Monitoring Advisory Committees

Early 1960's – Initial recommendations

External advisory committees for review of multicenter cooperative trials first started being used in the 1960s. The Greenberg Report (1967), convened by the then National Heart Institute, recommended a role for an advisory group of experts, not directly involved with a trial, to review the protocol and conduct of the trial and provide advice to the Institute. The report also included a recommendation that a mechanism be put in place for early trial closure should "accumulated data answer the original question sooner than anticipated, if it is apparent that the study will not or cannot achieve its stated aims or if scientific advances since initiation render continuation superfluous" (Heart Special Project Committee, 1988).

1979 NIH Office of Science Policy

Recommends every clinical trial have provisions for data/safety monitoring.

The NIH policy for Data and Safety Monitoring applies to both NIH extramural research and all non-exempt human subject research conducted at the NIH Intramural Research Program.

1998 NIH Office of Science Policy

Since the NIH's 1998 Data and Safety Monitoring (DSM) policy, the scope, flexibility, and applicability of DSM requirements have expanded, with a current push to modernize the policy to reflect evolving research designs, technologies, and global standards.

Key Developments Since 1998

Broader scope of covered research

The 1998 policy focused mainly on clinical trials, but over time NIH has extended DSM requirements to a wider range of human subjects' research, including observational studies, behavioral and social science research, implementation science, and non-clinical trials. This reflects the recognition that all human subjects research can benefit from structured monitoring.

Tailored monitoring approaches

Modern practice emphasizes matching the monitoring plan to the study's size, risk level, complexity, and data type. Monitoring can range from PI-only oversight to independent Data and Safety Monitoring Boards (DSMBs), with plans now explicitly addressing data quality, safety, scientific integrity, protocol adherence, and study continuation.

Key Developments

Institutional and institute-specific guidance

While the core NIH policy remains, individual Institutes and Centers (ICs) have developed their own DSM guidelines, creating a layered approach to oversight. For example, NCI, NIAID, and NIMH have tailored DSM policies to their research areas.

Summary of changes

- **Expanded coverage** to all human subjects' research, not just clinical trials.
- **More flexible, risk-based monitoring** tailored to study design and complexity.
- **Incorporation of privacy/security considerations** in DSM plans.
- **Active modernization effort** to update the policy for current research realities.
- **Institute-specific adaptations** to address specialized research needs.

Clinical Research- Office of Science Policy

NIH Office of Science Policy Modernization Initiative

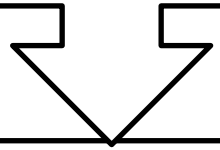
The ***NIH Office of Science Policy*** is actively working to modernize the Data and Safety Monitoring policy to enhance efficiency and rigor.

The 2026 public engagement process seeks input on:

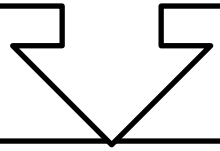
- Which study characteristics should influence the choice of monitoring approach.
- Key components of an effective *Data Safety Monitoring* plan.
- Which types of research should be covered under the updated policy, including all clinical research and all research involving humans, even with de-identified data.

NIH IRB Policy 503 – Data and Safety Monitoring

All non-exempt human subjects research protocols must include: a data safety monitoring plan (DSMP) that is commensurate with the level of risk of the research to monitor the data collected to ensure the safety of subjects, consistent with regulatory criteria for approval by an IRB at 45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6), and consistent with NIH policy (e.g., the *Policy for Scientific Review of Clinical Protocols Utilizing the NIH Intramural Program Submission Requirements and Review Criteria*).



The Data Safety Monitoring Plan must be described in the protocol submitted to the IRB for review.



Institutes and Centers (ICs) are required to ensure a system for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of research subjects and the validity and integrity of the data.

Policy 503 PI Responsibilities

The PI is responsible for the following:

a. Providing to the IRB a ***Data Safety Monitoring Plan*** for all non-exempt human subject research protocols.

As applicable, the ***Data Safety Monitoring Plan*** should:

I. Identify the data and safety monitoring entity (e.g., PI, medical monitor or Data Safety Monitoring Board (DSMB)).

II. The investigator should also provide enough detail in the DSMP, commensurate with the level of risk and complexity of the study.

IRB Risk Determination

The IRB's determination of risk refers to the **overall risk level** assigned to a research protocol based on the nature, likelihood, and acceptability of harm or discomfort to participants, as defined in federal regulations (45 CFR 46.102(j) and 21 CFR 56.102(j)).

The IRB risk classification determines the **level of IRB review** (full committee, expedited, or exempt) and the baseline monitoring expectations.

IRB risk classifications

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Greater than minimal risk studies are those in which the probability or magnitude of harm or discomfort exceeds what is ordinarily encountered in daily life or routine examinations, requiring full IRB committee review.

Guidelines for Determining the Appropriate Monitoring Entity

Definition of Minimal Risk

Minimal risk means the likelihood and severity of harm or discomfort from research are no greater than those found in daily life or routine exams (45 CFR 46.102).

Monitoring Minimal Risk Studies

The principal investigator can safely monitor studies that fall under minimal risk.

Guidelines for Determining the Appropriate Monitoring Entity

Definition of Low Risk

Low risk refers to situations where there is a minor increase above minimal risk. This means that the intervention or procedure involves experiences that are reasonably similar to those found in routine or anticipated medical, dental, psychological, social, or educational settings, as outlined in 45 CFR 46.406.

Monitoring of Low Risk Studies

Low risk study monitoring: Studies classified as low risk can be adequately monitored for safety by the principal investigator.

Guidelines for Determining the Appropriate Monitoring Entity

Definition of Moderate Risk

Moderate risks are justified by the potential benefits to subjects and expected knowledge, as described in 45 CFR 46.111. They pose greater risk than low-risk studies but less than high-risk studies, with safeguards in place to quickly address adverse events.

Monitoring Moderate Risk Studies

Moderate risk studies may require oversight beyond the principal investigator, such as an Independent Safety Monitor (ISM) or a Safety Monitoring Committee (SMC), to ensure comprehensive supervision.

Guidelines for Determining the Appropriate Monitoring Entity

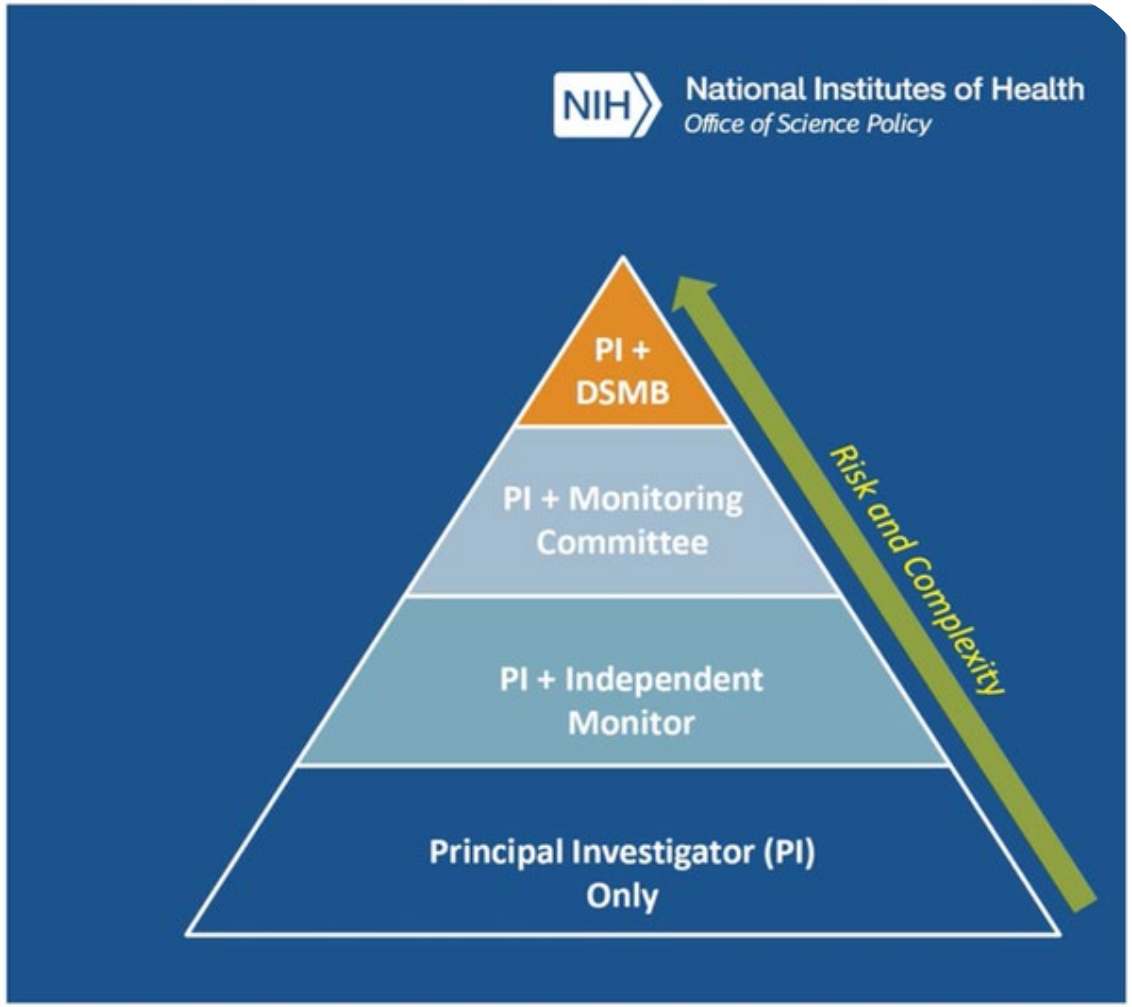
Definition of High Risk Studies

Studies classified as high risk are those in which participation may result in permanent physical or mental changes, hospitalization, or even death. These studies often involve procedures where, although there may be a direct benefit to the participant, the risks are considerable. In such cases, there is a higher probability of serious, long-lasting, or irreversible events related to the study.

Monitoring Requirements for High Risk Studies

High risk study monitoring : High risk studies require a higher level of oversight than can be provided solely by the principal investigator or a single independent safety monitor. In addition to the investigator, these studies must have additional monitoring, such as a formally established independent *Safety Monitoring Committee (SMC)* that is specifically responsible for overseeing the safety monitoring of the study.

NIH Office of Science Policy – Monitoring Framework



Consistently, collect, monitor, and review accumulated data, over the course of the clinical research study to ensure:

- Quality and scientific reliability of data
- Continued trial progression
- Continued scientific merit
- Participant safety

Defining the Purpose of Data and Safety Monitoring

The purpose of data and safety monitoring (DSM) in research is to protect the safety and welfare of study participants, ensure the validity and integrity of research data, reproducibility of research data and maintain the ethical and regulatory standards of the study.

It is a core requirement for non-exempt human subjects research, especially in clinical trials, and is embedded in federal regulations such as 45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6).

PI Responsibilities for Data and Safety Monitoring

PI responsibilities cover the following:

Participant safety: Monitoring for adverse events, serious adverse events (SAEs), unexpected problems involving risk to participants, and events leading to treatment discontinuation.

Ensuring Data integrity and validity: Ensuring data accuracy, completeness, and compliance with protocol requirements, including blinding, adherence to eligibility criteria, and proper documentation.

Study conduct: Verifying that the trial is progressing according to the approved protocol, with appropriate recruitment, retention, and data quality assessments.

Regulatory compliance: Aligning with GCP, IRB/FDA requirements, and applicable laws.

Stopping rules: Defining conditions under which the trial may be stopped early, such as when significant benefits or risks are identified or when the study is unlikely to achieve its primary goals.

Understanding Safety Monitoring

The **primary purpose of safety monitoring** in human subject research is to protect the rights, safety, and well-being of participants while ensuring the integrity and reliability of the research data.

Safety monitoring is a **continuous, systematic process** that involves collecting, evaluating, and managing any untoward medical occurrences in research participants. It is mandated by regulatory guidelines such as **ICH-GCP** and ethical standards like the **Declaration of Helsinki.**

In Practice Safety Monitoring Involves:

Document AEs/SAEs in the progress note

- Include start and stop dates of the events, and whether treatment was or was not necessary.
- Did the AE worsen during study participation?

Documenting and classifying AEs/SAEs in case report forms.

Assessing causality and expectedness to determine if the event is related to the investigational product and/or study procedures.

Reporting within strict timelines per IRB and/or sponsor reporting guidelines.

Oversight by independent bodies such as Independent Safety Monitor (ISM), Safety Monitoring Committee (SMC) or Data Safety Monitoring Committee (DMC).

In Summary

Safety monitoring is not only a procedural requirement—it is a core ethical and scientific safeguard that ensures clinical trials are conducted responsibly, with participant safety as the top priority.

The Purpose of Data Monitoring

Maintaining Data Integrity

Routine monitoring by the PI and the study team ensures the **data collected is accurate, complete, and consistent** with source documents.

This includes ongoing monitoring of Case Report Forms (CRFs), verifying all data entered is accurate. Accurate data is critical for the scientific validity of the trial and for making reliable conclusions about the research.

Protocol Adherence and Regulatory Compliance

Regular monitoring by the study team verifies the study team is **following the approved protocol, standard operating procedures (SOPs), and Good Clinical Practice (GCP) guidelines**.

Compliance with regulatory requirements from bodies such as the FDA, ICH, and IRB is essential to ensure ethical conduct, and prepare for audits and/or FDA inspections.

Risk Identification and Mitigation

Monitoring by the study team allows for **early detection of deviations, errors, or inconsistencies**.

By identifying issues proactively, study teams can implement corrective measures, preventing costly delays, data loss, or study suspension. This proactive approach helps keep the study on schedule.

COLLABORATION BETWEEN study team members and the PI is the foundation for human subject research

NIH human subject research is inherently collaborative. Whether a study is conducted solely at the NIH or across multiple institutions.

The **Principal Investigator (PI)** and the entire study team must work together to design, conduct, and report the research in compliance with federal regulations, ethical principles, and NIH policies. This teamwork ensures that all aspects of the study — **from protocol design to data management — meet the highest standards.**

The Purpose and Scope of the DSMP

The DSMP must state its purpose — to protect the safety and welfare of research participants, ensure data validity, and maintain study integrity — and define the scope of monitoring activities.

Core Elements of the DSMP

Data Integrity and Accuracy: Monitoring activities (PI/study team) should ensure that collected data are complete, accurate, and consistent with the approved protocol. This includes methods for data verification, case report forms, and analysis plans for efficacy and safety endpoints.

Communication Procedures: The DSMP should define how monitoring results are communicated to the PI, research team, IRB, sponsor, independent safety monitor, FDA, or other relevant entities, including timelines for reporting adverse events, serious adverse events, or unanticipated problems.

Data and Safety Monitoring Responsibilities: The plan should identify individuals or entities responsible for monitoring, such as the Principal Investigator (PI), study medical monitor, independent safety monitor, or an independent safety monitoring committee.

Study Coordination and Documentation: Procedures for systematic study coordination, investigator delegation, and documentation of monitoring activities, reports, and regulatory compliance should be included to ensure study integrity.

Participant Safety – Key Points

Subject Safety

Stopping Rules

Privacy and Confidentiality

Interim Analysis and Review Frequency

Sections of NIH IRB Protocol Templates that Apply to the DSMP

Schedule of Activities	The Schedule of Activities (SoA) is a crucial component of a protocol. It serves as a roadmap for the study, detailing the planned study visits (or encounters) and the associated activities that will occur at each visit. The SoA is essential for understanding how the objectives of the study will be implemented and is used to manage the progress of study participants throughout the trial.
Known Potential Risks	Defining known risks in the protocol is a **critical step for protecting participants, ensuring regulatory compliance, and maintaining study integrity**.
Inclusion/Exclusion Criteria	Inclusion/exclusion criteria are essential for defining the study population, **protecting participants**, ensuring valid and reliable results, and meeting regulatory standards. They must be carefully designed to reflect both scientific rigor and ethical responsibility, while also considering the broader implications for patient access and generalizability of findings.
Study assessment and procedures	Study assessment and procedures in the protocol are not just administrative details—they are the backbone of a successful trial. They ensure scientific validity**, participant safety**, ethical compliance, regulatory adherence, and operational feasibility. A protocol that clearly defines and operationalizes these elements sets the stage for a well-run, credible, and impactful study.

Sections of NIH IRB Protocol Templates that Apply to the DSMP

Adverese Events and Serious Adverse Events

The adverse event (AE) section in a clinical research protocol is a critical component because it defines how the study will identify, document, assess, and report any untoward medical occurrences in participants. This section directly impacts participant safety, regulatory compliance, data integrity, and the credibility of the study.

Safety Oversight

The **safety oversight section** in a protocol is a critical component that ensures the **protection of participant**s, regulatory compliance, and the integrity of study data. It outlines the who the monitoring entity is, the frequency of the data and safety reviews, and processes for identifying, assessing, documenting, and reporting safety events throughout the study.

Clinical Monitoring

The **clinical monitoring section** in a protocol is a critical component that outlines how the PI and the sponsor will oversee the study to ensure **participant safety, data quality, and regulatory compliance**. It is not merely a procedural checklist — it is a strategic safeguard that directly impacts the validity and reliability of study results.

Quality Assurance (QA) and Quality Control (QC)

QA ensures the process of the trial meets quality standards, while QC ensures the data are accurate and reliable. Together, they **protect participants**, ensure compliance, maintain data integrity, and support the validity of research outcomes—making them indispensable in any clinical research protocol.

In Summary

A well-constructed DSMP is a **prospective, written plan** that ensures **participant safety**, data validity, and regulatory compliance. It integrates **safety monitoring, data monitoring, communication, stopping rules, and documentation**, and is tailored to the study's **risk, complexity, and population**.

FDA Guidance on Risk-Based Monitoring

FDA's *Risk-Based Approach to Monitoring of Clinical Investigations (APR2023)* guidance provides a framework for RBM in trials, which can be adapted for natural history/observational studies.

Food and Drug Administration

Food and Drug

Applying Risk-Based Strategies to a Protocol

Risk-based monitoring (RBM) is a **proactive, prioritized approach** to overseeing research studies that focuses on identifying, assessing, and mitigating the most significant risks to **data integrity, participant safety, and protocol compliance.**

Core Principles of Risk-Based Monitoring

The core principles of risk-based monitoring (RBM) include:

Risk Identification and Assessment

Before a study begins, the principal investigator and the study team should identify potential risks to participant safety, data integrity, and protocol compliance.

This includes:

- **Protocol complexity** (e.g., complex procedures, high-risk interventions)
- **Critical processes** (e.g., informed consent, investigational product handling, adverse event reporting). Risk assessment involves evaluating the likelihood and impact of each risk, often using a risk matrix, to determine which areas require the most attention.

Core Principles of Risk-Based Monitoring

Risk Control

Once risks are identified, targeted monitoring strategies are implemented to mitigate them. This may include:

- **Enhanced training** for study personnel and with the addition of new study personnel.
- **Real-time data analysis** to detect emerging issues early.

Risk Review and Reporting

Throughout the study, risks are continuously monitored and reassessed.

This involves:

- **Ongoing data review** to detect trends or deviations.
- **Timely intervention** when risks are identified.
- **Documentation and reporting** of risk findings as required by the sponsor and the IRB or other regulatory agencies.
- **Adaptation of monitoring plans** as the study progresses.

Implementation Steps for Risk-Based Monitoring

Define the Study Context – Understand protocol complexity, and data flow.

Map Risk Factors – Identify high-impact processes and potential failure points.

Assign Risk Levels – Categorize risks by likelihood and impact.

Design a Monitoring Plan – For the study team.

Execute and Review – Apply monitoring strategies and adjust as new risks emerge.

Document and Report – Maintain clear records of risk assessments, actions taken, and outcomes.

Summary of Data and Safety Monitoring

Subject Safety: Detect and respond to adverse events (AEs), serious adverse events (SAEs), and unanticipated problems (UPs) promptly.

Data Integrity: Ensure accuracy, completeness, and compliance with the protocol.

Confidentiality and Privacy: Protect participant data and maintain confidentiality .

Scientific Validity: Maintain scientific integrity, reproducibility and allow timely study termination if necessary.

Schedule a DSMP Consultation

Schedule a DSMP consultation during the protocol development phase.

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