

 <b>Research Integrity Office</b>	<b>Human Research Protection Program Regulatory Sheet</b>	
<b>Title: Data and Safety Monitoring</b>	Date Effective 10/31/2007	Supersedes P&P dated: N/A
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**BACKGROUND**

The purpose of monitoring is to protect and promote the safety of subjects and validity and integrity of data by ensuring prompt detection and reporting of unanticipated problems and adverse events. Monitoring provisions can vary with respect to their methods, but regardless of study design, monitoring should be done on a regular basis. When designing and approving research, the investigator(s) and the IRB should give appropriate consideration to the spectrum of adverse events that might occur in subjects. The IRB needs to receive and review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the adverse events that may be caused by the intervention involved in the research. Depending on the risks of the research and the likelihood that the research could involve risks to subjects that are unforeseeable, the IRB must ensure, if appropriate, that the research includes adequate provisions for monitoring the data collected to ensure the safety of subjects. Meaningful detection of unanticipated problems and adverse events is predicated on an appropriately designed monitoring system.

**SCOPE**

This policy details when data and safety monitoring is required and if so, what type and degree of monitoring provisions should be in place.

**AUTHORITY**

46.111(a)(6) requires that when it's appropriate, the research plan must make adequate provisions for monitoring the data collected to ensure safety of subjects.

NIH policy (June 10, 1998) requires monitoring that should be commensurate with the risks to the subjects for all clinical trials (<http://grants1.nih.gov/grants/guide/notice-files/not98-084.html>). Further Guidance for Phase I and Phase II Trials was issued by the NIH (<http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>)

**FDA Guidance**

<http://www.fda.gov/cber/gdlns/clintrialdmc.pdf>

46.109(e) authorizes the IRB to observe or have a third party observe the research.

**I. POLICY**

**A.** The monitoring provisions should be tailored to the expected risks of the research, the type of subject population being studied and the nature, size and complexity of the research protocol.

**B.** Monitoring exists on a continuum and depending on the nature of the study, one of these monitoring entities may be required:

1. Investigator Monitor

2. Independent Monitor
3. Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)
4. OHSU Cancer Institute (CI)

C. The monitoring provisions must be described in sufficient detail for the IRB to determine whether they are appropriate for the research.

D. All research requires some level of monitoring and principal investigators are responsible for monitoring their studies. However, the IRB must approve the plan for monitoring data and safety for all research except minimal risk research where OHSU is the only site

## II. PROCEDURES

### A. When to Include Monitoring Provisions in your IRB Application

1. When submitting a study for IRB review and approval that is:
  - Greater than minimal risk research,
  - A Multi-Site study where OHSU is the coordinating center, or
  - A study where there is an NIH requirement for a Data and Safety Monitoring Plan (DSMP)

The IRB application must include appropriate monitoring provisions, which includes designation of a monitoring entity.

### B. Required Monitoring Provisions

1. The type of data or events that are to be reviewed under the monitoring provisions.
2. The monitoring entit(ies) responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a DSMB/DMC, and/or some other entity).
3. The role(s) of the monitoring entities.
4. The time frames for reporting adverse events and unanticipated problems to the monitoring entity.
5. Schedule of monitoring reviews by each monitoring entity.
6. Definition of specific triggers or stopping rules that will dictate when some action is required.
7. Procedures for communicating to the IRB(s), and as applicable, the study sponsor, the investigator(s), and other appropriate officials, the outcome of the reviews by the monitoring entity. Refer to the OHSU Policy on Reporting Unanticipated Problems and Adverse Events for reporting timelines to the IRB.
8. The monitoring provisions should be tailored to the expected risks of the research; the type of subject population being studied; and the nature, size (in terms of projected subject enrollment and the number of institutions enrolling subjects), and complexity of the research protocol.

### C. Determining the type of Monitoring Entity

#### 1. Investigator Monitor

- a. This type of monitor is appropriate when the study involves:
  - a small number of subjects; and
  - the study is conducted only at one site; and
  - the study involves low risk to subjects.
- b. In such cases, ongoing monitoring of events by the investigator, and prompt reporting of unanticipated problems to the IRB and, when applicable, the FDA, the NIH, or others, may be adequate.

#### 2. Independent Monitor

- a. This type of monitor is often appropriate to monitor data and safety for clinical trials that do not anticipate serious irreversible events and that involve:

- an intervention (for example, to relieve symptoms) that poses only moderate risk to subjects; and
  - short term treatments where effects are evaluated over periods of a few days to a few months; and
  - a smaller number of subjects where the study is completed quickly and the risk can be adequately assessed through simple comparisons.
- b. In these studies, valuable secondary objectives such as characterization of the effect (i.e., magnitude, duration, time to response), assessment of the effect in population subsets, comparison of several doses/or comparison of the new product to an active control can be ethically pursued even when the conclusion regarding the primary efficacy outcome is clear. Early termination for effectiveness is rarely appropriate in such studies. First, the study may be essentially completed by the time any interim analysis to evaluate effectiveness could be undertaken. Second, the effectiveness of an intervention, for example, to relieve symptoms, would not generally be so compelling as to override the need to collect the full amount of safety data, or to collect other information of interest and importance that characterizes the effect.

**3. Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)**

- a. In general, a DSMB/DMC is the most appropriate way to monitor data and safety for studies that involve:
- Large numbers of subjects where risk may better be assessed through statistical comparisons of treatment groups;
  - Blinded study treatment groups where the validity and integrity of the study may be adversely affected by having an individual or group associated with the design and conduct of the study break the blind;
  - Multiple clinical sites where there is a need for investigators to submit reports of adverse events to a central reporting entity, such as a coordinating center or statistical center, responsible for preparing timely summary reports of adverse events for distribution among the clinical sites, and to the IRBs;
  - High risk interventions where death or severe disability is a major risk of research participation; and/or
  - Controlled trials with mortality or major morbidity as a primary or secondary endpoint where increased morbidity or mortality may better be assessed through statistical comparisons of morbidity or mortality among treatment groups.

The establishment of DSMBs is required by the NIH for multi-site clinical trials or those involving high risk interventions. This would include, in most cases, phase III clinical trials but may also be required for multi-site or high risk phase 1 and 2 trials.

**D. Submitting your Monitoring Provisions for Approval**

1. Once you have determined whether your proposed research requires monitoring provisions and the correct monitoring entity, the monitoring provisions must be submitted to the IRB for approval.
2. If your protocol contains all of the requirements for monitoring provisions and/or there is an NIH or other DSMP in place, complete the appropriate sections in the IRB application. Upload a submission memo that indicates where the DSMP can be found in existing documents. If using the Oregon Cancer Institute (CI) download a copy of their approved DSMP from the CI website and upload with your submission.
3. If your protocol does not contain all of the requirements for monitoring provisions and there is not a DSMP in place, then complete the [OHSU DSMP Template Form](#).

**E. IRB Review of the Monitoring Provisions**

1. The IRB will review the monitoring provisions to ensure that they will adequately aid in the protection of human subjects by detecting adverse events and unanticipated problems.

2. The IRB review will consider the design of the monitoring provisions and the appropriateness of the monitoring entity.

## **F. DEFINITIONS**

Data and Safety Monitoring - The process for reviewing real time events and accumulated outcomes data from an ongoing trial to ensure the continuing safety of current participants and those yet to be enrolled, as well as the continuing validity and scientific merit of the trial and appropriate stopping rules.

Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) – An independent formal committee that is established specifically to monitor data throughout the life of a study to determine if it is appropriate, from both the scientific and ethical standpoint, to continue the study as planned. DSMBs/DMCs are typically made up of individuals who have expertise in the field, experience in the conduct of clinical trials, and/or statistical knowledge, and who do not have any serious conflicts of interest, such as financial interests that could be substantially affected by the outcome of the trial, strong views on the relative merits of the interventions under study, or a relationship with the sponsor or those in trial leadership positions that could be considered reasonably likely to affect their objectivity.

Investigator Monitor – The Principal Investigator or a Co-investigator who is responsible for data and safety monitoring.

Independent Monitor - A qualified and objective individual or group not directly involved with the design and conduct of the study (e.g., safety officer, designated Medical Monitor or Monitoring Group). These individuals may or may not be employees of OHSU or the study sponsor. However, conflict of interest is an important consideration when employees of the study sponsor have the primary responsibility for monitoring data from the standpoint of scientific integrity and participant safety.

Minimal risk - 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.

Monitoring provisions – The description of the plan for data and safety monitoring and the type of monitoring entity.

## **G. REFERENCES**

1. NIH policy (June 10, 1998): <http://grants1.nih.gov/grants/guide/notice-files/not98-084.html>. NIH
2. Further Guidance for Phase and Phase II Trials: <http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>.
3. FDA Guidance: <http://www.fda.gov/cber/gdlns/clintrialdmc.pdf>