**GUIDANCE #: G-004**

**Data and Safety Monitoring Plans/Boards (DSMP/DSMB)**

**Purpose**

This document describes guidelines for writing a Data and Safety Monitoring Plan (DSMP) and for formation of Data and Safety Monitoring Boards (DSMB); providing guidelines with regard to inclusion of DSMPs in the study protocol, the content of the DSMP, formation and roles of DSMBs, and content of DSMB reports.

**Definitions**

Data and Safety Monitoring Plan (DSMP): A written plan for monitoring the safety of study participants, scoring and reporting adverse events, assuring data accuracy and completeness, assuring compliance with the protocol, and assuring that any action resulting in a temporary or permanent suspension of the research study is reported as soon as possible to the investigator, sponsor and IRB.

Data and Safety Monitoring Board (DSMB): A group of individuals charged with monitoring an ongoing research study for study quality and for the safety of study participants during the conduct of the study. The DSMB members provide their expertise and recommendations to the study investigators. A key feature of a DSMB is its’ independence from study investigators.

**Procedure**

After choosing the appropriate template, the protocol must be modified to reflect the unique attributes of the research study. Minimal risk studies that do not involve drugs or devices generally do not require a DSMB. However, the IRB will make the final risk determination. The following are excerpts from DSMPs that may serve as templates for inclusion in a protocol document.

**DSMP Template for a Minimal Risk Study**

The principal investigator (PI) is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [*e.g., monthly, quarterly, etc*]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator, the Institutional Review Board (IRB), OHRP, FDA or [*enter the names of other oversight bodies that have this authority]* have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, the PI is responsible for reporting serious, unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB, any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project [*describe how the investigator will meet this obligation*, e.g., through regular study meetings, via email as they are reviewed by the principal investigator.] *[Where appropriate, modify the following sentence to apply to the specific research protocol.]* The protocol’s research monitor(s), e.g., study sponsor(s), funding and regulatory agencies, Data Safety Monitoring Boards(DSMBs), and regulatory and decision-making bodies will be informed of [*specify types of adverse events that require reporting to these oversight bodies*] adverse events within 10 days *[enter other appropriate duration]* of the event becoming known to the principal investigator.

**Example: DSMP for a Moderate Risk Study**

**Personnel responsible for the safety review and its frequency:**

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The IRB or [e.g. FDA, OHRP, *enter the names of other oversight bodies that have this authority,* have the authority to stop or suspend the study or require modifications.

The risks associated with the current study are deemed moderate for the following reasons: (choose those that apply)

* We do not view the risks associated with the \_\_\_\_\_\_\_\_\_\_ as minimal.
* We do not view the risks associated with the combined use of \_\_\_\_\_\_\_\_and\_\_\_\_\_\_\_\_\_ as minimal.
* Given the now established safety and validity of the current \_\_\_\_\_\_\_\_\_ in our prior work, we do not view the proposed studies as high risk.
* Given our experience with the combined co-administration\_\_\_\_\_\_\_\_\_, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

**Attribution of Adverse Events:** Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Insert

Investigator Name) according to the following categories:

* Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
* Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
* Possible: Adverse event may be related to investigational procedures(s)/agent(s).
* Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
* Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

**Plan for Grading Adverse Events:** The following scale will be used in grading the severity of adverse events noted during the study:

* Mild adverse event
* Moderate adverse event
* Severe or medically significant

**Plan for Determining Seriousness of Adverse Events:**

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

* is life-threatening OR
* results in in-patient hospitalization or prolongation of existing hospitalization OR
* results in persistent or significant disability or incapacity OR
* results in a congenital anomaly or birth defect OR
* results in death OR
* based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
* adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its “seriousness” when determining whether reporting to the IRB is necessary.

**Plan for reporting** **serious AND unanticipated AND related adverse events, anticipated** **adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the IRB**

The investigator will report the following types of adverse events to the IRB: a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB within 10 days of it becoming known to the investigator, using the appropriate forms found in IRB Manager.

Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol’s research monitor(s), e.g. study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

* All Co-Investigators listed on the protocol.
* Sponsor
* National Institutes of Health
* Food and Drug Administration (Physician-Sponsored IND #\_\_\_\_\_\_\_)
* Foundation (Grant\_\_\_\_\_\_)

The principal investigator (Insert Investigator Name) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

**Example: DSMP for a High Risk Study**

**Personnel responsible for the safety review and its frequency:** The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or [enter the names of other oversight bodies that have this authority,] have the authority to stop or suspend the study or require modifications.

**The risks associated with the current study are deemed high for the following reasons:**

(choose those that apply)

* We do not view the risks associated with the \_\_\_\_\_\_\_\_\_\_ as minimal/moderate.
* We do not view the risks associated with the combined use of \_\_\_\_\_\_\_\_ and \_\_\_\_\_\_\_\_ as minimal/moderate.
* Given the now established safety and validity of the current \_\_\_\_\_\_\_\_\_ in our prior work, we do not view the proposed studies as minimal/moderate.
* Given our experience with the combined co-administration\_\_\_\_\_\_\_\_\_, we do not view the proposed studies as minimal/moderate.

Since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods, we provide a plan for monitoring the data and safety of the proposed study as follows:

**Attribution of Adverse Events:** Adverse events will be monitored for every subject participating in the study and attributed to the study procedures / design by the principal investigator (Insert Investigator Name) according to the following categories:

* Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
* Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
* Possible: Adverse event may be related to investigational procedures(s)/agent(s).
* Unlikely: Adverse event is likely not to be related to investigational procedures(s)/agent(s).
* Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

**Plan for Grading Adverse Events:** The following scale will be used in grading the severity of adverse events noted during the study:

* Mild adverse event
* Moderate adverse event
* Severe adverse event

**Plan for Determining Seriousness of Adverse Events:** In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

* is life-threatening OR
* results in in-patient hospitalization or prolongation of existing hospitalization OR
* results in persistent or significant disability or incapacity OR
* results in a congenital anomaly or birth defect OR
* results in death OR
* based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the criteria described on the Reportable Event Form before submitting the event to the IRB.

**Plan for reporting serious AND unanticipated AND related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the IRB.**

The investigator will report the following types of adverse events to the IRB: a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events and unanticipated problems involving risks to subjects or others will be reported to the IRB within 10 days of it becoming known to the investigator, using the appropriate forms found in IRB Manager.

Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol’s research monitor(s), e.g., industrial sponsor, the DSMB, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

* All Co-Investigators listed on the protocol.
* Sponsor
* National Institutes of Health
* Food and Drug Administration (Physician-Sponsored IND #\_\_\_\_\_\_\_)
* Medical Research Foundation (Grant\_\_\_\_\_\_)

The principal investigator (Insert Investigator Name) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

**For High Risk Studies, in addition to a DSMP, a DSMB may be required.**

**Requirement for DSMB**

There is no single rule for what types of studies require a DSMB. The NIH requires DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants (National Institutes of Health, 1998) and states that generally a DSMB is required for Phase III clinical trials (National Institutes of Health, 2000). Many of the individual NIH institutes have their own policies or requirements for a DSMB, and investigators should ensure that they meet the requirements of the funding agency or sponsor.

**Independence of DSMB**

DSMB members should not have conflicts of interest with regard to the research study. While the most obvious type of conflict of interest is financial, there can also be professional, intellectual and emotional conflicts. Generally, DSMB members and the key personnel of the study should not be professional supervisors or mentors of each other, and should not be current co- investigators or collaborators. Representatives of the manufacturer of the drug(s) or device(s) being tested, and other individuals with vested interests in the outcomes of the study, should not serve on the DSMB.

Each DSMB member should be asked about potential conflicts at the first meeting of the DSMB and any such conflicts should be discussed and acted on as appropriate. At each subsequent meeting, members should be asked if they have any new conflicts to disclose. A DSMB may decide that each member should submit written conflict of interest disclosures for documentation and to raise the level of awareness of this important issue. Complete elimination of all real and perceived conflicts of interest is generally impossible if DSMB members are to be knowledgeable and experienced in the medical subject being studied. PBRC may institute a plan to mitigate risks.

**Composition and Roles of a DSMB**

A DSMB will ordinarily be multidisciplinary and should always include members with relevant clinical and statistical expertise in order to correctly interpret the data and ensure patient safety. A DSMB may consist of as few as three members, but this number should be large enough to include a representation of all needed skills and experience. The desired clinical expertise of the DSMB members should be dictated by the particular disease and patient population being studied. Ad hoc specialists may be invited to participate as a non-voting member at any time if additional expertise is needed. Individuals with financial or other conflicts of interest should not be members. Members should be independent from the direct management of the study. Ideally, all DSMB members should have experience with the design, conduct, and interpretation of clinical trials and study monitoring.

The DSMB should meet prior to the enrollment of the first subject to review the research protocol, informed consent documents and plans for safety and data monitoring of the study. This review is to determine the risks and benefits to research subjects, protection and safety of the subjects and to offer suggestions for improving the study design. In addition, the Board should reach agreement on the data that will be required for review. Determination of the schedule of future meetings, appointment of the chair and voting members, who receives minutes, and the signing of conflict of interest statements occur during pre-enrollment meeting. Appropriate goals of a DSMB include ensuring safety of trial participants and ensuring overall integrity of the trial through periodic review and evaluation of accumulated study data for study conduct and progress, participant safety and, when appropriate, efficacy. Based on these considerations, the board makes recommendations to the study investigators concerning continuation, modification, or termination of a study. In order to achieve these goals, a DSMB will typically:

* Review major modifications to the study protocol before their implementation
* Review safety data, ordinarily in the form of summary statistics, although a DSMB may decide to review individual adverse event reports
* Review subject accrual and timeliness of study completion
* Evaluate the quality of study conduct including compliance with the protocol or treatment, timeliness, retention and quality of the data collected
* Assess participant risk versus benefit based on interim analyses
* Evaluate interim analysis results in light of protocol-specified early stopping rules
* Consider whether any modifications in the protocol are warranted, including possibly terminating the study early
* Be available to the investigator for consultation concerning any adverse study events.
* Consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

Early stopping may be warranted if there is strong evidence of either a treatment benefit such that it is considered unethical not to make the treatment available to all patients, or of a lack of a treatment difference with a low likelihood of reversing this finding with further accrual and/or follow-up. Ordinarily, the protocol should have pre-specified stopping rules giving guidelines for reaching these decisions. Other reasons for early stopping include unintended harm due to study participation, inability to answer the study questions (e.g., because of low accrual, low event rate, poor study conduct, high dropout rate, etc.), or evidence external to the study rendering it unethical to continue the study.

After each meeting, the DSMB should make a written statement within 4 weeks of meeting regarding the quality of the study and safety of participants and a brief recommendation either to continue the study without changes or to modify the study in specified ways with appropriate justification. Suggested modifications may include addressing safety concerns, suspension or early termination due to inadequate performance or rate of enrollment, or according to pre- established statistical guidelines, and optional approaches to consider such as adding study centers or extension of recruitment due to unsatisfactory or suspicious performance.

**Timing and Frequency of DSMB Meetings**

DSMB meetings will take place at least annually. The Board may meet periodically (quarterly, semi annually, or annually) if the risk to the subject is high, the population is vulnerable, there is a large volume of data to review, and/or after a pre-determined number of subjects have been accrued in the study. The Chairman may also call ad hoc meetings depending on safety or efficacy concerns. Meetings may be conducted by teleconference at the request of Board members.

**DSMB Meeting Agenda**

1. The Investigator will provide the Board with the information that was determined at the pre-enrollment meeting.
2. As per the Data Safety Monitoring Plan, The Board will:
   1. determine adherence to treatment plan
   2. review interim analysis, if applicable, and determine specific data to be analyzed
   3. evaluate end point/stop point rules
   4. review protocol violations and deviations to assess adequacy of study
   5. ensure documentation of informed consent
   6. enrollment
      1. followed eligibility criteria
      2. enrollment numbers
      3. visit compliance
      4. screening failure information
   7. review IND/IDE information
   8. discuss investigator or key personnel changes
   9. review completeness and quality of data collection forms
   10. evaluate the aggregate analysis of adverse events/serious adverse events
   11. review vital signs, clinical tests, etc.
   12. review confidentiality
3. DSMB Meeting Outcome - The major outcomes following data review include:
   1. continuing the trial unchanged
   2. modify the protocols and/or consent form (It may be unethical to continue giving a placebo after a new treatment has been proven to be effective or to continue a new treatment when there is no chance the trial will be positive.)
   3. terminate the trial
4. DSMB Minutes - Minutes from the meeting will be maintained. Following the Board meeting, a report should be provided to the investigator, the IRB, and the Sponsor.