

ELEMENTS OF A SAFETY MONITORING PLAN

Definitions

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

Federal Research Regulations and IRB Policy

The Common Rule and FDA regulations state that the IRB may only approve research if there are adequate provisions for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6) & 21 CFR 812.4 & 312.5-6).

NIH policy states that every clinical trial should have provisions for data and safety monitoring (NIH 1979).

IRB Policy

A safety monitoring plan is required for all studies that are greater than minimal risk, as determined by the IRB. The IRB requires that the full safety monitoring plan be *summarized* in the IRB application. The study team must maintain the *full* safety monitoring plan as part of the study operating procedures or study protocol.

Description

In order to monitor safety, the study team must also monitor the data collected, such that an accurate recording of all adverse events and other applicable data elements can be reviewed for safety purposes. For this reason, the data and safety monitoring plan may be combined for some studies.

Elements of a safety monitoring plan are discussed in detail below and include:

- Who is responsible for performing the safety monitoring?
- How often will monitoring be performed?
- What components of the study will be monitored for safety purposes?
 - Study accrual rate
 - Compliance with eligibility criteria
 - Participant adherence with assigned therapy, intervention, or study procedures
 - Investigator adherence with the approved protocol and investigative plan
 - Adverse events and other problems or trends that may indicate a safety concern for participants
 - Interim analysis to determine if the study will be able to answer the study hypotheses or meet study aims
- How will monitoring be documented and responded to appropriately?

Who is responsible for performing the safety monitoring?

One or more individuals may be responsible for monitoring participant safety. These individuals may be internal to the study or may be independent of the study team. This may include the following individuals:

- The PI
- An independent physician or faculty member
- A safety monitor
- A data and safety monitoring board or committee (DSMB/DSMC)

When writing this section of the plan, include:

- Justification that the number of individuals responsible for monitoring is enough to accomplish the monitoring activities.

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- 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 but thoroughly.

How often will monitoring be performed?

Monitoring should be conducted at an appropriate frequency 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; and
- Research data is valid, capturing all appropriate information that can be used to answer the research question.

The frequency of monitoring may need to be increased for any of the following factors:

- The study involves high-risk procedures or a high-risk/vulnerable study population
- The anticipated enrollment rate is high
- The number of data points being collected is large
- The study procedures are complex

When writing this section of the plan, include justification that the intended frequency of monitoring satisfies all of the points described above.

What components of the study will be monitored?

In general, the following components can be monitored for all types of studies:

Study accrual rate

The safety monitoring entity must determine if the accrual rate is appropriate for achieving study aims. The safety monitoring entity may make recommendations for amending the study to improve enrollment.

Protocol compliance

This includes compliance with

- a) eligibility criteria;
- b) participant adherence with assigned therapy, intervention, or study procedures;
- c) PI adherence with the approved protocol; and
- d) accuracy and completeness of study data.

The level of compliance and problems associated with compliance must be determined (via data monitoring) and then reported to the safety monitoring entity. The safety monitoring entity must then determine if non-compliance prevents the study from achieving study aims, compromises data analysis, or places participants at additional risk. The safety monitoring entity may require corrective actions or changes to the study to address compliance issues.

All adverse events and other problems or trends that may indicate a safety concern for participants

Adverse events and other problems must be reported to the monitoring entity, including the PI's analysis of each event/problem. The safety monitoring entity must then determine if the events/problems indicate safety concerns for the participant that must be addressed. The safety monitoring entity must consider the documented stopping and un-blinding criteria and justifications for individual participants, as well as stopping criteria for the study. The safety monitoring entity may recommend stopping the study due to safety concerns.

Interim analysis to determine if the study will be able to answer the study hypotheses or meet study aims

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Interim analysis should be performed as appropriate intervals. The safety monitoring entity may recommend stopping the study due to futility or inadequacy of the data.

How will monitoring be documented and responded to appropriately?

After a safety 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 via an amendment application.

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
- Regulatory agencies, such as the FDA

Points to Address

New Study Application: 1. **Safety Monitoring Plan page:** Answer the questions by providing a summary of the overall safety monitoring plan for the study.

References & Links

<i>Article: Monitoring the Monitors</i>	<i>White S, Field L, Wolf D. Monitoring the Monitors. Applied Clinical Trials. September 2007; p52-60</i>
<i>NIH Guidance</i>	<i>NIH Guide for Grants and Contracts, Volume 8, No. 8 (1979)</i>
<i>IGS: Elements of a Data Monitoring Plan</i>	To be updated
<i>Data and Safety Monitoring Using Self Assessments</i>	To be updated
<i>Data and Safety Monitoring Guidance (IRB)</i>	To be updated

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