

Policy II3B Data and Safety Monitoring

Scope

This policy describes requirements related to data and safety monitoring of research, thereby contributing to the safety and well-being of research participants who are a part of the proposed research protocol. This policy applies to all investigators at University of Nevada, Reno (the University) or its research affiliates who conduct human research.

Policy Statement

All non-exempt human subjects research protocols submitted to the Institutional Review Board (IRB) for review must include an explicit Data and Safety Monitoring Plan (DSMP). The plan must detail how the Principal Investigator (PI) will conduct monitoring of human research participants' data and safety commensurate with the risks associated with their participation in research conducted at the University and affiliate sites. In addition, for multi-center clinical trials in which a University or research affiliate PI serves as the overall PI, the DSMP must include a detailed plan describing how the University PI will conduct data and safety monitoring for the subjects at all other sites.

The formation and use of a Data and Safety Monitoring Board or Committee (DSMB/DSMC) may be required by the IRB in certain circumstances depending on the level of risk to research participants or when a real or potential interest of a study investigator or the University poses, or may pose a conflict of interest. When a DSMB exists, the DSMP must include plans for submitting DSMB reports to the IRB and other research oversight committees.

The IRB is responsible for evaluating the appropriateness of the DSMP when it performs initial and continuing protocol reviews and during the latter, for assessing reports of same when these reports do not identify a serious adverse even or unanticipated problem involving risks to subjects or others. (See IRB Policy II2F and related procedures for definitions and additional information about reporting requirements for adverse events and unanticipated problems.)

Reason for the Policy

Data and safety monitoring is considered to be an essential component in the protection of human research participants. Investigators and the IRB must ensure that an adequate and appropriate DSMP is proposed and approved prior to the commencement of human subjects research, or that sufficient justification exists in the research protocol for not including a DSMP.

The inclusion of a DSMP for human subjects research (or justification of same when the level of risk is such that a plan isn't warranted) allows both the PI and IRB to readily identify, monitor and quickly address and report any events or problems which may present a risk to study participants. By examining the accruing data for indications of benefits or harm (including physical, psychological, economic or

social harm), the investigator, the IRB or the DSMB can assess new risks or anticipated risks that appear in greater severity or frequency than originally anticipated, and can determine if the study may progress as planned, requires amendments to better protect subjects or should be terminated.

Definitions

Adverse Event

45 CFR 46 does not define or use the phrase “adverse event” but DHHS OHRP “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events” defines an adverse event thusly: “Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research...” and further states that adverse events include both physical and psychological harms.

Adverse Event, Internal

Adverse events experienced by subjects enrolled by the investigator at the investigator’s institution. (In the context of a single-center clinical trial or research study taking place only at the investigator’s institution, all adverse events would be considered internal.

Adverse Event, External

Adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. Investigators at all participating institutions learn of external adverse events via reports from the sponsor, sponsor-initiated DSMB or coordinating center of a multicenter clinical trial.

Data and Safety Monitoring Board or Committee

A group charged with protecting subject safety by examining the accruing data for indications of benefit or harm that is established by the investigator, sponsor or steering committee or coordinating center of a study. The DSMB/DSMC makes a judgment as to whether the research should continue and may recommend changes to the research protocol, consent documents or both. The DSMB/DSMC for multi-site research looks at global data, as investigators forward all adverse event reports and safety data to a data coordinating center, which compiles the data for the DSMB/DSMC to review at predefined intervals. Data presented to the DSMB/DSMC is either completely unblinded, or categorized by treatment arm. As such, the DSMB/DSMC is able to determine whether a clear effect exists in one arm of the study versus the other arms. The DSMB/DSMC for single-site research receives adverse events reports and other safety data from the PI.

Data and Safety Monitoring Plan

A plan, tailored to a particular protocol, that describes who has the responsibility to monitor study data and the frequency at which study data is monitored to ensure the safety of human subjects and integrity of study data.

Related Event

An event is “related” if it is possibly, probably, or definitely caused by the research procedures.

Minimal Risk

Risk whereby the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Examples may include blood draws of small volumes for research purposes, the collection of biological specimens for research purposes by noninvasive means, the collection of data from medical records, and most research employing surveys, interviews, or focus groups.

Note: The regulations at 45 CFR 46 reference two risk categories: no more than minimal and greater than minimal.

Serious Adverse Event

Any adverse event that results in any of the following outcomes: death; a life-threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or 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.

Unanticipated Event

Problems, risks or events that occur during the conduct of the research, but were not expected and therefore are not cited in the written protocol, the consent form(s) or the Investigator's Brochure. Unanticipated events also include problems, risks or adverse events that were expected but occur with greater severity or frequency than originally anticipated.

Unanticipated Problems Involving Risks to Subjects or Others

See IRB Policy II2F Reporting Adverse Events and Unanticipated Problems

II3B1 Required Elements of the DSMP

The DSMP must document the procedures and means 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 DSMP must include

- a description of the monitoring of the progress of the trial, the safety of participants, data accuracy and protocol compliance.

- a description of the mechanism and timeframe for appropriate reporting of adverse events, unanticipated problems, protocol noncompliance and protocol deviations to the IRB, the FDA, or the government agency program official or sponsor representative responsible for the grant or contract; and
- an assessment of risk level determination. overall risk assessment associated with the protocol may be assessed by the investigator as no more than minimal and greater than minimal.

II3B2 DSMP Requirements Based on Risk

II3B2a Requirements for a DSMP for Minimal Risk Research

Research in which risks are no more than minimal, unlikely and easily and fully mitigated (e.g., survey research or analysis of existing behaviors involving non-sensitive subject matter that uses a rigorous process for coding data), may not warrant a DSMP. In such cases, the PI must provide sufficient justification for not using a DSMP.

When DSMP for minimal risk research is warranted, the plan must include the following:

- identification of the individual(s) who will be responsible for monitoring the data, assuring protocol compliance and conducting the safety reviews;
- the required frequency of the reviews;
- statement that the research involves no more than minimal risk, and when applicable,
 - a description of any expected adverse events such as bruising or minor infection from a blood draw, or breach of confidentiality; or
 - a statement that adverse events are not anticipated; and
- a plan for reporting to the IRB serious unanticipated adverse events and unanticipated problems involving risks to subjects or others at the University or affiliate sites, or other sites for multicenter trials.

II3B2b Requirements for a DSMP for Research with Greater than Minimal Risk

At a minimum, the DSMP for research with greater than minimal risk must include the following:

- identification of the individuals who will be responsible for monitoring the data, conducting safety reviews, reporting safety concerns to the IRB or sponsor (as applicable); and assuring protocol compliance or reporting non-compliance;
- specified frequency of safety reviews;
- explicit statement of greater than minimal risk and a description of any expected adverse events;

- plan for *assessing* the seriousness and expectedness of adverse events, including expected adverse events that occur in greater severity or frequency than originally anticipated;
- plan for grading adverse events (see guidance II3B GD1 Data and Safety Monitoring Plan for suggestions for grading adverse events); and
- plan for determining the relatedness of adverse events (unless determined to be serious);
- plan for *reporting* to the IRB serious unanticipated adverse events, anticipated adverse events occurring at a greater frequency than expected, and unanticipated problems involving risks to subjects or others at the University or other sites, when applicable for multi-center trials; and
- plan for reporting unanticipated adverse events and unanticipated problems to co-investigators on the study, and, as appropriate, to the protocol's research monitors such as DSMB/DSMC, study sponsors, funding and regulatory agencies and regulatory and decision-making bodies.

II3B4 Investigator Responsibilities

The DSMP must describe how the investigator intends to provide ongoing supervision and evaluation of the activities of the study, including the frequency and severity of adverse events, and whether new risks have been identified. The DSMP also must describe how the investigator will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit and other factors that may affect study outcome. Ongoing oversight should also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may affect participant safety of the ethics of the research.

II3B5 Multi-Center Clinical Trials

A University investigator who serves as the sponsor of a multi-center trial has additional responsibilities for coordinating the trial across all sites. These responsibilities include, but are not limited to, ensuring ongoing IRB approval at other study sites; monitoring adverse events and reporting to the IRB, DHHS OHRP, the FDA, the sponsor and other bodies that monitor or have reporting requirements related to the conduct of the study; and retaining copies of all relevant documentation of IRB approval and adverse events and unanticipated problems reports. A multi-center clinical trial may require a central monitoring entity to perform these functions.