NIH POLICY FOR DATA AND SAFETY MONITORING

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National Institutes of Health Policy

It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

Background

A clinical trial entails a relationship between participants and investigators, both of whom must fulfill certain obligations for the effort to succeed. Participants must be fully informed of the study requirements throughout the conduct of the trial and should comply with the rigors of the research protocol or be allowed the opportunity to withdraw from participation. The investigators must protect the health and safety of participants, inform participants of information relevant to their continued participation, and pursue the research objectives with scientific diligence.

Although there are potential benefits to be derived from participation in clinical research, the IRBs and the NIH must ensure, to the extent possible, the safety of study participants and that they do not incur undue risk and that the risks versus benefits are continually reassessed throughout the study period.

With this issuance, the NIH reaffirms the 1979 policy (NIH GUIDE, Volume 8, No, 8, June 5, 1979) developed by the NIH Clinical Trials Committee. Among its recommendations was the concept that "every clinical trial should have provision for data and safety monitoring." The Committee further acknowledged that "a variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the clinical trial. In many cases, the principal investigator would be expected to perform the monitoring function."

In 1994, the Office of Extramural Research established the Committee on Clinical Trial Monitoring to review the oversight and management practices of the ICs for phase III clinical trials. One of the outcomes of this Committee's review was a strong recommendation that "all trials, even those that pose little likelihood of harm, should consider an external monitoring body." This policy affirms the Committee's recommendations concerning DSMBs.

Principles of monitoring data and safety

All clinical trials require monitoring -- Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III); etc. Monitoring should be commensurate with risks -- The method and degree of monitoring needed is related to the degree of risk involved. A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.

Monitoring should be commensurate with size and complexity þ Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

Practical and Implementation Issues:

Oversight of Monitoring

This policy provides each IC with the flexibility to implement the requirement for data and safety monitoring as appropriate for its clinical research activities. Thus, IC staff may either conduct or sponsor the monitoring of data and safety of ongoing studies or delegate such responsibilities to a grantee or contractor. Oversight of monitoring activities is distinct from the monitoring itself and should be the responsibility of the IC regardless of whether the monitoring is performed by NIH staff or is delegated. Oversight of monitoring must be done to ensure that data and safety monitoring plans are in place for all interventional trials, that the quality of these monitoring activities is appropriate to the trial(s), and that the IC has been informed of recommendations that emanate from monitoring activities.

Institutes and Centers Responsibilities

Though ICs may perform a variety of roles in data and safety monitoring and its oversight, the following are the minimum responsibilities of sponsoring ICs.

Prepare or ensure the establishment of a plan for data and safety monitoring for all interventional trials.

- Conduct or delegate ongoing monitoring of interventional trials.
- Ensure that monitoring is timely and effective and that those responsible for monitoring have the appropriate expertise to accomplish its mission.
- Oversee monitoring activities.
- Respond to recommendations that emanate from monitoring activities.
- Performance of Data and Safety Monitoring

The ICs will ensure the integrity of systems for monitoring trial data and participant safety, although they may delegate the actual performance to the grantee or contractor. Monitoring must be performed on a regular basis, and conclusions of the monitoring reported to the IC. Recommendations that emanate from monitoring activities should be reviewed by the responsible official in the IC and addressed. The ICs also have the responsibility of informing trial investigators concerning the data and safety monitoring policy and procedures. Considerations such as who shall perform the monitoring activities, the composition of the monitoring group (if a group is to be used), the frequency and character of monitoring meetings (e.g., open or closed, public or private), and the frequency and content of meeting reports should be a part of the monitoring plans. IRBs should be provided feedback on a regular basis, including findings from adverse-event reports, and recommendations derived from data and safety monitoring.

Monitoring activities should be conducted by experts in all scientific disciplines needed to interpret the data and ensure patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available if warranted.

Ideally, participants in monitoring outcomes of a trial are in no way associated with the trial. For trials that are conducted as part of a cooperative group, a majority of the individuals monitoring outcome data should be external to the group. ICs should require policies that evaluate whether the participants have conflicts of interests with or financial stakes in the research outcome; and when these conflicts exist, policies must exist to manage these in a reasonable manner.

Generally, data and safety monitoring boards meet first in open session, attended by selected trial investigators as well as NIH program staff or project officers and perhaps industry representatives, and then in closed session where they review emerging trial data. When "masked" data are presented or discussed, no one with a

proprietary interest in the outcome should be allowed. Participants in the review of "masked" or confidential data and discussions regarding continuance or stoppage of the study should have no conflict of interest with or financial stake in the research outcome. However, if there is an open session, they could be present.

Confidentiality must be maintained during all phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations. Besides selected NIH program staff, other key NIH staff, and trial biostatisticians, usually only voting members of the DSMB should see interim analyses of outcome data. Exceptions may be made under circumstances where there are serious adverse events, or whenever the DSMB deems it appropriate.

Individuals or groups monitoring data and safety of interventional trials will perform the following activities:

Review the research protocol and plans for data and safety monitoring.

Evaluate the progress of interventional trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome. Monitoring should also 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.

Make recommendations to the IC, IRB, and investigators concerning continuation or conclusion of the trial(s).

Protect the confidentiality of the trial data and the results of monitoring.

Examples of Monitoring Operations

The following provides examples of appropriate types of monitoring and oversight for different types of studies. These are illustrative only. The ICs must develop and implement monitoring activities and oversight of those activities appropriate to the study, population, research environment, and the degree of risk involved.

Phase I: A typical phase I trial of a new drug or agent frequently involves relatively high risk to a small number of participants. The investigator and occasionally others may have the only relevant knowledge regarding the treatment because these are the first human uses. An IC may require the study investigator to perform continuous monitoring of participant safety with frequent reporting to IC staff with oversight responsibility.

Phase II: A typical phase II trial follows phase I studies and there is more information regarding risks, benefits and monitoring procedures. However, more participants are involved and the toxicity and outcomes are confounded by disease process. An IC may require monitoring similar to that of a phase I trial or supplement that level of monitoring with individuals with expertise relevant to the study who might assist in interpreting the data to ensure patient safety.

Phase III: 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 participants followed for longer periods of treatment exposure. While short-term risk is usually slight, one must consider the long term effects of a study agent or achievement of significant safety or efficacy differences 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.

FURTHER GUIDANCE ON A DATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS, June 5, 2000 NOTICE: OD-00-038

National Institutes of Health

Policy: Beginning with the October 2000 receipt date, investigators must submit a monitoring plan for phase I and II clinical trials to the funding Institute and Center (IC) before the trial begins.

Background

In June 1998, the National Institutes of Health (NIH) issued a policy on data and safety monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) that requires oversight and monitoring of all intervention studies to ensure the safety of participants and the validity and integrity of the data. The policy further elaborates that monitoring should be commensurate with risks and with the size and complexity of the trials. The NIH already requires data and safety monitoring, generally, in the form of Data and Safety Monitoring Boards (DSMBs) for phase III clinical trials. For earlier trials (phase I and II), a DSMB may be appropriate if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations.

This document provides further guidance for monitoring of phase I and II trials. This guidance does not take the place of Institutional Review Board (IRB) guidelines, Food and Drug Administration (FDA) requirements, or special NIH guidelines e.g., NIH Guidelines for Research Involving Recombinant DNA Molecules. Specifically, phase I and II gene transfer trials must comply with additional requirements imposed by the latter NIH Guidelines, e.g., reporting of adverse events to the Office of Biotechnology Activities.

Monitoring plan

For phase I and II clinical trials, investigators must submit a general description of the data and safety monitoring plan as part of the research application. This plan will be reviewed by the scientific review group and any comments and concerns will be included in an administrative note in the summary statement. A detailed monitoring plan, however, must be included as part of the protocol and submitted to the local IRB and reviewed and approved by the funding Institute and Center (IC) before the trial begins. We strongly encourage the IRB to review the plan. Each IC should have a system for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data. IC oversight of the monitoring activities is distinct from the monitoring itself. Oversight of monitoring must be done to ensure that monitoring plans are in place for all phase I or II trials and that the IC is informed of recommendations and any necessary actions that emanate from the monitoring activities.

At a minimum, all monitoring plans must include a description of the reporting mechanisms of adverse events to the IRB, the FDA and the NIH. Investigators must ensure that the NIH is informed of actions, if any, taken by the IRB as a result of its continuing review. ICs have the flexibility to determine the reporting requirements of adverse events. The reporting requirement to the NIH may range from individual adverse event reports to summary reports from the monitoring group. In specific cases where the funding IC is the sponsor of the test agent, i.e., holder of the Investigational New Drug (IND) application, investigators must submit individual adverse event reports to the IC (as sponsor) in accordance with FDA regulations. Occasionally, there are phase I or II trials that have established safety monitoring committees. In these cases, summary reports of the committees' discussions of adverse events must be submitted to the IC and IRB. The reporting requirements for adverse events, as approved by the ICs, are in addition to the annual progress reports to the NIH for type 5 awards (non-competing awards).

The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the trial. In phase I and II trials, a number of factors influence risk. A phase I trial of a new drug or agent may involve increasing risk, to a small number of participants, as the drug is escalated in dosage. For phase II trials, there is sometimes information about risks in normal subjects, but risk may be increased as more participants are involved and the toxicity and outcomes may be confounded by the disease process. In situations involving potentially high risks or special populations, investigators must consider additional monitoring safeguards.

For many phase I and phase II trials, independent DSMBs may not be necessary or appropriate when the intervention is low risk. Continuous, close monitoring by the study investigator may be an adequate and appropriate format for monitoring, with prompt reporting of toxicity to the IRB, FDA and/or NIH. In some instances, the study investigator or the IRB may determine that an independent individual may be needed for monitoring. In studies of small numbers of subjects, toxicity may more readily become apparent through close monitoring of individual patients, while in larger studies risk may better be assessed through statistical comparisons of treatment groups.

For multisite phase I and II trials, study investigators should organize a central reporting entity that will be responsible for preparing timely summary reports of adverse events for distribution among sites and the IRBs. The frequency of the summary reports will depend on the nature of the trials. Additional NIH guidance for reporting adverse events for multisite clinical trials with a DSMB has been published in 1999. (See http://grants.nih.gov/grants/guide/notice-files/not99-107.html)

Grantee institutions with a large number of clinical trials may develop standard monitoring plans for phase I and II trials. Thus, individual study investigators will be able to include the IRB-approved monitoring plan in their submission to the NIH. However, such plans should always be evaluated for appropriateness to the particular investigation.