Understanding the Purpose and Scope of Data and Safety Monitoring

NIDDK Biostats Webinar: The Data Lifecycle

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Presenter: Patti A Young, Regulatory Affairs Specialist

Contact Information: patti.young@nih.gov

Affiliation: NIDDK IRP Office of the Clinical Director

Purpose and Scope

This document consolidates Data and Safety Monitoring (DSM) concepts and practical guidance for NIDDK human subjects research. It translates presentation content into a structured reference to support protocol development, monitoring plans, and operational oversight.

Introduction to Data and Safety Monitoring

Data and safety monitoring is a critical component of human subjects research. A comprehensive monitoring plan should define responsibilities, review cadence, and reporting criteria; include robust data quality reviews, secure data handling, and prompt reporting of unanticipated problems; and ensure alignment with institutional, local, and federal guidelines (including informed consent and appropriate approvals).

Core Principles of Data and Safety Monitoring

- Minimize risks described in the IRB-approved protocol; match monitoring methods and intensity to study risk, size, and complexity.
- For *minimal-risk or low-risk* studies: The *Principle Investigator* can assess and report; for *moderate to high risk*: an *ISM* or an *SMC* is required in addition to the *Principle investigator*.
- Verify data quality used in study analyses; independent monitors/committees rely on accurate data; integrity assessment is part of monitoring.
- Clearly outline PI's initial risk determination and monitoring requirements within the protocol.

Selecting the Monitoring Entity (per Policy 503)

The Principal Investigator (PI) makes the initial determination of the appropriate safety monitoring entity: *PI-only*, *PI + Independent Safety Monitor (ISM)*, or *PI + Safety Monitoring Committee (SMC)*. Monitoring should be independent of investigators and free of conflicts of interest.

Roles and Responsibilities

- PRINCIPAL INVESTIGATOR (PI): The PI is ultimately responsible for participant safety and the conduct of the trial, regardless of additional reviewers.
- INDEPENDENT SAFETY MONITOR (ISM): The ISM's primary role is to provide **objective, real-time safety oversight** for studies, that are minimal to low risk or of short duration.
- SAFETY MONITORING COMMITTEE (SMC): Adds disease-specific expertise and biostatistics, appropriate for moderate/high risk trials.
- DATA AND SAFETY MONITORING BOARD (DSMB): Required for Phase III clinical trials; and multi-site studies and may be required in other trials to ensure safe/effective conduct.

Risk Stratification for Safety Monitoring

Table 1 — Assessment of Risk for Safety Monitoring: Definitions and Examples

Risk Level	Definition	Examples
Minimal Risk	No more risk than daily life or routine physical/psychological examinations (45 CFR 46.102).	Blood draw; physical exam; routine psychological testing; surveys/questionnaires; observation; nutrition; behavior studies.
Low Risk	Minor increase over minimal risk; experiences commensurate with actual/expected medical, dental, physiological, social, or educational situations.	Healthy volunteer studies with well-described procedures (e.g., IV infusion, euglycemic clamp, indirect calorimetry); studies with special populations.
Moderate Risk	Risks reasonable relative to benefits/knowledge; greater than low but not as serious as high; protections allow prompt identification and minimization of AEs.	Placebo arms for recognized disease; non-FDA approved drugs/combinations; baseline knowledge to extrapolate AE risk; anticipated mild/moderate AEs; low risk in vulnerable populations; sensitive information collection.
High Risk	Substantial risk or uncertainty; increased probability of serious, prolonged, or permanent events; complex, large, or standard-of-care-altering trials.	Phase III clinical studies; complex multicenter studies; invasive procedures with substantial risk; IDE device implantation; new chemical/drug with limited human toxicology; gene therapy; serious AEs possibly due to condition/disease.

Data and Safety Monitoring Plan (DSMP) — Required Elements

1. Monitoring Responsibilities: Determine the appropriate monitoring entity during protocol development and risk review.
2. Review Frequency: Define intervals for PI/study team monitoring; specify intervals for independent monitoring when applicable.
3. Data Quality Audits: Conduct regular audits for accuracy, completeness, and consistency; document monitoring activities and outcomes.
4. Secure Data Storage: Implement encryption and restricted access for sensitive information to protect confidentiality.
5. Reporting Unanticipated Problems: Establish prompt reporting procedures to regulatory authorities and stakeholders.
6. Compliance: Adhere to institutional, local, and federal guidelines; obtain necessary approvals and informed consent.

NIH IRB Protocol Sections Relevant to the Data and Safety Monitoring Plan

Protocol Section	Relevance to DSMP
Schedule of Activities (SoA)	Roadmap of planned visits/encounters and activities; implements objectives and manages participant progress.
Known Potential Risks	Critical step to protect participants, ensure regulatory compliance, and maintain study integrity.
Inclusion/Exclusion Criteria	Defines the study population; protects participants; ensures valid, reliable results; meets regulatory standards.
Study Assessments & Procedures	Backbone of a successful trial; ensures scientific validity, participant safety, ethical and regulatory adherence, and operational feasibility.
Adverse Events (AE) & Serious Adverse Events (SAE)	Defines identification, documentation, assessment, and reporting of medical occurrences; impacts safety, compliance, data integrity, and credibility.
Safety Oversight	Specifies monitoring entity, review frequency, and processes for identifying, assessing, documenting, and reporting safety events.
Clinical Monitoring	Outlines PI/sponsor oversight to ensure safety, data quality, and compliance; strategic safeguard for validity and reliability.
Quality Assurance (QA) & Quality Control (QC)	QA ensures process quality; QC ensures data accuracy/reliability — both protect participants, ensure compliance, and support research validity.

Essential Elements of Risk-Based Monitoring

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

These principles guide how monitoring resources are prioritized to protect participant safety, ensure data integrity, and improve trial efficiency.

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.

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.

What is a Risk Matrix?

A **risk matrix** is a structured tool used in research to assess and prioritize risks by combining two main factors: **likelihood** (probability) of a risk occurring and **impact** (severity) of that risk if it does occur. It helps researchers visualize and compare risks, making it easier to decide on mitigation strategies.

How it Works

- **Likelihood**: Often categorized as certain, likely, possible, unlikely, or rare.
- **Impact**: Typically classified as high, medium, or low, or more detailed categories such as catastrophic, critical, marginal, or minor.

The matrix plots these categories in a grid, with each cell representing a risk level (e.g., "High Likelihood + High Impact" = high-priority risk).

Step-by-Step Use of a Risk Matrix

1. **Identify risks** – e.g., participant recruitment delays, protocol deviations, adverse events, data entry errors.
2. **Rate likelihood** – How probable is the risk? (e.g., 1 = very unlikely, 3 = likely)
3. **Rate impact** – How severe would the consequence be? (e.g., 1 = minor, 3 = major)
4. **Assign risk category** – Multiply likelihood × impact to get a risk score; map to the matrix.
5. **Mitigation** – For high-risk items, develop mitigation plans (e.g., extra monitoring, training, protocol adjustments).

Example: Simplified Risk Matrix

Table 2 - Example Table (Likelihood × Impact)

Likelihood	High	Medium	Low
High Impact	Critical	High	Medium
Medium Impact	High	Medium	Low
Low Impact	Medium	Low	Low

COLOR CODING (EXAMPLE):

- **Red**= Critical (High likelihood + High impact)
- **Yellow**= High (High likelihood + Medium impact, or Medium likelihood + High impact)
- **Green**= Low (Low likelihood + Low impact)

Practical Data and Safety Monitoring Activities

- Document AEs/SAEs in progress notes (start/stop dates; treatment; worsening during participation).
- Classify AEs/SAEs in case report forms (CRFs).
- Assess causality and expectedness for investigational products/procedures.
- Report per IRB/sponsor timelines.
- Establish oversight as appropriate (ISM, SMC, DSMB).

Operational Oversight Examples

- Ensure proper informed consent procedures.
- Ensure investigational products (drugs/supplements/devices) are handled correctly and documentation is complete.

Compliance and References

- OHRP 45 CFR 46 (including 46.102, 46.111, 46.406).
- FDA 21 CFR 56 (IRBs).
- ICH-GCP; Declaration of Helsinki.
- NIH Office of Science Policy — Clinical Research.
- NIH IRB Policy 503 – Data and Safety Monitoring.

Schedule a Data and Safety Monitoring Plan Consultation

We recommended you schedule a DSMP consultation during the protocol development phase. You can also reach out with questions or clarifications at any time.

Patti A Young
Email: patti.young@nih.gov