

Policies and Procedures

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1. PURPOSE

This policy defines the requirements for inclusion of a data and safety monitoring plan in interventional clinical research protocols submitted to the Creighton University Institutional Review Board (IRB) for review and approval. This policy is established to comply in part with the requirement for IRBs to determine “where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects” [45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6)].

2. DATA AND SAFETY MONITORING PLANS

The Creighton University Institutional Review Board (IRB) requires the inclusion of a data and safety monitoring plan in all interventional clinical research protocols that involve more than minimal risk to subjects. The plan must be described in sufficient detail for the IRB to determine whether it is appropriate for the research. All human subject research proposals submitted for review by the Creighton University IRB are subject to this policy.

Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care and for ensuring the study is conducted at his/her investigative site in accordance with the IRB-approved protocol and applicable IRB regulations and requirements.

When a Creighton University investigator is the lead investigator of a multi-site project, the data and safety monitoring plan shall include procedures on the management of information from all sites relevant to the protection of subjects, and how this information will be reported to the IRB. This data shall include all unanticipated problems involving risks to subjects or others, interim results, and protocol modifications.

3. DEFINITIONS

- 3.1. *Interventional clinical research* means any prospective study involving human subjects designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention (i.e., drugs, devices, treatments or procedures, behavioral or nutritional strategies), or about human physiology.
- 3.2. *Minimal risk* means 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

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physical or psychological examinations or tests [45 CFR 46.102(j) and 21 CFR 56.102(i)].

4. GUIDANCE ON DATA AND SAFETY MONITORING PLANS

The following information is provided to assist investigators in establishing an appropriate data and safety monitoring plan for their research.

4.1. What is data and safety monitoring?

- 4.1.1. *Data and safety monitoring* is the process for reviewing accumulated outcome data from an ongoing clinical trial to ensure the continuing safety of current subjects and those yet to be enrolled, as well as the continuing validity and scientific merit of the trial

4.2. What does a data and safety monitoring plan need to include?

- 4.2.1. The data and safety monitoring plan should include the following:
 - 4.2.1.1. The type of data or events to be captured under the monitoring plan
 - 4.2.1.2. Who will be responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC), and or some other entity)
 - 4.2.1.3. The time frames for reporting unanticipated problems and adverse events to the monitoring entity, such as the research sponsor, coordinating or statistical center, independent medical monitor, or DSMB/DMC
 - 4.2.1.4. The frequency of assessments of data or events captured by the monitoring plan, such as points in time or after a specific number of subjects are enrolled
 - 4.2.1.5. Definition of specific triggers or *stopping rules* that will dictate when some action is required. *Stopping rules* are predetermined guidelines used to determine the study should be altered or

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stopped, based on review of study-related events that occur during the conduct of the study. Stopping rules should be specific about the endpoints used and the decisions to be made. Studies may be stopped, for example, when there is a greater than expected rate of morbidity or mortality, or when the experimental arm of a head-to-head comparison study is shown to be better or worse statistically than the standard care arm

- 4.2.1.6. As appropriate, procedures for communicating to the IRB, the study sponsor, and other appropriate entities the outcome of the reviews by the monitoring entity

4.3. What type of data safety monitoring plan is appropriate?

- 4.3.1. A data and safety monitoring plan should be tailored to the nature, size, and complexity of the research protocol, the expected risks of the research, and the type of subject population being studied. Appropriate plans may fall anywhere along a continuum from monitoring by the principal investigator or group of investigators to the establishment of an independent DSMB/DMC

- 4.3.1.1. Investigator monitored plan. This type of plan is appropriate when the study involves a small number of subjects; the study is conducted only at one site; and the range of possible study events that could have an important impact on the risks and benefits of research subjects is narrow. In such cases, continuous monitoring of events by the investigator, and prompt reporting of toxicity to the IRB and, when applicable, the FDA, the NIH, or others, may be adequate

- 4.3.1.2. Monitor/Monitoring Group monitored plan. A qualified and objective individual or group not directly involved with the design and conduct of the study (e.g., safety officer, designated medical monitor or monitoring group) could perform this function. These individuals may or may not be employees of Creighton University or the study sponsor. However, conflict of interest is an important consideration when employees of the study sponsor have the primary responsibility for monitoring data from the standpoint of scientific integrity and subject safety.

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4.3.1.2.1. This type of plan is often appropriate to monitor data and safety for clinical trials that involve:

4.3.1.2.1.1. endpoints that are not serious irreversible events;

4.3.1.2.1.2. an intervention (for example, to relieve symptoms) is not high risk and the effects of which would not generally be so compelling as to ethically warrant early termination for effectiveness ;

4.3.1.2.1.3. short-term treatments for which effects are evaluated over periods of a few days to a few months; and

4.3.1.2.1.4. a smaller number of participants when the study is completed quickly and the risk can be adequately assessed through simple comparisons

4.3.1.2.2. In these studies, valuable secondary objectives such as characterization of the effect (i.e., magnitude, duration, time to response), assessment of the effect in population subsets, comparison of several doses, or comparison of the new product to an active control can be ethically pursued even when the conclusion regarding the primary efficacy outcome is clear. Early termination for effectiveness is rarely appropriate in such studies. First, the study may be essentially completed by the time any interim analysis to evaluate effectiveness could be undertaken. Second, the effectiveness of an intervention, for example, to relieve symptoms, would not generally be so compelling as to override the need to collect the full amount of safety data, or to collect other information of interest and importance that characterizes the effect.

4.3.1.3. DSMB/DMC

4.3.1.3.1. An independent Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) external to

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the trial organizers and investigators could perform this function. A DSMB/DMC is a formal committee established specifically to monitor data throughout the life of a study to determine whether it is appropriate, from both a scientific and ethical standpoint, to continue the study as planned

4.3.1.3.2. In general, an independent DSMB/DMC is the most appropriate way to monitor data and safety for studies that involve:

4.3.1.3.2.1. **Large numbers of subjects** when risk may better be assessed through statistical comparisons of treatment groups;

4.3.1.3.2.2. **Blinded study treatment groups** when the validity and integrity of the study may be adversely affected by having an individual or group associated with the design and conduct of the study break the blind;

4.3.1.3.2.3. **Multiple clinical sites** when there is a need for investigators to submit reports of unanticipated problems, including adverse events, to a central reporting entity, such as a coordinating center or statistical center, responsible for preparing timely summary reports of unanticipated problems for distribution among the clinical sites and to the IRBs;

4.3.1.3.2.4. **High-risk interventions** when death or severe disability is a major risk of research participation; and/or

4.3.1.3.2.5. **Controlled trials with mortality or major morbidity as a primary or secondary endpoint** when increased morbidity or mortality may better be assessed through statistical comparisons of morbidity or mortality among treatment groups

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5. DSMB/DMC MEMBERSHIP, CHARTERS, AND RESPONSIBILITIES

- 5.1. DSMBs/DMCs are typically made up of individuals who have expertise in the field, experience in the conduct of clinical trials, and/or statistical knowledge, and who do not have any conflicts of interest, such as financial interests that could be substantially affected by the outcome of the trial, strong views on the relative merits of the interventions under study, or relationships with the sponsor or those in trial leadership positions that could be considered reasonably likely to affect their objectivity.
- 5.2. DSMBs/DMCs typically operate under a written charter that includes well-defined standard operating procedures that address the following:
 - 5.2.1. Meeting schedule (frequency) and format (in person or by telephone)
 - 5.2.2. Meeting structure and confidentiality (who will attend all or part of DSMB/DMC meetings and who will have access to interim data)
 - 5.2.3. Format, method, and timing of interim reports to the DSMB/DMC
 - 5.2.4. Procedures for assessing conflict of interest of potential DSMB/DMC members
 - 5.2.5. Other issues relevant to committee operations, such as membership, voting, quorum, and handling of minutes
- 5.3. Responsibilities
 - 5.3.1. The DSMB/DMC charter may be drafted by either the sponsor or the DSMB/DMC; however, both must agree to the procedures outlined in the charter
 - 5.3.2. Responsibilities of DSMBs/DMCs may be broad or narrow in scope, and include some or all the following responsibilities:
 - 5.3.2.1. Monitoring for effectiveness
 - 5.3.2.2. Monitoring for safety
 - 5.3.2.3. Monitoring study conduct (rates of recruitment, ineligibility, noncompliance, protocol violations and dropouts, completeness

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and timeliness of the data, degree of concordance between site evaluation of events and centralized review, balance between study arms on important prognostic variables, accrual within important subsets)

- 5.3.2.4. Consideration of external data, such as release of results of a related study that may have implications for the design of the ongoing study, or even its continuation
- 5.3.2.5. Making recommendations to the sponsor (or other group delegated by the sponsor to make decisions about the trial) concerning continuation of the trial with or without modifications, temporary suspension of enrollment or trial intervention, or termination of the trial based on review of interim data
- 5.3.2.6. Maintaining meeting minutes

6. SAMPLE DSMB/DMC CHARTERS

- 6.1. A number of sample DSMB/DMC charters are publicly available (see web sites listed below). These links are provided for reference only and are not templates formally approved by Creighton University. These can be found at NIH.gov.
 - 6.1.1. National Institute of Aging DSMB Charter Template
 - 6.1.2. National Heart, Lung and Blood Institute DSMB Charter Template

7. NIH SPONSORED RESEARCH

- 7.1. The NIH has established a policy that requires each of its Institutes and Centers (IC) to have a system for the appropriate monitoring of the conduct of clinical trials to ensure the safety of subjects and the validity and integrity of the data for all NIH-supported or conducted clinical trials. Investigators must comply with monitoring requirements of the relevant funding agency in addition to those of the Creighton University IRB. The establishment of DSMBs is required for multi-site clinical trials involving interventions that entail potential risk to the subjects. This would include, in most cases, phase III clinical trials. A phase III trial frequently compares a new treatment to a standard treatment or to no treatment, and treatment allocation may be randomly assigned and the data masked. These studies usually involve a large number of subjects followed for longer periods of treatment exposure. Even if the short-term risk to a subject is

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small, one must consider the long-term effects of a study agent and whether significant safety or efficacy differences emerge between the control and study groups for a masked study. An IC may require a DSMB to perform monitoring functions. This DSMB would be composed of experts relevant to the study and would regularly assess the trial and offer recommendations to the IC concerning its continuation. For more information on NIH Policy, see below:

- 7.1.1. The NIH Policy for Data and Safety Monitoring which can be found under “data and safety monitoring” at NIH.gov.
- 7.1.2. Further Guidance On A Data And Safety Monitoring For Phase I And Phase II Trials which can be found under “data and safety monitoring” at NIH.gov.

8. ADDITIONAL RESOURCES FOUND AT NIH.GOV

- 8.1. FDA Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees
- 8.2. UNICEF/UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards
- 8.3. National Cancer Institute Data and Safety Monitoring Guidelines