HUMAN RESEARCH PROTECTION

Data and safety monitoring in research

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Resource type GUIDANCE

Purpose: To provide researchers with guidelines on how to develop a Data and Safety Monitoring Plan (DSMP) for clinical research.

Note: This guidance should be considered in addition to specific requirements by entities with authority to review and approve Data and Safety Monitoring Plans (DSMPs) and Data and Safety Monitoring Boards (DSMBs) such as federal agencies (e.g. NIH), the reviewing IRB, scientific review committees (SRCs), study sponsors, or study coordinating centers.

Visit the Hennepin Healthcare HRPO webpage for information and current forms:
https://www.hhrinstitute.org/researcher-resources/ohsr/

Definitions and regulatory requirements

One of the regulatory criteria for IRB approval is that the research provides adequate provisions for monitoring data to ensure safety of subjects and research integrity. The specific monitoring strategy will depend on the risk, size, and scope of the study, and may involve individuals or groups. The IRB reviews the plan and determines if the plan has adequate provisions in place for monitoring the data collected to ensure the safety of participants.

Data Monitoring: The regular evaluation of data and documentation collected during a study to ensure both adherence to the approved investigative plan and the validity of data collected (White 2007).

Safety Monitoring: The observations required to minimize threats to the safety and welfare of research subjects (White 2007).

A written Data and Safety Monitoring Plan (DSMP) prospectively identifies and documents monitoring activities intended to protect the safety of the subjects, the validity of the data, and the integrity of the research. The DSMP may also identify when to terminate a participant's participation (i.e., individual stopping rules) and/or the appropriate termination of a study (i.e., study stopping rules).

What research studies require data and safety monitoring plans?

All studies, no matter the risk level, should have a DSMP that protects the safety of subjects, the validity of the data, and the integrity of the research study. The plan should be commensurate with the risks and complexities of the study. For example, studies whose only procedure is review of existing medical records should have a data monitoring plan to ensure accuracy, integrity and security of the data.

All greater than minimal risk research must have a have an IRB-approved DSMP. Certain studies (e.g., Phase II and Phase III randomized, blinded trials involving life-threatening diseases) are required to include an independent (defined as independent of the research study team) Data and Safety Monitoring Board (DSMB) established to monitor the safety events and data associated with the study on an ongoing basis. Greater than minimal risk research will not be approved by the IRB without an adequate plan for independent monitoring. See *When is a Data and Safety Monitoring Board required?* below for more information.

Who is responsible for the oversight of the data and safety monitoring plan?

Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. Individuals or groups who may conduct monitoring include:

- Principal Investigator
- Designated monitor associated with the sponsor or the study
- Independent safety officer
- Internal steering committee or internal data monitoring committee made up of representatives of the sponsor and study investigators
- Data Safety Monitoring Board (DSMB) made up of representatives who are independent of the study sponsor and investigators (See *When is a Data and Safety Monitoring Board required?* below)

The DSMP must clearly describe the individuals and/or groups and justification for the selection including:

- Justification that the number of individuals responsible for monitoring is enough to accomplish the monitoring activities
- Justification that the expertise of the individuals responsible for monitoring is appropriate to detect safety concerns and make appropriate recommendations for the study
- Justification that an independent safety monitoring entity is or is not needed
    - An independent safety monitor can view the data and documentation objectively, providing unbiased feedback to the study team. An independent safety monitor may also have monitoring-specific expertise, which allows the monitor to complete the review efficiently and thoroughly
- The division of study components that are reviewed by each individual with monitoring responsibilities (e.g., the study coordinator reviews the consent and eligibility documentation, while the independent monitor reviews the case report forms and data set)

When is a Data Safety Monitoring Board (DSMB) required?

Establishment of a DSMB for certain greater than minimal risk research is the most appropriate way to monitor data and safety for:

- Blinded studies
- Studies involving a vulnerable population (e.g., pediatric, geriatric, cognitively impaired)
- Studies involving high-risk interventions
- Studies involving high expected rates of morbidity or mortality in the study population
- Studies involving a high chance of early termination
- Studies involving multiple sites

The IRB has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed.

The composition of a DSMB Charter must include:

- purpose of the DSMB
- responsibilities of the members
- operation and format of the DSMB meetings
- monitoring guidelines
- reporting processes (to and from the DSMB)
- research data to be monitored and how data will be provided

The composition of a DSMB must include:

- Multidisciplinary representation, including physicians from relevant medical specialties and biostatisticians. This may include other experts such as bioethicists, epidemiologists and basic scientists. A biostatistician is required if efficacy assessment is part of the monitoring plan. A medical ethicist should be considered for protocols involving unusually high-risks or broad public health considerations.
- Members who are free of significant conflicts of interest (i.e., financial, intellectual, professional, or regulatory).
- The appropriate number of members (3-5) depending on the type of study and types of expertise needed.

DSMB meetings should be held at a frequency commensurate with risks, size, and complexity of the protocol. The DSMB should meet at least annually and more often (quarterly or semi-annually) if the protocol involves high-risk, vulnerable populations, or a large volume of data.

Note: The National Institutes of Health (NIH) requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants.

How often should monitoring be performed?

Frequency of data and safety monitoring will be dependent on the nature of the research study; at a minimum, formal monitoring should be performed annually. The frequency should be established to ensure that:

- Additional risks to subjects can be identified in a timely manner such that decisions can be made about their care
- Safety concerns about the study can be identified in a timely manner such that decisions can be made about the conduct of the study
- Study accrual rates can be assessed and interim analysis performed in a timely manner such that decisions can be made about the conduct of the study
- Research documentation is complete
- Data collection is complete, with as few missing data points as possible
- Data is collected accurately, with errors
- Research data is valid, capturing all appropriate information that can be used to answer the research question

When establishing the frequency of monitoring, consider whether the research involves any of the following:

- High-risk procedures or a high-risk/vulnerable study population
- Anticipated high enrollment rate
- Complex eligibility criteria and consent process
- Complex study procedures
- Collection of a large number of data points
- Absence of pre-programmed data entry failsafe

When writing this section of the plan, include justification for the intended frequency of monitoring.

What should be monitored?

In developing an appropriate DSMP, consideration should be given to incorporate the following elements:

Study accrual rate – evaluation of the progress of the research study, including subject recruitment and retention (i.e., is the accrual rate appropriate for achieving study aims), and an assessment of the timeliness and quality of the data.

Subject Safety –

- review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is any change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated. If appropriate and if specified in the IRB protocol, interim analyses of the efficacy of the intervention should be performed in accordance with previously defined stopping rules.
- assessment of external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic developments, results of related studies) that may have an impact on the safety of study participants or the ethics of the research study
- documentation that all adverse events and problems have been recorded in the study record and appropriately reported to the IRB, the sponsor, the FDA, etc.

Subject Privacy – monitoring conducted to assure individual's rights are protected.

Data Confidentiality – monitoring conducted to assure data is secured.

Data Integrity – monitoring conducted to assure data is accurate and complete. Monitoring of data assures adherence to the approved clinical study.

Product Accountability – monitoring conducted to assure drug(s) or device(s) are tracked and accounted for at all times during the study.

Study Documentation – monitoring conducted to assure that required documentation and reports are on file, accurate, and complete. This includes all documentation that must be maintained according to federal regulations, IRB policy, and institutional policy, as well as study participants records including informed consent, as applicable. For example, informed consent documentation should include documentation that all participants have provided informed consent using the IRB-approved consent documents and process.

Study Coordination – monitoring conducted to assure that investigator delegation and communication with the research team is planned and systematic. This includes all documentation of required qualifications and training of research staff, as well as documentation that study procedures were only performed by qualified personnel.

Protocol compliance – documentation that all study procedures, from recruitment/enrollment through study closure, have been completed in compliance with the study protocol and study operating procedures. This may include randomization procedures, if applicable, to document that all participants were randomized according to procedures described in the approved protocol.

How should monitoring be documented and responded to appropriately?

After a monitoring review has been completed, a written report of the findings should be created. The PI should consider the findings with other members of the study team and determine if corrective actions are necessary, which may include:

- Amending the protocol or consent form
- Re-consenting participants
- Additional data collection from participants
- Withdrawal of participants from the study
- Suspension or closure of the study

Any changes made to IRB-approved documents or information must be submitted to the IRB for approval prior to initiating the change.

The PI must also determine whether the findings and corrective actions must be reported to any of the following entities, as applicable:

- IRB
- Study sponsor
- Safety monitoring entity, such as a DSMB
- Regulatory agencies, such as the FDA

References & resources

45 CFR 46.111(a)(6)

21 CFR 56.111(a)(6)

NIH Data Safety Monitoring: https://grants.nih.gov/policy/humansubjects/policies-and-regulations/data-safety.htm

FDA Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring

Harvard Catalyst Data and Safety Monitoring Guidance: https://catalyst.harvard.edu/pdf/regulatory/DSMB-P_Guidance.pdf

Mayo Clinic Data and Safety Monitoring Plan Guidelines: https://www.mayo.edu/research/documents/43-data-and-safety-monitoring-guidelinespdf/doc-10026780

University of Pittsburgh Data Safety Monitoring Plan: http://www.irb.pitt.edu/data-and-safety-monitoring-plan

University of Pittsburgh Data Safety Monitoring Board/Committee: https://www.irb.pitt.edu/sites/default/files/DSMB_4.1.2014.pdf

University of Utah IGS: Elements of a Data Monitoring Plan: http://irb.utah.edu/_pdf/IGS-ElementsOfaDataMonitoringPlan.pdf

University of Utah IGS: Elements of a Safety Monitoring Plan: https://irb.utah.edu/_resources/documents/pdf/IGS%20-%20Elements%20of%20a%20Safety%20Monitoring%20Plan%20E0114.pdf

White S, Field L, Wolf D. Monitoring the Monitors. Applied Clinical Trials. September 2007; p52-60