FIU IRB Data and Safety Monitoring Guidelines

1. INTRODUCTION

The central guardian of participants' safety and welfare in clinical trials that are federally funded is the Office of Human Research Protections (OHRP), a department of the U.S. Department of Health and Human Services (DHHS); and the Office of Human Affairs, a department of the U.S, Food and Drug Administration (FDA). Enforcement the protection of human subjects is based on the Code of Federal Regulations, Title 45, Part 46 and Title 21, Part 50 respectively. It is therefore the policy that local Institutional Review Boards (IRBs) have provision for the appropriate oversight and monitoring of the conduct of interventional, clinical and prevention trials, as well as Investigational New Drugs (INDs) to ensure the safety of participants and the validity and integrity of the data.

As provided in federal guidelines, a DSM plan or system is required for all types of clinical trials (phase I, II, and III). For purposes of this policy, a *clinical trial* is operationally defined as a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. FIU requires data and safety monitoring procedures that are specific to each study, and that are commensurate with the risk, size and complexity of the research project. The data and safety monitoring policy of FIU requires an investigator to have established a system to: 1) monitor the progress of the trial to assure the safety of participants or the ethics of the study; 2) assure data accuracy and protocol compliance; and 3) assure compliance with the prompt written requirements regarding the reporting of adverse events. The reporting of adverse events is in addition to, and does not take the place of, the requisite annual reports, periodic reports to the IRB at intervals appropriate to the degree of risk in the study, or reports providing the IRB with changes or amendments to an approved study.

Where external funding is being requested for a clinical trial, the principal investigator must adhere to the requirements of both the funding agency and university policy for data and safety management.

2. DESIGN OF A DSM PLAN

There is no simple formula for how often data should be reviewed or how frequently relevant parties should meet. These decisions are usually set out in the protocol and are reviewed by the DSMB. A detailed description of the following is required in a DSM Plan:

The following Information shall be provided by the Investigator:

1. The names of proposed individuals to serve on the DSM committee/board.
2. Date of first DSM meeting (must occur prior to beginning of trial).
3. How minutes will be taken and distributed.
4. Frequency for DSM meetings and submission of reports to the IRB (must be at least annually).
5. How the progress of the trial and safety of the participants will be monitored.
6. How the data accuracy and protocol compliance will be assured
7. The types and formats of reports to be received from the statistician.
8. The policy (if applicable) on whether and how the members may be unblinded.
9. What interim data (if any) may be released to the study investigators (e.g. overall event rate).
10. Study end point or 'Stopping Rules'.
11. Other applicable information that requires review and approval.

Required statements to be included in a DSM Proposal/Plan:

1. A statement about plans for the assurance of compliance with the requirements regarding the reporting of adverse events (AE). Guidelines and AE reporting documents are available on line as well as in the IRB office. At minimum, an AE plan must include the use of an ***AE Table*** for monitoring procedures (on line).
2. Statements of risks and benefits.
3. A statement of confidentiality of documents.
4. A statement describing the transmission of DSM recommendations to the IRB and funding agency. ***Note:*** it is ultimately the responsibility of the PI to assure the receipt of all information in writing by the IRB/Funding Agency in a timely manner.

3. CONSIDERATIONS FOR THE DESIGN OF A DSM PLAN

To assist the study team and the monitoring committee/board in formulating a DSM plan the following considerations should be reviewed.

3.1 Study Phase

Phase I, II and III studies generally require different levels of safety monitoring scrutiny. For many phase I and phase II trials, an independent Data Safety Monitoring Board (DSMB) may not be necessary or appropriate when the intervention is low risk or because of their small size and short duration. Instead, continuous, close monitoring by the study investigator may be an adequate and appropriate format for monitoring, with prompt reporting of an adverse event. In situations involving potentially high risks or special populations, investigators must consider additional monitoring safeguards. For example, for studies involving children, investigators may consider the use of a consent monitor to ensure that informed consent or assent is properly administered. In addition, those trials with high risk (gene transfer, stem cell, etc.) will require a DSMB.

As studies progress through Phase II and III, a DSMB is required. As the intensity and frequency of safety monitoring increases and as the number of subjects and sites increase, dosing levels are tested, and subjects are randomized to interventions. The need to document the safety profile of the drug, or likely adverse events, and to insure data integrity requires more frequent and more rigorous views of the data.

3.2 Regulatory Considerations

There are additional administrative considerations if the trial requires compliance with FDA regulations. Monitoring should conform to Good Clinical Practice (GCP) and International Committee on Harmonization (ICH) guidelines. Study phase (I-III) and plans for Investigational New Drug Application (IND) submission also influence the frequency and intensity of monitoring studies. A safety profile is required to prevent adverse events. Further, other safety concerns such as futility of outcome, protocol adherence, site performance, and data quality need careful scrutiny.

3.3 Trial Design

The design of the trial is, in part, related to the study phase. As studies move from Phase I through Phases II and III, more subjects are required, and again, greater variability in both study implementation and subject population may occur. In addition, adverse events are more likely to emerge as more people are exposed to the intervention. In multi-center clinical trials, there is greater need to examine site-specific data collection and outcomes and inter-site differences.

Later Phase II and all Phase III studies are generally designed as randomized, controlled, clinical trials. Because the subject and investigator are blinded, it cannot be determined if the adverse events that occur are related to the drug. Thus, careful review of the data both in the aggregate and by treatment group in a blinded fashion should take place at regularly scheduled intervals. If adverse events occur in different proportions in the study groups and there are concerns regarding the negative effects of the intervention, then the study statistician and/or the DSMB may decide to unblind themselves to protect the safety of the study subjects.

3.4 Disease/Syndrome under Investigation

The nature of the disease being studied may influence the safety-monitoring plan. When the natural history of a disease is known, the investigators and the monitors are more likely to anticipate the nature and frequency of adverse events. However, investigators must consider additional monitoring safeguards when vulnerable populations and/or high-risk diseases are involved. For example, studies involving the elderly or pediatric populations may require more extensive and detailed monitoring. A DSMB will be required for those studies involving high risk such as gene therapy or stem cells.

A monitoring plan should consider the nature of the intervention. The level of scrutiny will depend on the severity of the disease and may require frequently scheduled safety reviews. The same approach

may be needed if the disease is serious and/or life threatening and endpoints are anticipated to occur frequently and/or early in the study.

3.5 Study Population

The nature of the disease and the trial design will influence the size and characteristics of the subject population. Phase I and II studies have smaller subject populations and treatment studies for diseases are likely to include subjects of similar demographic and health statuses. Phase III studies have larger subject populations.

The diversity of a study population can be controlled, to some degree, by the inclusion/exclusion criteria which determine who is eligible to participate in a study. It is therefore important to strike a balance between inclusion and exclusion criteria so that subjects can be recruited to a study in a timely and cost effective manner and that the study yields results that are of high quality and confirm the efficacy of the intervention. This consideration protects the subject's safety in that he/she is not committed to a study that is unduly extended over time or that shows no hope of successfully evaluating the intervention.

The safety plan should specify a review of the rate of subject accrual by site (if applicable) and by the study overall, the sites' adherence to inclusion/exclusion criteria and other protocol requirements, and the expected compliance rate of the subjects. Careful monitoring of the recruitment, enrollment and retention activities will help to protect the safety of study subjects, integrity of the study, and the quality of the data.

If subject accrual is expected to occur quickly, then safety monitoring should take place early and may be tied to a percent of the total population to be accrued.

3.6 Study Intervention

The more that is known about the study treatment, the easier it is to plan for the monitoring of the study. As discussed, treatments that have been studied previously are more likely to have a known safety profile and the frequency and type of adverse events can be anticipated. However, the safety of a treatment is also related to the population being treated, the indication for its use, dosing level and frequency, the presence of co morbid diseases, and the subject's time on study drug. All of these factors need to be considered in deciding on the frequency and intensity of safety monitoring as well as the types of reports, e.g., number of adverse events per subject.

3.7 Endpoints/Outcome Variables

Endpoints that are well defined and immediate are easier to monitor. Acute illnesses are more likely to have these types of outcomes. For example, treatment of an acute infection with the study drug is likely to yield clear-cut results in a relatively short period of time. In contrast, outcomes from chronic illnesses such as diabetes and heart disease may require a longer treatment intervention and follow-up period. Thus, the subject's time on study intervention and in the study from baseline through final follow-up will influence the type and frequency of safety monitoring.

3.8 Stopping Rules

A 'stopping rule', also called 'discontinuation guidelines', specifies the outcome differences detected between groups during an interim analysis that can stop a clinical trial. One of the benefits of stopping rules is that they can prevent over-reaction to random highs or lows in treatment response rates and adverse events since they generally require very low threshold p-values in interim analyses to indicate significance.

However, stopping rules are not sufficient to justify stopping a trial for several reasons:

- ***New Information*** **-** There may be new information available such as the results of other trials, a change in the understanding of the underlying biology or outside evidence of unacceptable adverse effects.
- ***Limits of Assumptions*** **-** Assumptions in the trial design regarding sample size and power, subject recruitment, the adverse event profile, and anticipated treatment affect differences may prove to be false when the trial is underway.
- ***Limits of Rules*** **-** Rules cannot be developed for all potential study scenarios and contingencies.

Stopping a trial early, even if justified, has consequences. With less than a full complement of events recorded, the confidence intervals associated with estimates of treatment effects are larger. Another consequence of early stopping is to bias the estimates of treatment effect upward. Therefore, stopping rules should be defined in the statistical plan or early in a study and require realistic estimates of sample size to be effective. Stopping rules are no more reliable than the data on which they are based. Thus, the quality of the data must be ascertained for the interim analyses.

(Taken from the NIDDK Generic and Safety Monitoring Plan)

4. DSM MONITORING RESPONSIBILITIES

Responsibility for data and safety monitoring depends on the phase of the study and exists on a continuum from monitoring by the principal investigator/project manager conducting the study to monitoring by a data and safety monitoring board (DSMB).

4.1 The IRB is responsible for:

1. The delegation of ongoing monitoring of trials,
2. Oversight of the monitoring activity,
3. Ensure that monitoring is timely and effective and that those responsible for monitoring have the appropriate expertise to accomplish its mission. Monitoring should occur at least yearly, but sometimes more frequently,
4. Providing written notification to the investigator, appropriate institutional officials, funding agency, OHRP and FDA as required by law of actions taken in regards to recommendations that emanate from monitoring activities, and
5. The enforcement of decisions concerning continuation or conclusion of the trial(s) based on the recommendations provided by the monitor.

4.2 The Principal Investigator of the study is responsible for:

1. The submission of a detailed DSM plan and management of monitoring procedures.
2. Receiving IRB approval of the proposed DSM plan prior to the beginning of the trial. The proposed plan will be confirmed upon the first meeting of the monitoring committee/board.
3. The investigator must acquire Informed Consent from potential participants. Most importantly, the investigator is responsible for the ongoing informed consent process. Participants must be kept up-to-date on any new information that may impact their decision to remain enrolled in the trial.
4. Perform ongoing monitoring (day-to-day management, quality control) of the study implementation parameters (e.g. recruitment, follow-up, compliance), not including treatment group comparisons, in an attempt to promptly identify issues that may threaten the integrity of the study or subject safety.
5. The investigator must make themselves aware of university reporting requirements related to data and safety monitoring, progress reports and adverse events; as well as reporting requirements to the sponsoring agency (if any). All research personnel (persons participating in the conduct of the proposed research) must be made aware of AE procedures and the project contact person in the event of an adverse event.
6. The implementation of recommendations resulting from a DSM meeting only after they have been approved by the local IRB.
7. The submission of a DSM report at least annually with continuing IRB review for the IRB protocol.
8. The provision of a DSM plan to funding agencies, if trial is funded, and ensure that the agency is informed of actions, if any, taken by the IRB as a result of continuing review.

4.3 The Data & Safety Monitor(s) is responsible for:

1. Determining along with the investigator the frequency and character of the meetings (open/closed, public/private) and frequency and content of reports,
2. Reviewing the research protocol and instituting plans for data and safety monitoring (frequency and the type of monitoring to be conducted),
3. Evaluating the progress of a trial, including a periodic assessment of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites,
4. Evaluating other factors that can affect a study when interpreting the data, such as scientific or therapeutic developments that may have an impact on safety of the participants or the ethics of the study,
5. Preparing summary reports that provide feedback and recommendations to the IRB and investigators concerning continuation or conclusion of the trial(s) in regards to recruitment, treatment effects, retention, compliance and safety issues; and
6. Protecting the confidentiality of the trial data and the results of monitoring.

5. DSM MEMBERSHIP & FUNCTION

5.1 DSM Membership and Appointment

Principal investigators are required to submit nominations for data and safety monitors along with their proposal. The proposed membership must be reviewed and approved by the IRB. In general the members should be nominated and selected based on their experience, reputation for objectivity, absence of conflicts of interest (and the appearance of same), and knowledge of clinical trial methodology. DSM committees/boards consist of voting and nonvoting members. Voting members may be from within or outside the institution, *but a majority should not be affiliated with the institution*. Professionals who are affiliated with the trial are non-voting members of a DSM committee/board. In addition, voting members directly involved with the conceptual design or analysis of a particular trial must be excused from all DSM discussion of the particular trial and must not receive that portion of the DSM report related to the particular trial. The chairperson of the DSM committee/board will be selected from among the voting members. DSM members affiliated with the institution should view themselves as representing the interest of patients and not that of the institution.

5.2 DSM Process and Meetings

DSM meetings will be held at least annually and more often as determined by the IRB based on the level of risk to participants. The initial DSM meeting should take place face-to-face. However, annual or interim meetings may be conducted by convened conference calls or in person.

Following the initial meeting, the DSMB should meet at designated intervals to review accumulated data on safety and, if appropriate, conduct an interim analysis. Meetings may either be convened as conference calls or in person, although it is recommended that the initial meeting and meetings to discuss interim analyses should be face-to-face. The Chairperson may call an emergency meeting of the DSMB at any time should questions of patient safety arise.

An appropriate format for DSMB meetings consists of an open and a closed session. The open sessions may be attended by investigators, institution staff, and persons from the funding agency, and should always include the principal investigator and the study statistician. Issues discussed at open sessions usually include conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

The closed session is normally attended only by voting DSM committee/board members. The DSM committee/board may request appropriate others (e.g., study statistician) to attend portions of the closed session. All safety and efficacy data as well as any interim analyses must be presented at this session. Final recommendations regarding safety concerns and recommendations regarding continuation or termination of the study are discussed. Should it be decided to issue a termination recommendation, full vote will be required. In the event of a split vote, majority vote will rule and a minority report should be appended. The discussion at the closed session is completely confidential. A

summary of the final recommendations is prepared for distribution to the PI, IRB, and FDA as appropriate.

5.3 DSM Reports

5.3.1 Interim Reports

Interim reports are generally prepared by the study statistician and distributed to the DSMB, preferably at least 5 days prior to a scheduled meeting. These interim reports should be numbered and provided in sealed envelopes. The contents of the report are determined by the DSM committee/board. Additions and other modifications to these reports may be directed by the DSM committee/board on a one-time or continuing basis. Interim data reports generally consist of two parts.

- **Part One (Open Session Report)** provides information on study aspects such as accrual, baseline characteristics, and other general information on study status.
- **Part Two (Closed Session Report)** may contain data on study outcomes, including safety data and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential.

Copies distributed prior to and during a meeting are collected by the study statistician(s) following the meeting. Data files to be used for interim analyses should undergo established editing procedures to the extent possible according to procedures established by the PI in concurrence with the DSM committee/board. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping are clearly defined.

5.3.2 Reports from the DSMB

A formal report from the Chair, approved by the committee/board, should be sent to the PI. It is the responsibility of the PI to assure that DSMB reports are sent to the co-investigators and to the IRB(s) of all study sites, and, if appropriate, the monitoring board of the funding agency and the FDA.

Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSM committee/board at any time by majority vote. Such a recommendation should be transmitted to the PI, IRB Chairperson, VP of Research as rapidly as possible, by immediate telephone and FAX if sufficiently urgent. In addition, the appropriate funding agency officials should be notified. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSM report. The report should not include unblinded data, discussion of the unblinded data, etc.

If the DSM committee/board recommends a study change for patient safety or efficacy reasons, or that a study is closed early due to slow accrual, the principal investigator must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator does not concur with the DSM committee the IRB must be notified in writing of the reason for disagreement. The principal investigator, the DSM committee Chairperson, an Adverse Event Committee designee, and the

IRB Chairperson will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and Adverse Event committee members to seek advice to assist in reaching a mutually acceptable decision.

Sample Reports can be found at the NIDDK web site or as Appendix A to be modified by the user.

5.4 Confidentiality Procedures

No communication, either written or oral, of the deliberations or recommendations of the DSM committee/board will be made outside of the DSM committee/board except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to any non-member of the DSM committee/board, except as indicated above in the Recommendations section, until the recommendation to release the results are accepted and implemented. Each member of the DSM committee/board, including non-voting members, must sign a statement of confidentiality.

5.5 Conflict of Interest

DSM committee/board members are subject to the institution and awardee's policies regarding standards of conduct. Individuals invited to serve on the DSM committee as either voting or non-voting members will disclose any potential conflicts of interest, whether real or perceived, to the trial principal investigator/project manager and the appropriate institutional officials(s), in accordance with the institution's policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest. Potential conflicts that develop during a member's tenure on a DSM committee/board must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSM committee/board will be made in accordance with the institution's policies.

DEFINITIONS

For the purpose of this policy the following definitions are applicable:

1) ***Adverse Events*** are defined as "unanticipated problems" or "events which are both serious and unexpected" for research identified as having greater than minimal risks to the participating human subjects.

2) ***Behavioral clinical trials*** try to modify or improve behaviors associated with disease or disease risk. This may include behavior modification techniques, such as exercise programs or stress reduction training. It may also include behavioral intentions aimed at increasing physical activity in an effort to prevent disease morbidity or mortality.

3) ***Benefits associated with clinical trial participation*** **-** Clinical trials that are well-designed and well-executed are the best treatment approach for eligible participants to:

   - Play an active role in their own health care.
   - Gain access to new research treatments before they are widely available.
   - Obtain expert medical care at leading health care facilities during the trial.
   - Help others by contributing to medical research.

4) ***Clinical Trial*** is operationally defined as a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Observational or epidemiological studies that involve human subjects and that require informed consent are covered by this policy.

5) ***DSM Board –*** An independent group that should include physicians, independent statisticians, other scientists, mental health professionals, content experts (specific for area of research being conducted), and lay representatives. In general, a DSMB is warranted if: 1) It is a Phase III clinical trial; 2) It is a multi-site clinical trial; 3) Has a high risk intervention; 4) Has over one hundred participants; 5) It is a masked Phase II clinical trial with high risks; or 6) It is a requirement of the funding agency.

6) ***DSM Committee –*** At minimum, a DSM committee would consist of 3 members, an independent statistician, a content expert and the PI (non-voting).

7) ***DSM Individual*** **-** An independent monitor with expertise relevant to the study would be assigned to perform the monitoring function or to assist in data interpretation to ensure patient safety in trials with small numbers of subjects (Phase I or low risk Phase II). This individual may choose to perform monitoring duties by closely monitoring individual participants, or in larger studies by the use of statistical comparisons of treatment groups. Statistical comparisons would be performed on data submitted by the PI to the DSM individual.

8) ***DSM Principal Investigator*** **-** The PI would be expected to perform the monitoring function as part of the general oversight and scientific leadership of the study for many trials with protocols

that involve no more than minimal risk and are "small-scale" (Phase I). Such PI's must comply with prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others.

9) ***Endpoint*** - Overall outcome that the protocol is designed to evaluate. Common endpoints are severe toxicity, disease progression, or death.

10) ***Interventions*** - Primary interventions being studied: types of interventions are Drug, Gene Transfer, Vaccine, Behavior, Device, or Procedure.

11) ***Minimal Risk*** is a risk where the probability and magnitude of harm or discomfort anticipated in the proposed 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.

12) ***Prevention Trials*** look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

13) ***Protocol*** - A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

14) ***Quality of Life Trials*** (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

15) ***Randomized Trial*** - A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilized.

16) ***Risks associated with clinical trial participation –*** The following are possible risks to participating in clinical trials:

- There may be unpleasant, serious or even life-threatening side effects to treatment.
- The treatment may not be effective for the participant.
- The protocol may require more of their time and attention than would a non-protocol treatment, including trips to the study site, more treatments, hospital stays or
- complex dosage requirements.

11) ***Screening Trials*** test the best way to detect certain diseases or health conditions.

12) ***Stopping Rules*** - A 'stopping rule' specifies the outcome differences detected between groups during an interim analysis that can stop a clinical trial. The stopping rules reflect one of the following conditions:

- There is clear evidence of harm or harmful side-effects of the treatment;

- There is no likelihood of demonstrating treatment benefit; or
- There is overwhelming evidence of the benefit of the treatment.

17) ***Treatment Trials*** test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

18) ***Trial Phases***
    - Phase I – researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Phase I of a clinical trial includes physiologic, toxicity, and dose finding studies.
    - Phase II – the study drug or treatment is given to a larger group of people (100-300) to see if it is effect and to further evaluate its safety. Phase II studies are normally efficacy studies.
    - Phase III- the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. Phase III studies include efficacy, effectiveness and comparative trials.