Institutional Review Board Policies and Procedures Manual

SECTION 13: DATA SAFETY MONITORING AND REGULAR REPORTING REQUIREMENTS

13.1 DATA AND SAFETY MONITORING

A. Data and Safety Monitoring of Clinical Trials

In accordance with the federal requirements that IRBs determine "where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of the subjects" (45 CFR 46.111 (a)(6) and 21 CFR 56.111(A)(6)) all protocols that involve more than minimal risk to subjects conducted at the Institution require a description of data and safety monitoring procedures. Minimal risk means that the probability and magnitude of the 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 (45 CFR 46.102(i) and 21 CFR 56.102(i)).

Data and safety monitoring allows for the review of accumulated data from ongoing research to ensure the continuing safety of current and future study subjects, as well as the continuing validity and scientific merit of the study.

i. Elements of a Data Safety Monitoring Plan

   a. The type of data and events to be captured

   b. An outline of who is responsible for monitoring the data, including unanticipated problems and adverse events, and reporting of events

   c. The time frame and frequency for the monitoring and reporting of events

   d. The guidelines as to when the research will be stopped or altered based on the review of the data

   e. A description of procedures for communicating the results of the data review to the IRB

B. Establishment of Formal Data and Safety Monitoring Board/Committee

In order to ensure the safety of subjects and the integrity of study data, many investigators and research sponsors have begun outlining specific procedures for data and safety monitoring of clinical trials by establishing formal Data and Safety Monitoring Boards (DSMBs) and Data Monitoring Committees (DMCs). A DSMB/C is comprised of individuals with pertinent expertise that review accumulating data from an ongoing clinical trial on a regular basis. These individuals then advise the sponsor or the investigator regarding the continuing safety and scientific merit of the trial.

i. Federal Requirements for Establishing a Formal DSMB/C

   NIH guidance clarifies that monitoring should be commensurate with size, complexity, and risks of the research. NIH policies require the establishment of a formal DSMB for most Phase III clinical trials. They further advise that a DSMB may be appropriate for a Phase I or a Phase II clinical trial, depending upon the degree of risk of the intervention, the vulnerability of the study population, the number of sites involved, and the study design (e.g., double blind).

   Current FDA regulations, on the other hand, impose no requirements for the establishment of DSMBs/Cs in clinical trials except in cases of emergency research where informed consent requirements are waived (21 CFR 50.24(a)(7)(iv)). Because

of the recognition of the increased need for the use of DSMBs/Cs in industry-sponsored trials, the FDA has established guidelines for data and safety monitoring oversight.

As stated in the FDA *Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees*, "DMCs have generally been established for large, randomized multisite studies that evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. Because monitoring of accumulating results is almost always essential in such trials, DMCs should be established for controlled trials with mortality or major morbidity as a primary or secondary endpoint. They may also be helpful in settings where trial subjects may be at elevated risk of such outcomes even if the study intervention addresses lesser outcomes such as relief of symptoms. Although DMCs may prove valuable in other settings as well, a DMC is not needed or advised for every clinical study. Several factors are relevant to determining whether to establish a DMC for a particular trial. These relate primarily to safety, practicality, and scientific validity."

ii. IRB Review of Formal DSMB/C Data Safety Monitoring Plans

As a part of the initial review, the IRB will review the data safety monitoring plan established by the formal DSMB/C including the DSMB/C Charter. Generally, the data safety monitoring plan will include how the data will be monitored for safety of subjects, for effectiveness of research interventions, review of study conduct and data accuracy. The content of the data safety monitoring plan is typically contained in a DSMB/C Charter which outlines well-defined standard operating procedures for the DSMB/C. A DSMB/C charter also includes:

a. A description of committee composition;

b. A description of meeting schedules, structure and format;

c. The format of interim results and reports;

d. An outline of specific clinical criteria for withdrawal of a subject based on safety or toxicity concerns;

e. The rules for stopping or amending the study due to safety concerns;

f. The plans to perform interim efficacy statistical analyses;

g. The type of data (e.g., blinded or unblinded) that will be accessed by the monitor(s) or DSMB/C;

h. The affiliations and qualifications of safety monitor(s); and

i. The frequency of monitoring visits and/or DSMB review.

iii. Monitoring When No Formal DSMB/C is Established

The IRB recognizes that not all trials require monitoring by a formal, external DSMB/C. In some cases, the IRB may recommend or require that such a Board be established for a research study. Specifically, a DSMB/C may be required if the IRB determines that interim monitoring of study data is essential to ensure the safety of trial subjects, or if the IRB believes that individuals outside of the research team should be

consulted for an objective assessment of interim data to identify any emerging concerns.

iv. IRB Reporting Requirements of Data and Safety Monitoring

Summary reports of ongoing data and safety monitoring are to be submitted for IRB review via the Renewal application in the electronic IRB system. Such reports should exclude any confidential information (such as interim data and the specific results of interim analyses). Each report submitted to the IRB should include a determination regarding the appropriateness of continuing the research based on the reviewed adverse events, interim findings, and any recent relevant literature.

If a report indicates that there are changes to the risks to subjects, study protocol, consent form, or investigator's brochure as a result of the findings/recommendations of the DSMB/C, a Modification is to be submitted in the electronic IRB system. When the overall risk/benefit ratio of the study may be impacted by the information in the report, no new subjects should be enrolled in the research until the IRB has reviewed and approved the changes recommended by the DSMB/C.

13.2 REGULAR REPORTING REQUIREMENTS

Federal regulations require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems, adverse events, or protocol deviations involving risks to subjects or others (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)). This would include the early termination of a study or study site by the PI or Sponsor.

Any information relevant to the protection of research subjects must be reported to the IRB, including, but not limited to, unanticipated problems, adverse events, and protocol deviations that involve risks to subjects or others, interim results, and/or protocol modifications. If the PI is the lead researcher of a multi-site study, events from any site must be reported to the IRB in order to determine if the management of information relevant to the protection of subjects is adequate.

A. Events Requiring Reporting to the IRB

i. Unanticipated Problems

An *unanticipated problem* refers to a problem, event, or information item that is (a) unexpected, given the nature of the research procedures and the subject population being studied; (b) related or possibly related to participation in research and (c) suggests that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

A problem, event, or information item is unanticipated if the specificity, severity, or frequency of the event is not expected based on (a) information contained in the protocol, investigator's brochure, informed consent document, drug or device product information or other research materials; and (b) the characteristics of the subjects, including underlying diseases, behaviors, or traits. Changes made to the research without prior IRB approval in order to eliminate apparent or immediate harm must be reported as unanticipated problems.

Investigators are required to inform the IRB promptly of any unanticipated problems, serious adverse events/adverse events, and protocol deviations that meet the following criteria: unexpected, related to the study, and increase risks to subjects or others.

ii. Serious Adverse Events/Adverse Events

An *adverse event* is an untoward physical or psychological occurrence in a human subject participating in research, which occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. The event may be any unfavorable outcome, including abnormal laboratory result, symptom, disease, or injury. Adverse events may be expected or unexpected, may not necessarily be caused by the research, and may be serious or not. *Serious adverse events* include those resulting in death, life-threatening injury, hospitalization, or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly or birth defect. Events not meeting the above criteria but requiring intervention to prevent one of these outcomes are also considered serious adverse events.

Adverse events that are unanticipated, related to the research, and serious or involve risks to subjects or others, qualify as a subset of unanticipated problems.

Any *serious adverse event* that is unanticipated with regard to specificity, severity, or frequency for the investigational agent and the population or disease being studied and is related or possibly related to the study intervention(s) must be reported to the IRB when the event occurs at our Institution. Generally, events listed in the investigator brochure and consent form as having been previously observed do not need to be reported. Similarly, adverse events that are consistent with the natural history of the underlying disease do not need to be reported to the IRB. However, if the severity of the event is greater than events previously observed, or the frequency is greater than anticipated, the event qualifies as unanticipated and if there is any reasonable possibility that it might be related to the study intervention it should be reported to the IRB.

Investigators often receive reports of serious adverse events occurring at other sites. These do not need to be reported to the IRB according to this policy. However, any amendments to study protocols and related documents that result from such events require IRB approval.

iii. Protocol Deviations/Violations

A *protocol deviation* is any aberration, whether accidental, unintentional, or intentional, from the IRB-approved protocol/research plan.

Emergent deviations are those occurring in an emergent situation, such as when a departure from the protocol is required immediately to protect the life or physical well-being of a participant. In such cases, there is no time to prospectively seek the approval of the IRB. Emergent protocol deviations require prompt (within 10 days) reporting to the IRB via an Incident Report in Electronic IRB system.

Major deviations are those which produce or have the potential to produce actual harm to a participant or others, affect the scientific soundness of the protocol or the rights, safety, or welfare of human subjects. Whenever possible major, non-emergent intentional or planned protocol deviations require approval by both the sponsor (if applicable) and the IRB prior to implementation. Examples of these types of deviations include, but are not limited to 1) exception to eligibility criteria, 2) significant changes to timing of drug administration or procedures, 3) modifying safety monitoring procedures to reduce study-related risks, etc. Investigators must submit planned major protocol deviations to the IRB for review via a Modification in the electronic IRB system.

Minor or administrative deviations are those which do not affect the scientific soundness of the protocol or the rights, safety, or welfare of human subjects. These minor deviations do not need to be reported to the IRB as they do not have potential to cause harm to the research subject or others, but they may be required to be reported to the study sponsor (if applicable). Examples of these types of deviations include follow up visits or procedures occurring outside, but in approximation to, the protocol required window, missed assessments that do not affect safety, etc.

B. Reporting Events to the IRB

Submit an Incident Report via the electronic IRB system to report any internal serious adverse events, protocol deviations, and/or unanticipated problems that meet the reporting criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Reports must be submitted to the IRB as soon as possible, but no later than 10 days after the PI becomes aware of the event. The PI should comprehensively describe the event in the context of the study protocol and provide their assessment of the event's relevance to the study. All deaths occurring in subjects enrolled at our Institution, that were not expected given the population enrolled, need to be reported within two business days of the PI becoming aware of the event.

If the protocol and/or consent form requires revision in response to reporting an event to the IRB, the proposed revisions should be submitted as a Modification in Electronic IRB system. In such a case, when the overall risk/benefit ratio of the study may be impacted by the event, no new subjects should be enrolled until the IRB has reviewed and approved the proposed revisions. If a temporary halt of enrollment poses significant problems, the PI should immediately contact ORIC staff for guidance.

In order to protect the privacy of research subjects, reports are not to contain individually identifiable subject information. The investigator must remove all information which directly identifies a subject from all reports and supporting material before submitting them to the IRB.

C. IRB Review Procedures for Reportable Events

When a submission for any Incident Report is received by the IRB, the following will take place:

i. The RCC will review the submission documents. If additional information is needed, the RCC will email the PI and their staff and/or request the additional information directly through the electronic IRB system.

ii. The RCC will review the response from the PI or their study staff and will forward the submission to the IRB Chair or Vice-Chair(s).

iii. The IRB Chair or Vice Chair will make the determination on whether the event meets the criteria of an unanticipated problem and determine if additional actions are required. These actions may include the following:

a. Modification of the protocol;

b. Modification of the information disclosed during the consent process;

c. Providing additional information to current or past subjects;

d. Requirement for re-consent of current subjects;

e. Modification of the periodic review schedule;

f. Monitoring of the research;

g. Monitoring of the consent process;

h. Referral to other Institutional entities such as, but not limited to, the IO and the Scientific Director; and/or

i. Suspension or termination.

iv. Any changes required to the study protocol, informed consent process or documents due to a change in risk(s) or safety to study subjects will be reviewed by the convened IRB

v. The IO will be kept informed of any unanticipated problems, serious adverse events, or protocol deviations that increase risks to subjects or others, and will report these to the appropriate regulatory agencies as required:

a. OHRP, when research is covered by DHHS regulations;

b. FDA, when the research is FDA-regulated;

c. Other government agencies when the research is overseen by those agencies, and they require reporting separate from that to OHRP;

d. Other organizations, such as sponsors or contract research organizations, when appropriate; and

e. Other sites involved in the research, when appropriate.

Note: The Institution need not report to regulatory agencies already made aware of the event through other mechanisms, such as reporting by the Researcher, sponsor, or another Organization.

vi. All events meeting the definition of unanticipated problems that increase risks to subjects/others or involves more than minimal risk will be reported to the convened IRB for deliberation and for a vote on the management and proposed corrective action.

D. Suspension or Termination of IRB Approval

The IRB has the authority to suspend or terminate research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. A suspension is a temporary cessation of some or all research activities. A termination is a permanent cessation of all research activities. The IRB Chair or Vice-Chair are authorized to suspend or terminate research on an urgent basis and will promptly notify the

PI of any decision. If the situation is not urgent and time permits, the convened IRB will make the decision to suspend or terminate research. Any decision to suspend or terminate research by the IRB Chair or Vice-Chair, or if the suspension or termination was decided by someone other than the IRB Chair or Vice-Chair, will be discussed at the next convened IRB meeting. The notification will include the reasons for the suspension or termination. For a suspension, the notification will include a description of any actions to be taken before the suspension may be lifted.

If the IRB decides to suspend or terminate its approval of a research project, the IRB will ascertain whether there are subjects enrolled in the research. If subjects are currently enrolled, the IRB will work with the PI to ensure a plan is in place to appropriately notify subjects and that procedures for subject withdrawal will consider the rights, safety, and welfare of those subjects. The PI is expected to provide the IRB with information regarding additional adverse events or related outcomes after a suspension or termination. Any decision by the IRB to suspend or terminate IRB approval will be reported within 30 days to OHRP and to the FDA (if applicable).