

FURTHER GUIDANCE ON A DATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS

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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.

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