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.