

II3B GD1 Data and Safety Monitoring Plan

Overview

This guidance is provided for the use of University of Nevada, Reno (the University) investigators and research staff as a supplement to the policy on data and safety monitoring (Policy II3B) and to further describe the application of the policy.

Note: This guidance applies when a Data and Safety Monitoring Plan (DSMP) is warranted by the risk level of a research study. A DSMP may not be necessary for research involving no more than minimal risk and when minimal risks are not likely, easily and sufficiently mitigated or both. In these instances, investigators must indicate that a DSMP will not be used for the research, explain why one isn't warranted and justify the exclusion of such a plan.

II3B1 Content Requirements of the DSMP

The DSMP must describe how the investigator intends to provide ongoing supervision and evaluation of the activities of the study, including whether new risks have been identified and whether appropriate progress is being made.

The DSMP must describe the procedures and means that will be used to protect the welfare and safety of subjects and to protect the integrity of the data. When the study sponsor is performing data and safety monitoring activities, the investigator must provide a brief plan that describes how the local monitoring responsibilities will be integrated into the sponsor's DSMP and accomplished by the investigator, and how IRB reporting requirements will be met.

The type and degree of monitoring must be commensurate with the degree of risk involved, the size and complexity of the study, and should be appropriate to the study population and research environment. The plan must include provisions for data review and performance of safety reviews, at a specified frequency appropriate for the level of risk undertaken by research participants. The plan must also include provisions for reporting non-compliance, serious adverse events and unanticipated problems involving risks to subjects (henceforth referenced as Unanticipated Problems) or others as required by IRB policy, federal regulations and guidance, sponsors (when applicable) and other internal and external organizations as appropriate.

II3B2 Required Elements of the DSMP

The following is a more detailed explanation of the elements required of a DSMP, as set forth in Policy II3B Data and Safety Monitoring.

I13B2a The DSMP Must Identify the Individuals Responsible for Implementing the Plan, Specify the Frequency of and Parameters for Reviews

1. The Plan should identify the individuals who are responsible for monitoring the study.

Example: The principal investigator or named designee, e.g., co-investigator, will monitor the data and conduct safety reviews, at a specified frequency appropriate to the level of risk.

2. The Plan should specify the frequency of reviews, including how often or under what special circumstances the Data Safety Monitoring Board or Committee (DSMB/DSMC) or responsible individual (and the PI when indicated) will evaluate the data to determine if the study should continue unchanged, be amended, closed to enrollment or terminated.
3. The Plan should define the parameters whereby the DSMB/DSMC or responsible individual will analyze the monitoring and safety review data, (e.g., by segments of time, by subject or other specific and predetermined parameters or outcomes).

The focus of the analysis is to determine whether enrollment should continue or be closed, whether the research or trial should continue as originally designed or if it should be amended. If the data indicate such a step is necessary to protect research subjects, the principal investigator, study sponsor, DSMB (if one exists), IRB and other University oversight committees have the authority to stop or suspend the study or require modifications.

I13B2b The DSMP Must Include an Explicit Statement of Risk

The principal investigator must state the level of risk associated with participation in the study and must explain why that designation is appropriate. Risk assessments are necessary to facilitate consideration of safety issues and to design the DSMP to be appropriate to the level of risk presented to subjects.

Risks considerations should evaluate physical risks and psychological risk, as applicable; and possible harms to subjects if confidential or sensitive data are inadvertently disclosed. The Plan should indicate whether vulnerable populations are included in the research study and if so, should include parameters for assessing any additional safeguards, when incorporated into the research. If the research involves investigational agents or devices, or the use of placebos, parameters are needed for addressing risks associated with these research designs. The Plan should also assess risks related to the underlying health of the study populations.

I13B2c The DSMP Must Describe How Relatedness of Adverse Events Will Be Determined

The principal investigator is responsible for determining the likelihood that an adverse event is related to the study and must assess the relatedness. (See IRB Policy I12F, Reporting Adverse Events and Unanticipated Problems and related procedures.)

Note: *Internal (i.e., local) serious adverse events must be reported to the IRB regardless of relatedness.*

Example of Categories for Evaluating Relatedness of Adverse Events

1. Definite: Adverse event is clearly related to investigational agent(s) or other study intervention(s)
2. Probable: Adverse event is likely to be related to investigational agent(s) or other study intervention(s)
3. Possible: Adverse event may be related to investigational agent(s) or other study intervention(s)
4. Unlikely: Adverse event is likely not to be related to investigational agent(s) or other study intervention
5. Unrelated: Adverse event is clearly not related to the investigational agents(s) or other study intervention(s)

Other scales for assessing and categorizing the relatedness adverse events may be used as long as the criteria are clearly defined and referenced in the DSMP.

I13B2d The DSMP Must Include Plans for Grading Adverse Events and Identifying Serious Adverse Events

The principal investigator must provide a plan for categorizing or grading adverse events using a scale similar to the one provided below. The plan should indicate what sorts of events would be included in each category.

Assessing and Categorizing the Intensity or Severity of Adverse Events

The DSMP must include information about how the intensity or severity of adverse events will be assessed and categories (i.e., graded). Clinical protocols may have unique approaches for grading AEs; the P.I. should consult the investigator brochure, master protocol, sponsor or both for specific grading scales. Multi-center studies generally include such a table, sometimes called a toxicity table in the master protocol.

If a grading scale is not described in the master protocol or the research is being conducted at a single site and does not have a specific grading scale, investigators may consider using the Common Toxicity Criteria (CTC) scale. The CTC scale may be viewed at <http://ctep.cancer.gov/>. Once at this website, click on Reporting Guidelines, next click on Common Toxicity Criteria, then click on Common Toxicity Criteria Document (PDF) for the actual CTC table.

CTC Grades for Categorizing the Severity of Adverse Events

(Example grading system taken from the USDHHS, NIH, NCI Common Terminology Criteria for Adverse Events, June 14, 2010.)

The following grades refer to the severity of an adverse event.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; or limiting age-appropriate instrumental ADLs such as preparing meals, shopping for groceries or clothes, using the telephone, managing money
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs such as bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

I13B2e Serious Adverse Events

In addition to grading the severity of an adverse event, the PI must determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death or a life-threatening experience;
2. inpatient hospitalization or prolongation of existing hospitalization;
3. a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or
4. any other adverse event that, 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.

Examples of Adverse Events Reportable as Serious Adverse Events:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome);
- A series of adverse events that, on analysis, is both unanticipated and a problem for the study; specifically, the series of adverse events represents a signal that the adverse events were not just isolated occurrences and that the events significantly affected the rights and welfare of participants;
- An adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents and is expected to occur in study participants at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in participant population), but that occurs at a greater frequency or severity than expected; and
- Any other adverse event that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to assure the protection of human participants.

I13B2f The DSMP Must Include IRB Reporting Requirements

The DSMP must specify that the research will be compliant with IRB requirements for reporting local unanticipated serious adverse events; local anticipated serious adverse events occurring at a greater frequency or severity than expected; and Unanticipated Problems, including those occurring locally and those reported in communication from the sponsor or external DSMB/DSMC for multi-site research. Reports must be in writing and made in a timely manner (48 hours for serious adverse events and within five business days for Unanticipated Problems) using the Unanticipated problems/Adverse Event Report. The investigator must assess the need for changes to the protocol, procedures, consent documents or all three; and must describe any immediate steps taken to protect human subjects.

For more information about reporting adverse events and Unanticipated Problems see IRB Policy I12F and the associated procedures.

I13B2g The DSMP Must Describe All Other Reporting Requirements

The DSMP must specify that the Principal Investigator will review all adverse events and describe when and how the PI will report local serious adverse events to fellow investigators and key study personnel, sponsors, research monitors (if any), DSMB/DSMC, regulatory agencies and any other oversight bodies as applicable to the specific research; and when and how the PI will report external adverse events determined to be Unanticipated Problems.

For Multicenter trials when the University is the coordinating site, the PI is responsible for reviewing safety reports forwarded by sponsors, research monitors, DSMB/DSMC or cooperative groups. As the PI assesses these reports, he or she should categorize the events as serious or non-serious, and unanticipated or anticipated.

Reporting requirements should be based upon IRB Policy I12F, which includes information for reporting non-serious, unanticipated and anticipated adverse events.

The DSMP should also describe stopping rules; the description should include the variables and parameters that would evoke the need to stop the research and the processes involved in this action.

I13B3 When is a DSMB/DSMC Required?

The IRB may, in certain circumstances, require a DSMB depending on the level of risk or if there is a potential for a significant conflict of interest.

A DSMB/DSMC may be appropriate

1. In any study where the risk is greater than minimal;
2. When a Principal Investigator holds the IND for the investigational agent being used in the study;

3. For Phase I and II trials if the studies have multiple clinical sites, are blinded, or employ particularly high-risk interventions or enroll vulnerable populations;
4. When the University is the coordinating site of a multicenter study; or
5. As a mechanism of managing a real or potential Conflict of Interest including when a Principal Investigator is the inventor of an intervention being tested.

II3B4 DSMB Attributes

When a DSMB is involved, the Plan should describe the DSMB's organization, membership, responsibilities and operations. Membership should include appropriate scientific and bio-statistical expertise.

Generally the DSMB should be independent from the sponsor and investigator team although degree of independence required depends on the risk level associated with the trial.

The DSMB should be responsible for reviewing comprehensive, cumulative, un-blinded safety reports and employing stopping rules if there is evidence of differential effects in either risk or benefit. The descriptions of standard operating procedures should include frequency and documentation of periodic reviews, and submittal of written summary or minutes to the principal investigator. The investigator, upon receipt, must submit the DSMB findings and recommendations to the IRB.

When the University of affiliate principal investigator is required by the IRB to constitute a DSMB, the following will likely be required:

- All DSMB members, or the majority of DSMB members, do not have University or affiliate appointments.
- DSMB members do not have interests, financial or otherwise, in the outcome of the study.
- DSMB members who may be internal to the University or affiliate do not have reporting relationships to members of the research team.
- DSMB members who are internal to the University or affiliate are not members of the same department or section as the principal investigator.