

# The Clinical Research Center Research Practice Manual



## Data and Safety Monitoring Plans/Boards (DSMP/DSMB) – RPG-11

### Guideline

#### 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 study data and the safety of study participants during the conduct of a clinical research study. A written DSMP ordinarily appears in the study protocol document.

##### **Data and Safety Monitoring Board (DSMB):**

A group of individuals charged with monitoring an ongoing clinical 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. Other commonly used terms for a DSMB include Data Monitoring Committee (DMC), and Data and Safety Monitoring Committee (DSMC).None identified.

### Procedure

Investigators must adhere to Boston Children's Hospital policies and to the policies of their funding sources. Should Hospital and CRC policies conflict, Hospital policy will supersede CRC policy. Of particular relevance is the Committee on Clinical Investigation document "[Data and Safety Monitoring Plans](#)".

##### **Data and Safety Monitoring Plan (DSMP):**

Requirement for DSMP DSMPs are required for all clinical studies involving more than minimal risk.

## Content of DSMP

A DSMP should include descriptions of systems for monitoring the progress of the study, 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 a clinical trial is reported as soon as possible to the investigator, sponsor and IRB as deemed appropriate. Not all of these topics need to be addressed within the DSMP; there may be references to other sections of the protocol or to an appendix that contains the relevant material. For example, in the protocol outline published by the Committee on Clinical Investigation, there are separate sections titled “Data and Safety Monitoring Plan” “Risks and Discomforts,” and “Adverse Event Criteria and Reporting Procedures”. The DSMP section would ordinarily refer to the other two sections for relevant information. Guidelines for Adverse Event Criteria and Reporting Procedures also appear in the [\*CCI Guidelines & Policies\*](#).

With regard to safety and reporting of adverse events, ordinarily, the DSMP states that there is a data collection form for recording adverse events and for scoring the severity of the event and the likelihood of relationship to the research study. The actual adverse event criteria and definitions may be located elsewhere in the protocol. The DSMP should delineate who is responsible for reviewing and reporting adverse events, to whom they are reported, and on what schedule this monitoring and reporting will occur. At a minimum, review of adverse events should occur annually and reports should go to the IRB, with unexpected and serious adverse events reported immediately as they occur. However, some studies may have more stringent monitoring and reporting mechanisms and requirements. Responsibility for monitoring may range from internal monitoring by the investigators themselves, for minimal risk studies, to independent DSMBs, for more complex studies with higher levels of risk. How these responsibilities are implemented should be detailed in the DSMP. For multi-center studies, there should be a mechanism for reporting all adverse events to some central body, such as a data coordinating center, so that safety data can be aggregated across the different centers.

Similar considerations apply to quality control and protocol compliance. More complex studies, larger studies, and those with greater risk will often have formal plans for ensuring the validity, integrity, and timeliness of the data and the integrity of the research study in general. A DSMB will often provide oversight to these procedures. In studies seeking FDA approval, external data auditors may be involved. In smaller and lower-risk studies, these procedures may be carried out informally, by study investigators. Plans for these procedures may include review of recruitment and retention, monitoring of data completeness, interim analyses of outcome data, quality control procedures, and early-stopping rules. Details of such plans may also be located in other sections of the protocol, e.g. in the Risks, Quality Control, and/or Statistical Considerations sections.

Several [\*examples of DSMPs\*](#) appear in the Related Contents section.

### **Data and Safety Monitoring Board (DSMB):**

The major reference for this section is Ellenberg, Fleming and DeMets (Ellenberg et al, 2002).

### 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.

Wittes points out that “a DSMB is useful only when the presence of a disinterested body adds value to the study” (Wittes, 2000). Ellenberg, Fleming and DeMets (Ellenberg et al, 2002) state that “trials that address major health outcomes and are designed to definitively address efficacy and safety issues should incorporate” independent monitoring by a DSMB. They go on to propose four criteria, suggesting that a DSMB should be implemented if two or more are met:

- 1) The trial is intended to provide definitive information about effectiveness and/or safety of a medical intervention.
- 2) There are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity.
- 3) The trial is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications.
- 4) It would be ethically important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed.

Many studies do not need independent monitoring by a DSMB. While each study should be considered individually, studies with the following characteristics would be less likely to benefit from independent monitoring.

- pilot and feasibility studies,
- studies of interventions designed to relieve symptoms or of reversible events,
- studies with primary outcome variables that are biologic or mechanistic in nature and for which the clinical implications of altering these outcomes are not established,
- short-term studies, especially when the participant can receive the active treatment after completing the comparative study (e.g., studies with an open label extension)
- small studies
- single-center studies.
- Phase I and early Phase II studies
- Studies for which early stopping for ethical reasons is not warranted

Even if a study may not need a formal DSMB, it still may benefit from some external monitoring and we do encourage investigators to seek ongoing input and advice from researchers not directly involved in the study. This may take the form of an advisory committee, which meets on a set schedule to review study progress. Such a committee could include study investigators as well as non-affiliated colleagues, mentors, or others with relevant expertise in the subject being studied and/or in clinical trial methods. The Society for Clinical Trials has published guidelines for data and safety monitoring for trials without traditional, fully independent DSMBs (SCT Working Group on Data Monitoring, 2006).

### Independence of DSMB

DSMB members should not have conflicts of interest with regard to the clinical trial. 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. DSMB members should not be involved in the care of study patients. 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.

Note that several NIH institutes have specific prohibitions against DSMB members being from the same institution as any study site. While this policy would be difficult to implement at Boston Children's Hospital, we do encourage soliciting at least some DSMB members from outside of Boston Children's Hospital.

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.

We recognize that 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.

#### 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, type of treatment 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. Many DSMBs for Boston Children's Hospital studies have members who are affiliated with Boston Children's Hospital. This is acceptable but extra care should be taken to ensure independence from the trial and from trial participants. Ideally, all DSMB members should have experience with the design, conduct, and interpretation of clinical trials and study monitoring.

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 the study protocol and plans for data and safety monitoring before enrollment begins.
- Provide written documentation confirming review of the protocol and agreement with the study design and the data and safety monitoring plan.

- 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. Recommendations will ordinarily be submitted by the investigator to their IRB at or prior to the next annual IRB review of the study.

#### Content and Presentation of DSMB Reports

Before each DSMB meeting, the study statistician(s) and support staff will prepare written open and closed reports, which should be distributed 1-2 weeks in advance of the meeting, and then present the reports during the meeting.

The study principal investigator and/or other study staff may also contribute to preparation and presentation of the open report. Close involvement of study staff is especially useful with respect to the medical background and motivation for the study design, operational issues, recruitment and retention, protocol amendments, deviations from protocol, adverse events, and general study conduct. They should also play a central role in any meeting where the DSMB reviews the study design and protocol before the study is activated.

Confidentiality, especially of the closed report, which should be collected and destroyed at the conclusion of each meeting, should be maintained during all phases of DSMB review and deliberations.

The content of the DSMB reports depends on the nature and the stage of conduct of the study. The open report will outline the goals of the study, major amendments to study protocol, and several of the following topics as appropriate. Data will be aggregated over the treatment groups.

- 1) Update on overall status of the study and important operational issues
- 2) Status of recruitment and accrual progress to date
- 3) Baseline characteristics
- 4) Information on data completeness and quality of data
- 5) Information on protocol compliance, retention and other quality-control measures

In most cases, outcome data, including safety and efficacy data, should not be presented in the open report. Even aggregate data (that is, pooled over treatment groups) can provide suggestive information about the relative risks and benefits of the treatments being studied. Therefore, careful consideration should be given to providing any outcome data in the open report.

The closed report will be based on the same data as the open report. While safety data are often presented by treatment group in the closed report, it is important not to make unnecessary repeated looks at comparative efficacy outcomes, which may violate the interim analysis plan. With these points in mind, the closed report may include:

- 1) Repeat of selected open report data, by treatment group
- 2) Statistical summary of adverse events, lab values and other safety data
- 3) Listings of individual adverse events, as appropriate.
- 4) Statistical summary of primary and key secondary outcome variables if required by the DSMB
- 5) Formal interim analyses and interpretation of the results as they relate to stopping rules

When data are presented separately by treatment group, we recommend using blinded codes such as X and Y in the written report, even when the intention is to identify the groups. It is usually necessary to use different sets of blind codes for the safety analysis and efficacy analysis to ensure objective review of the results. The key can be disclosed verbally during the meeting. This extra level of blinding will minimize the risk that information is disseminated to an unauthorized person. Some DSMBs choose to view group-specific results but remain blinded to group identity until they feel the need to know. This point has been debated in the literature (Meinert, 1988); we feel that a fully informed judgment requires knowledge of which treatment group is which.

Related Content shows a [\*template for an Open DSMB report\*](#). This is just a suggestion and the report does not have to follow this format exactly. Each trial is unique and the content of the report may be expanded or limited accordingly. Related Content also shows a [\*template for a Closed DSMB report\*](#). Often, the closed report can simply be a set of tables paralleling the open report, but broken down by treatment group and with very little explanatory text. The exception

is often efficacy data, which may not have been presented in the open report and may require more of an explanation and discussion in the closed report, especially if formal interim analyses are presented.

### DSMB Charter

Some DSMBs produce a written charter; agreed to in advance by the study investigators and DSMB members. A very detailed discussion of charters, with illustrative examples of text is provided by DAMOCLES Study Group (2005). The content of a charter may include:

- documentation of membership and the desired composition of the membership,
- designation of a chair,
- outline individual responsibilities such as who drafts minutes and written recommendations,
- who is responsible for the logistics of scheduling and organizing the meetings,
- the frequency of meetings,
- confidentiality,
- how conflicts of interest will be managed,
- meeting format (closed sessions, open sessions, in person, teleconference, etc...),
- distribution and disposition of meeting materials,
- what types of data will be monitored,
- report content,
- procedures for monitoring adverse events in real time (i.e., between scheduled meetings)
- access to interim data, and
- other procedural matters.

## **Related Content**

### **DSMP Examples**

The following are excerpts from DSMPs that may serve as templates for inclusion in a protocol document. Any individual study may need to include paragraphs modeled after more than one of the following excerpts, and there may be special considerations requiring the investigator to develop additional monitoring procedures specific to the study.

These examples assume that other sections of the protocol document contain descriptions of risks, adverse event (AE) criteria, AE reporting procedures, and statistical procedures for interim analyses. For more information, see "[\*Data and Safety Monitoring Plans\*](#)" published by the Committee on Clinical Investigation.

### Minimal Risk

The study is judged to be of minimal risk. Expected risks are described in protocol Section xx [refer to section on Risks and Discomforts]. Any adverse events that do occur will be recorded, scored for severity and for relationship to the study as described in Section xx (refer to section on Adverse Event Criteria and Reporting), and reviewed periodically by the study co-investigators. All serious and unexpected adverse events will be reported to the IRB within 72 hours.

### Greater than Minimal Risk

Because of the potential risk of adverse side effects, patients will be monitored closely during the study period with laboratory assessments and physical examinations as described in protocol Section xx [refer to section on Data Collection Assessments and Schedule]. Study participants will be able to contact one of the study physicians at any time with questions and concerns. All adverse events will be recorded, scored for severity and for relationship to the study as described in Section xx [refer to section on Adverse Event Criteria and Reporting]. Adverse event data will be reviewed periodically by the study co-investigators. All serious and unexpected adverse events will be reported to the chair of the DSMB and to the IRB within 72 hours.

### Genetic Information

The major risks outlined in this protocol are disclosure of genetic information and psychological stress from discussing the possible genetic causes and risks of disease. To prevent disclosure, information about participation in the study and data collected in the study will not be placed in the medical record. Data and samples will be coded with a unique identifier for each patient, and the key to the code will be kept in a locked file cabinet separate from research data. Only anonymized data and samples will be shared with collaborators. If any member of the research team suspects that a study participant is experiencing stress, he/she will offer the option of genetic counseling and notify the PI.

Such incidents will be recorded as adverse events and reported to the IRB at each annual review.

### Clinical Monitor

The investigator will provide direct access to source data and documents and will permit trial-related monitoring by the sponsor and regulatory agency, or their designees. Clinical monitoring will be in accordance with Good Clinical Practices (GCPs). The Clinical Monitor's responsibilities include reviewing accuracy and completeness of records and source documents, comparison of data coded on collection forms with source documents, monitoring of site facilities and procedures to ensure proper conduct of the protocol, and evaluation of timeliness and completeness of submitted data. The Clinical Monitor will summarize the findings of each site visit in written reports, identify and discuss major problems with the investigator, and make recommendations for the resolution of noted deficiencies.

### Formation of DSMB for multi-center study

The study will be monitored by an independent Data and Safety Monitoring Board (DSMB) appointed by NIAID, the funding agency.

### Formation of DSMB for local study

A Data and Safety Monitoring Board (DSMB) will be formed from Boston Children's Hospital or other local Boston experts. DSMB members will have no affiliation or other conflicts of interest with the study and will include physicians with expertise in [*list relevant areas of expertise*] and a biostatistician.

### Role of DSMB

The DSMB will review the study protocol before activation and will periodically review accrual and trial progress; accuracy, timeliness, and completeness of data; and compliance with protocol procedures. The DSMB will also assess safety and efficacy data and will consider the need for modifying (or terminating) the protocol to protect the safety of study participants. Early stopping guidelines are described in more detail in protocol Section xx [*refer to Statistical*

*Analysis Plan].*

Internal Data Monitoring

Monthly, the PI will meet with the Clinical Coordinator to review data for completeness and to discuss protocol deviations and any data collection problems that may have arisen. Steps will be taken to correct any

**Template: Open DSMB Report**

***Study Name***

**PI: Name**

# **Data Safety and Monitoring Report**

## **Open Session**

DSMB Meeting Date:

Prepared by:

Data Managed by:

Month day, year

Name(s)

Organization

Names(s)

Organization

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- **Introduction**

- ❖ **Study Background**

*Summarize study schema including study objectives, key design features such as study population, primary endpoint, sample size and visit schedule.*

- ❖ **Data and Safety Monitoring Plan**

*A brief summary of study monitoring plan including scope of monitoring, stopping rules, DSMB monitoring frequency and DSMB members.*

- ❖ **DSMB and Protocol Amendment History**

*Briefly describe when the study was opened, the number of prior DSMB reviews and summarize major recommendations from past DSMB meetings and the teams' responses.*

- ❖ **Scope of this DSMB Report**

*This report represents an interim analysis of data received on or before Month day, year.*

*OR*

*This report represents an interim analysis of data collected on visits which occurred on or before Month day, year.*

*(Ordinarily, the data freeze date should be at least 4-8 weeks prior to the DSMB meeting date to allow adequate time for data entry and cleaning, performing analyses, preparing and distributing the report.)*

*(None of the analyses presented in this open report should be broken down by treatment arms.)*

- **Administrative Report**

- ❖ **Study Accrual**

*This section usually reports the initiation date of accrual, total cumulative accrual up to the freeze date, and % of total target accrual. Table 1 gives the accrual by month. A figure of cumulative accrual and projected accrual vs. time may also be used. Comment on whether accrual is on target and project when accrual will be completed. In multicenter studies, it may be appropriate to report some of this information separately by site.*

## ❖ Baseline Patient Characteristics

*Table 2 presents baseline patient characteristics.*

*This table usually includes demographic information about the patients, like age, gender and race/ethnicity, stratification factor(s), and also study specific patient characteristics, like BMI, diagnosis type, treatment history, etc.*

## ❖ Study Status

**Table 3** summarizes the study status of enrolled subjects as of Month day, year. The table usually includes a breakdown of numbers of subjects under active follow-up and off study. Under the number off study, usually the number of subjects who completed study per protocol and the number who prematurely discontinued are given. Reasons for premature study discontinuation may also be summarized in the same or separate table. If death occurred in a study, it might be separated out from other adverse events in the table as a reason for discontinuation. Enrollment of ineligible patients is often summarized in this section as well.

*Incidence of protocol deviations (including of ineligible patients) is another measure of quality of study conduct. The information can be summarized in the text if protocol deviations are uncommon. If the rate of protocol deviation is higher than expected and the reasons are heterogeneous, a table like Table 4 may be necessary.*

*If treatment compliance is a concern, it may be necessary to carefully check how well the interventions are carried out in terms of medication adherence, accuracy in treatment implementation, rate of treatment crossover, etc.*

## ❖ Data Completeness

*This section summarizes how subjects are followed and whether data are collected as planned, especially the availability of key study variables. Typically completeness of follow-up visits as in Table 5 is reported. The study visits considered “expected” should allow enough of a time lag to be captured by the database system.*

*If the number of forms is not large, the availability of collected forms can be summarized as in Table 6.*

*Tracking completeness of forms may not reflect exactly the rate of missing data on the outcomes that are supposed to be collected through the forms. The completeness of key outcomes such as the primary outcome, and the corresponding baseline value may be summarized separately, as in Table 7.*

- **Safety Analysis Report**

*If the number of adverse events is small, it may be best to list all the adverse events as in Table 8. If the number of adverse events is relatively large, then the adverse events may be summarized by body system and preferred term as in Table 9, with a listing of only the serious adverse events as in Table 8. An alternative form of Table 9 is summarizing the adverse events by the worst grade each subject experienced during study follow-up as in Table 10.*



**Table 3 Study Status of Enrolled Subjects**

| Study Status                               | n<br>(total = xx) | % |
|--|-------------------|---|
| Active follow-up                           |                   |   |
| Off Study                                  |                   |   |
| Completed per protocol                     |                   |   |
| Premature discontinued                     |                   |   |
| Reason for premature Study Discontinuation | n                 | % |
| Lost to follow-up                          |                   |   |
| Withdrew Consent                           |                   |   |
| Adverse Event                              |                   |   |
| Other                                      |                   |   |
|  |                   |   |

**Table 4 Summary of Protocol Deviations**

| Details of Protocol Deviation | (n = ) |
|-------------------------------|--------|
| Eligibility error             | n (%)  |
| Dosing error                  | n (%)  |
| Treatment not taken           |        |
|                               |        |
|                               |        |

**Table 5 Completeness of follow-up visits**

| Study Week   | # expected | # observed | Proportion completed |
|--------------|------------|------------|----------------------|
| Week 0 Visit |            |            |                      |
|              |            |            |                      |
| Week 2 Visit |            |            |                      |
|              |            |            |                      |
| Week 4 Visit |            |            |                      |
|              |            |            |                      |
|              |            |            |                      |
|              |            |            |                      |
|              |            |            |                      |

**Table 6 Summary of Form Completeness**

| Study Week | Form number | From brief name       | # expected | # collected in Database | Proportion in Database |
|------------|-------------|-----------------------|------------|-------------------------|------------------------|
| Baseline   | 1           | Inclusion/Exclusion   |            |                         |                        |
|            | 2           | Medical History       |            |                         |                        |
|            | 3           | Initial physical exam |            |                         |                        |
|            | 4           | Baseline lab          |            |                         |                        |
|            |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |
| Week xx    | 4           | Followup lab          |            |                         |                        |
|            |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |
| Week xx    |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |
|            |             |                       |            |                         |                        |

**Table 7 Completeness of xxx Outcomes**

| Measurement week  | Expected number | Observed number | Proportion Complete |
|-------------------|-----------------|-----------------|---------------------|
| Week 0 (baseline) |                 |                 |                     |
|                   |                 |                 |                     |
| Week 4            |                 |                 |                     |
|                   |                 |                 |                     |
| Week 24 (Primary) |                 |                 |                     |
|                   |                 |                 |                     |

Table 8 List of Reported Adverse Events

| Subject ID | Entry Date | Adverse Event and Narrative  | Severity | Relation to study drug |
|------------|------------|--|----------|------------------------|
| 1          | 01/22/08   | <b>Constipation: 01/2008, reported 03/19/08</b><br>Patient reports feeling constipated which started approximately around the time of beginning of study drug.   | Mild     | Possibly               |
| 2          | 01/25/08   | <b>Stomach pain: 01/25/08 – 01/26/08</b><br>Mother reported when called to see why they did not show for 6wk f/u (3/13/08). Reported that his stomach hurt at the first dose of XXX. Subsided the next day, but patient never took study drug again. Patient withdrew from trial.<br><br><b>Serum Phos &gt; 4.9 mg/dL (value=5.2): 01/25/08, ongoing</b> | Moderate | Possibly               |
| 3          |            |  |          |                        |
| 4          |            |  |          |                        |

Table 9 Incidence of Adverse Events by Body System and Preferred Term

| Body System and Preferred Term | n* | %** (Total N=) | Total # of Events*** |
|--------------------------------|----|----------------|----------------------|
| <b>Overall</b>                 |    |                |                      |
| <b>Cardiovascular</b>          |    |                |                      |
| Myocardial Infarction          |    |                |                      |
| Increased Blood Pressure       |    |                |                      |
| etc.                           |    |                |                      |
| <b>Genitourinary</b>           |    |                |                      |
| Yeast Infection                |    |                |                      |
| Vaginal Bleeding               |    |                |                      |
| etc.                           |    |                |                      |
| <b>Gastrointestinal</b>        |    |                |                      |
| etc...                         |    |                |                      |

\* Number of participants experiencing an adverse event (participant is to be counted only once for each adverse event)  
 \*\* % of total number of participants in the study  
 \*\*\* Number of events

**Table 10 Summary of Adverse Events by Severity Grade**

| <b>Body System and Preferred Term*</b> | <b>Grade 2</b> | <b>Grade 3</b> | <b>Grade 4</b> |
|--|----------------|----------------|----------------|
| <b>Overall</b>                         | <b>n (%)</b>   | <b>n (%)</b>   | <b>n (%)</b>   |
| <b>Cardiovascular</b>                  |                |                |                |
| Myocardial Infarction                  |                |                |                |
| Increased Blood Pressure               |                |                |                |
| etc.                                   |                |                |                |
|  |                |                |                |
| <b>Genitourinary</b>                   |                |                |                |
| Yeast Infection                        |                |                |                |
| Vaginal Bleeding                       |                |                |                |
| etc.                                   |                |                |                |
|  |                |                |                |
| <b>Gastrointestinal</b>                |                |                |                |
|  |                |                |                |
| <b>etc...</b>                          |                |                |                |

\* *The number in each cell represents counts of subjects who experienced the grade as the worst grade for each particular type of adverse event during study follow-up.*

**Template: Closed DSMB Report**

***Study Name***

**PI: Name**

**Data Safety and Monitoring Report**  
**Closed Session**

DSMB Meeting Date:

Prepared by:

Data Managed by:

*Month day, year*

*Name(s)*

*Organization*

*Names(s)*

*Organization*

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## **1 Administrative Report by Treatment Arm**

### **1.1 Study Accrual by Arm**

*For single site studies, it is usually not necessary to present accrual by month for each arm. For multi-site studies, it may be advisable to present accrual by arm within each site if randomization is not stratified by site.*

### **1.2 Baseline Patient Characteristics by Arm**

Table 21 presents baseline patient characteristics by arm. Summarize

Table 2. This analysis helps examine whether randomization worked well.

Statistical testing comparing these characteristics is not necessary for randomized studies.

### **1.3 Study Status**

**Table 3** summarizes the study status of enrolled subjects by treatment arm as of Month day, year. This table is similar to the table in the Open Report except for breaking down by arm.

### **1.4 Data Completeness by Arm**

*This section presents data completeness by arm.*

*Sample tables are given in Table 13 - Table 16.*

## **2 Safety Analysis Report by Arm**

*It is usually not recommended to test the significance for every kind of adverse event among the arms because of the inflated type-I error rate. But formal testing may be performed for pre-specified important safety measure such as death rate, grade 3 or above event rate, time to some study specific adverse event, etc.*

*For studies which may have differential follow-up in the randomized arms, person-year event rate may be more objective safety measure for comparing safety among treatment arms.*

*Sample tables are given in Table 17 - Table 20.*

## **4 Efficacy Analysis Report by Arm**

*This section summarizes descriptive and primary analysis on the primary efficacy endpoint. Interpret results and the implication under the pre-specified stopping rule. In some circumstances, secondary endpoints and subgroup analyses may also be shown, to give a more comprehensive picture of outcomes, and to provide context.*

*However, it is important to keep within the scope of what is necessary for monitoring safety and quality. These objectives usually do not include data analyses done for scientific curiosity. The format of the tables or figures may vary widely from trial to trial, depending on the type of endpoints, need for subgroups analyses, and so on.*

## **4 Summary**

This section usually summarizes the main results in this report and highlight if any early stopping boundary is crossed or any other action that might be needed as a consequence of the results.

**Table 11. Patient Baseline Characteristics by Treatment Arm**

| Characteristic                           | Arm X<br>(n= ) | Arm Y<br>(n= ) | Total<br>(N= ) |
|--|----------------|----------------|----------------|
| Age in years, median (Q1, Q3)            | xx (xx, xx)    | xx (xx, xx)    | xx (xx, xx)    |
| Male gender, # (%)                       | xx (xx%)       | xx (xx%)       | xx (xx%)       |
| Hispanic or Latino Ethnicity, #(%)       | xx (xx%)       | xx (xx%)       | xx (xx%)       |
| Race, # (%)                              |                |                |                |
| White                                    |                |                |                |
| Black or African American                |                |                |                |
| Other categories as decided by the study |                |                |                |
| Study specific patient characteristics   |                |                |                |
|  |                |                |                |
|  |                |                |                |
|  |                |                |                |
|  |                |                |                |
|  |                |                |                |

**Table 12. Study Status of Enrolled Subjects**

| Study Status                               | Arm X<br>(n = ) | Arm Y<br>(n = ) |
|--|-----------------|-----------------|
| Active follow-up                           | n (%)           | n (%)           |
| Off Study                                  | n (%)           | n (%)           |
| Completed per protocol                     | n (%)           | n (%)           |
| Premature discontinued                     | n (%)           | n (%)           |
| Reason for premature Study Discontinuation |                 |                 |
| Lost to follow-up                          | n (%)           | n (%)           |
| Withdrew Consent                           | n (%)           | n (%)           |
| Death                                      | n (%)           | n (%)           |
| Adverse Event Other Than Death             | n (%)           | n (%)           |
| Other                                      | n (%)           | n (%)           |
|  |                 |                 |

**Table 13. Completeness of follow-up visits by Arm**

| Study Week | Arm X        |                  | Arm Y        |                  |
|------------|--------------|------------------|--------------|------------------|
|            | No. expected | No. (%) observed | No. expected | No. (%) observed |
| Week 0     |              |                  |              |                  |
| Week 2     |              |                  |              |                  |
| Week 4     |              |                  |              |                  |
|            |              |                  |              |                  |
|            |              |                  |              |                  |
|            |              |                  |              |                  |
|            |              |                  |              |                  |

**Table 14. Summary of Protocol Deviations**

| Details of Protocol Deviation | Arm X<br>(N = ) | Arm Y<br>(N = ) |
|-------------------------------|-----------------|-----------------|
| Eligibility error             | n (%)           | n (%)           |
| Dosing error                  | n (%)           | n (%)           |
| Treatment not taken           | n (%)           | n (%)           |
|                               |                 |                 |
|                               |                 |                 |

**Table 15. Summary of Form Completeness by Study Arm**

| Study Week | Form number | Arm X        |                     | Arm Y        |                     |
|------------|-------------|--------------|---------------------|--------------|---------------------|
|            |             | No. expected | No. (%) in Database | No. expected | No. (%) in Database |
| Baseline   | 1           |              |                     |              |                     |
|            | 2           |              |                     |              |                     |
|            | 3           |              |                     |              |                     |
|            | 4           |              |                     |              |                     |
|            |             |              |                     |              |                     |
|            |             |              |                     |              |                     |
|            |             |              |                     |              |                     |
| Week xx    | 4           |              |                     |              |                     |
|            |             |              |                     |              |                     |
|            |             |              |                     |              |                     |
|            |             |              |                     |              |                     |
|            |             |              |                     |              |                     |
|            |             |              |                     |              |                     |
| Week xx    |             |              |                     |              |                     |
|            |             |              |                     |              |                     |
|            |             |              |                     |              |                     |

**Table 16. Completeness of xxx Outcomes by Study Arm**

| Measurement week  | Arm X       |                 | Arm Y       |                 |
|-------------------|-------------|-----------------|-------------|-----------------|
|                   | Expected No | Observed No (%) | Expected No | Observed No (%) |
| Week 0 (baseline) |             |                 |             |                 |
|                   |             |                 |             |                 |
| Week 4            |             |                 |             |                 |
|                   |             |                 |             |                 |
| Week 24 (Primary) |             |                 |             |                 |
|                   |             |                 |             |                 |

**Table 17. List of Reported Adverse Events**

| Subject ID | Study Arm | Entry Date | Adverse Event and Narrative  | Severity        | Relation to study drug |
|------------|-----------|------------|--|-----------------|------------------------|
| 1          | X         | 01/22/08   | <b>Constipation: 01/2008, reported 03/19/08</b><br><b>Patient reports feeling constipated which started approximately around the time of beginning of study drug.</b>  | <b>Mild</b>     | <b>Possibly</b>        |
| 2          | Y         | 01/25/08   | <b>Stomach pain: 01/25/08 – 01/26/08</b><br><b>Mother reported when called to see why they did not show for 6wk f/u (3/13/08). Reported that his stomach hurt at the first dose of XXX. Subsided the next day, but patient never took study drug again. Patient withdrew from trial.</b> | <b>Moderate</b> | <b>Possibly</b>        |
|            |           |            | <b>Serum Phos &gt; 4.9 mg/dL (value=5.2): 01/25/08, ongoing</b>  |                 |                        |
| 3          |           |            |  |                 |                        |
| 4          |           |            |  |                 |                        |
|            |           |            |  |                 |                        |
|            |           |            |  |                 |                        |
|            |           |            |  |                 |                        |
|            |           |            |  |                 |                        |
|            |           |            |  |                 |                        |
|            |           |            |  |                 |                        |

**Table 18. List of Death Events**

| Subject ID | Study Arm | Entry Date | Death Date | Weeks from entry | Cause of Death      | Relationship to intervention |
|------------|-----------|------------|------------|------------------|---------------------|------------------------------|
| 1          | X         | 01/22/08   |            | 12               | <b>Heart attack</b> | <b>Possibly</b>              |
| 2          | Y         | 01/25/08   |            | 30               | <b>Car accident</b> | <b>Not related</b>           |
| 3          |           |            |            |                  |                     |                              |
| 4          |           |            |            |                  |                     |                              |
|            |           |            |            |                  |                     |                              |
|            |           |            |            |                  |                     |                              |
|            |           |            |            |                  |                     |                              |

**Table 19. Incidence of Adverse Events by Body System and Preferred Term**

| Body System and Preferred Term | Arm X<br>(N= ) |                     | Arm Y<br>(N= ) |                     |
|--------------------------------|----------------|---------------------|----------------|---------------------|
|                                | n (%)*         | Total # of events** | n (%)*         | Total # of events** |
| <b>Overall</b>                 |                |                     |                |                     |
| <b>Cardiovascular</b>          |                |                     |                |                     |
| Myocardial Infarction          |                |                     |                |                     |
| Increased Blood Pressure       |                |                     |                |                     |
| etc.                           |                |                     |                |                     |
|                                |                |                     |                |                     |
| <b>Genitourinary</b>           |                |                     |                |                     |
| Yeast Infection                |                |                     |                |                     |
| Vaginal Bleeding               |                |                     |                |                     |
| etc.                           |                |                     |                |                     |
|                                |                |                     |                |                     |
| <b>Gastrointestinal</b>        |                |                     |                |                     |
|                                |                |                     |                |                     |
| <b>etc...</b>                  |                |                     |                |                     |

\* *Number of participants experiencing an adverse event (participant is to be counted only once for each adverse event)*

\*\* *Each subject may contribute multiple counts if experience same event multiple times.*

**Table 20. Summary of Worst Grade Adverse Events by Arm and Grade**

|  | Arm X          |                |                | Arm Y          |                |                |
|--|----------------|----------------|----------------|----------------|----------------|----------------|
| <b>Body System and Preferred Term*</b> | <b>Grade 2</b> | <b>Grade 3</b> | <b>Grade 4</b> | <b>Grade 2</b> | <b>Grade 3</b> | <b>Grade 4</b> |
| <b>Overall</b>                         | <b>n (%)</b>   |
| <b>Cardiovascular</b>                  |                |                |                |                |                |                |
| Myocardial Infarction                  |                |                |                |                |                |                |
| Increased Blood Pressure               |                |                |                |                |                |                |
| etc.                                   |                |                |                |                |                |                |
|  |                |                |                |                |                |                |
| <b>Genitourinary</b>                   |                |                |                |                |                |                |
| Yeast Infection                        |                |                |                |                |                |                |
| Vaginal Bleeding                       |                |                |                |                |                |                |
| etc.                                   |                |                |                |                |                |                |
|  |                |                |                |                |                |                |
| <b>Gastrointestinal</b>                |                |                |                |                |                |                |
|  |                |                |                |                |                |                |
| etc...                                 |                |                |                |                |                |                |

\* *The number in each cell represents counts of subjects who experienced the grade as the worst grade for each particular type of adverse event during follow-up. The proportion is obtained by dividing the total number of subjects included in this interim analysis in the corresponding arm.*

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