NIDDK Data And Safety Monitoring Guidelines For Clinical Trials

Table of Contents:

Summary

This document summarizes the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) guidelines for data and safety monitoring (DSM) activities for all funded clinical trials. It is intended to assist investigators and institutions in the formulation of DSM plans for all phases of clinical trials submitted and funded by the NIDDK, in accordance with National Institutes of Health (NIH) requirements.

Generic DSM plans have been developed by the NIDDK for clinical studies requiring a Data and Safety Monitoring Board and those not requiring a DSMB. As a general rule of thumb, all studies funded by the NIH must have a DSM plan. Phase III clinical trials and clinical trials that involve high-risk populations and/or high-risk therapies require a DSM plan that includes a DSMB. Please read the following text and consult the appropriate NIDDK program director if you have questions about which DSM plan pertains to your study.

An additional level of protection for human subjects involved in clinical trials is a **Certificate of Confidentiality**. The Certificate of Confidentiality is a document issued to a researcher to afford special privacy protection to research subjects involved in research. A Certificate of Confidentiality can be used by the researcher to avoid involuntary disclosure (for example, subpoenas) of identifying information about research subjects. More information on this subject as well as the application process can be found on the NIDDK website under Certificates of Confidentiality.

Background

NIH policy (http://grants.nih.gov/grants/guide/notice-files/not98-084.html with additional description at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) requires that grantees have in place procedures for data and safety monitoring (DSM) activities for all funded clinical trials. This is to ensure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. The NIH DSM policy covers clinical trials of all phases for which grant support is sought. Applicants must submit a general description of the DSM plan for peer review as part of the grant application. The scientific review group will review this plan and any comments and concerns will be included in an administrative note in the summary statement. Prior to the issuance of a Notice of Grant Award, a more detailed plan must be submitted for review and approval by NIDDK staff.

Operational Definition of a Clinical Trial

For purposes of this document, a *clinical trial* is operationally defined as a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Observational or epidemiological studies that involve human subjects and that require informed consent are covered by this policy.

In the area of molecular or imaging *diagnostics*, a study is considered to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way the information from the diagnostic may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach, are not clinical trials and are not covered by this DSM policy, unless performing the diagnostic test itself imposes some risk on study subjects or requires informed consent by the study participants.

Behavioral clinical trials try to modify or improve behaviors associated with disease or disease risk. This may include behavior modification techniques, such as exercise programs or stress reduction training. It may also include behavioral intentions aimed at increasing physical activity in an effort to prevent disease morbidity or mortality.

Key Elements of a Data and Safety Monitoring Plan

NIDDK supported clinical trial monitoring activities should be commensurate with the nature, size, and complexity of the trial. The data and safety-monitoring plan may vary from a safety officer to a committee, also known as a Data And Safety Monitoring Board (DSMB). The DSMB will be appointed by either the NIDDK or the grantee institution with concurrence of the NIDDK. 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.

Individuals or groups monitoring data and safety of trials will review the research protocol with emphasis on data integrity and patient safety issues, including:

- ***Monitoring the progress of trials and the safety of participants.***
  Description of these monitoring processes should include a number of elements. Who actually monitors the trials? How often are the data examined in the course of trial conduct? What do the monitors look for? What procedures are in place to insure adequate feedback of information to researchers and medical decision-makers, so that trials involving excessive risk or exceptional benefits in relation to anticipated benefits are terminated appropriately? What is the oversight or supervisory role of institutional committees, if appropriate? What procedures does the institution have for coordinating multi-center trials, if applicable? Has the appropriate Investigational New Drug Application (IND) or Investigational Drug Exemption (IDE) been obtained prior to initiation of the study, if applicable?

  In relation to who actually has responsibility for monitoring a trial, DSM plans should explain how the institution averts or manages any conflict of interest implicit in having a Principal Investigator (PI) (or a direct report of the PI) as the only monitor of trials that pose significant risk to study subjects.

- ***Plans for assuring compliance with requirements regarding the reporting of adverse events (AE).***
  The plan should describe the processes and oversight that is in place for assuring that AE reporting requirements are actually met. For multi-center trials coordinated by the grantee Institution, the plan should outline procedures by which the Institution establishes a central reporting entity that collects and reports AE to all necessary destinations, including co-investigators at participating Institutions or other third party participants.

  The requirements for proper reporting of AE on clinical trials are complex. Possible destinations for AE reports include the NIDDK, the Institutional Review Board (IRB), the sponsor (if an industry sponsored investigational product is involved), the Food and Drug Administration (FDA), and, if gene transfer is involved, the NIH Office of Biotechnology Activities (OBA). Note that current federal regulations almost always require reporting of AE in all categories of clinical trials to the institutional IRB as well as to the FDA if the study is being done under an IND.

  Note also that there is no requirement that individual AE be reported in real-time to the NIDDK, unless the NIDDK is also the IND sponsor of the study or unless requested by the NIDDK. Where appropriate, investigators should summarize toxicities or adverse consequences of interventions as part of the progress reports in their non-competitive (Type 5), competitive (Type 2) renewal applications or as required by the NIDDK, the IRB or the DSMB.

- ***Plans for assuring that any action resulting in a temporary or permanent suspension of a NIDDK-funded clinical trial is reported to the NIDDK grant Program Official responsible for the grant.***
  These actions include, for example, any FDA actions that affect NIDDK-funded trials (***http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html***). It also includes actions by an IRB or by a commercial sponsor, or by the investigator or co-investigators, if an NIDDK-funded trial is involved.

- ***Plans for assuring data accuracy and protocol compliance.***
  Institutions should describe what quality-control procedures are in place for assuring data accuracy and completeness in studies funded by NIDDK.

  If an IND is in place, quality-control procedures are generally stipulated by the IND sponsor and may be simply referenced or summarized in the DSM plan. For studies not done under an IND, the grantee should describe whatever procedures are in place to assure data integrity and protocol adherence.

  Appropriate procedures may range, for example, from regular data verification and protocol compliance checks performed by a data manager and a PI , to a formal external data-audit process by an agent external to the institution.

Monitoring Plans by Study Phase (Examples)

The following provides examples of appropriate types of monitoring and oversight for different types of studies (http://grants.nih.gov/grants/guide/notice-files/not98-084.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). ***These are***

illustrative only. Monitoring activities should be appropriate to the study, population, research environment, and degree of risk involved. (See sections entitled, "Generic Monitoring Plan for Trials Not Requiring a Data and Safety Monitoring Board" and "Generic Monitoring Plan for Trials Requiring a Data and Safety Monitoring Board" for more detailed information.)

- **Phase I Study**
  A typical phase I trial of a new drug, agent or intervention 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. A study investigator may perform continuous monitoring of participant safety with frequent reporting to the Safety Officer and the NIDDK. The PI and the NIDDK Program Official should agree on the Safety Officer and the frequency and contents of the monitoring report. In rare instances that involve particularly high-risk interventions or high-risk populations (i.e. pediatric), the formation of a DSMB should be considered. The investigator and the NIDDK Program Official should agree on the appropriate monitoring plan prior to the initiation of the study.

- **Phase II Study**
  A typical phase II trial follows phase I studies and provides more information regarding risks, benefits, and monitoring procedures. However, more participants are involved and the toxicity or health risks and outcomes are confounded by disease process(es). Monitoring may be 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. However, a DSMB may be required especially if the study design supports masked data and the health risk is perceived to be high. The implementation of this approach should be part of the monitoring plan. The investigator and the NIDDK Program Official should agree on the appropriate monitoring plan prior to the initiation of the study.

- **Phase III Study**
  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 multiple clinical sites and 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. A DSMB, composed of experts relevant to the study area, is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The DSMB's function is to regularly assess the trial and offer recommendations to the NIDDK concerning its continuation.

Data and Safety Monitoring Board Activities

The DSMB will consist of individuals who are independent of the institution(s) and investigator(s) participating in the trial. DSMB members should have no financial ties to the outcome of the trial to avoid any conflicts of interest. The ongoing review of the data

by this independent committee assures the investigators that the trial can continue without jeopardizing patient safety.

Responsibilities of the DSMB

At periodic intervals during the course of the trial, as specified in the monitoring plan, the responsibilities of the DSMB are to:

- Review the research protocol, informed consent documents, and plans for data and safety monitoring;
- Evaluate the progress of the study(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site(s), and other factors that can affect study outcome;
- Consider factors external to the study when relevant information, such as scientific or therapeutic developments, may have an impact on the safety of the participants or the conduct of the trial;
- Report on the safety and scientific progress of the trial;
- Make recommendations to the PI, NIDDK, and, if required, to the FDA and IRB concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Conduct interim analysis of efficacy in accordance with stopping rules, which are clearly defined in advance of data analysis, if appropriate;
- Ensure data integrity;
- Ensure confidentiality of data and the results of monitoring; and
- Assist NIDDK by commenting on any problems with study conduct, enrollment, statistics, and/or data collection.

Membership and Appointment of the DSMB

In most instances the NIDDK appoints the DSMB. As a general rule, the NIDDK appoints the DSMB for:

- All Institute-initiated clinical trials;
- All investigator-initiated clinical trials supported by cooperative agreements; and
- Other investigator-initiated trial with direct costs exceeding $500,000 per year.

Typically, many of the studies noted above involve multiple clinical centers, are expensive and/or complex, have controversial aspects, involve invasive or risky procedures, and/or have the potential for a public health impact. The Institute will solicit recommendations from the investigator(s) for DSMB members; however, the membership of the DSMB will be the responsibility of the NIDDK. A NIDDK staff member serves as the Board's Executive Secretary (ES). For investigator-initiated clinical trials that do not meet the above criteria, appointment of members of the DSMB is the primary responsibility of the grantee institution with concurrence of the NIDDK Program Official and should be made independent of the PI. All DSMB recommendations are made to the NIDDK regardless of who appoints the DSMB.

The DSMB should consist of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Current collaborators or associates of the investigators involved in the study (i.e. same institution) are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required.

Disciplines represented on the DSMB should include experts in or representatives of the fields of:

- Relevant clinical expertise,
- Clinical trial methodology, and
- Biostatistics.

Additional DSMB membership consideration may be given to experts in medical ethics and a public ombudsman.

A Chairperson should be selected prior to the first meeting. The Chairperson is responsible for overseeing the meetings and developing the agenda in consultation with the NIDDK Program Official and the PI. The Chairperson is also the contact person for the DSMB. An NIDDK Program Official will serve as the DSMB Executive Secretary, as appropriate. Other NIDDK official(s) may serve as an ex-officio member(s) of the DSMB. The grantee institution shall provide the logistical management and support of the DSMB (e.g. coordinate the meeting and communications, pay for DSMB travel and stipend).

Board Process

The first meeting should take place face-to-face before initiation of the trial to discuss the protocol and to establish guidelines for monitoring. The Chair, PI, and ES (if appointed) should prepare the agenda to address the commencement of the trial, specifically stopping rules, interim analysis plan, etc.

Following the initial meeting, the DSMB should meet at designated intervals to review accumulated data on safety and, if appropriate, conduct an interim analysis. Meetings may either be convened as conference calls or in person, although it is recommended that the initial meeting and meetings to discuss interim analyses should be face-to-face. The Chairperson or the NIDDK Program Official may call an emergency meeting of the DSMB at any time should questions of patient safety arise.

An appropriate format for DSMB meetings consists of an open and a closed session. The open sessions may be attended by investigators, institution staff, and NIDDK staff, and should always include the principal investigator and the study statistician. Issues discussed at open sessions usually include conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

The closed session is normally attended only by voting DSMB members and the NIDDK ES. The DSMB may request appropriate NIDDK staff representative(s)

or others (e.g., study statistician) to attend portions of the closed session. All safety and efficacy data as well as any interim analyses must be presented at this session. Final recommendations regarding safety concerns and recommendations regarding continuation or termination of the study are discussed. Should the DSMB decide to issue a termination recommendation, full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended. The discussion at the closed session is completely confidential. A summary of the final recommendations is prepared by the DSMB ES with concurrence of the Chairperson for distribution to the PI, NIDDK, IRB, and FDA as appropriate.

Reports

***Interim Reports*:** Interim reports are generally prepared by the study statistician and distributed to the DSMB, preferably at least 5 days prior to a scheduled meeting. These interim reports should be numbered and provided in sealed envelopes within an express mailing package. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts.

> **Part One (Open Session Report)** provides information on study aspects such as accrual, baseline characteristics, and other general information on study status.
>
> **Part Two (Closed Session Report)** may contain data on study outcomes, including safety data and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential.

Copies distributed prior to and during a meeting are collected by the study statistician(s) following the meeting. Data files to be used for interim analyses should undergo established editing procedures to the extent possible according to procedures established by the PI in concurrence with the DSMB. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping are clearly defined.

***Reports from the DSMB*:** A formal report from the Chair or ES, approved by the DSMB, should be sent to the NIDDK who will distribute the summary findings to the PI and the sponsoring institution within six weeks of each meeting. It is the responsibility of the PI to assure that DSMB reports are sent to the co-investigators and to the IRBs of all study sites, and, if appropriate, the FDA.

Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. Such a recommendation should be transmitted to the PI, business official of the grantee institution, the NIDDK, and the FDA (if appropriate) as rapidly as possible, by immediate telephone and FAX if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the

regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, etc.

Mailings to the DSMB

On a scheduled basis (as agreed upon by the DSMB), blinded safety data should be communicated to all DSMB members or to the one member who serves as the designated Safety Officer. The NIDDK Program Official may also receive this data. Any concerns noted should be brought to the attention of the Chair or Safety Officer of the DSMB who will take appropriate action (e.g. call an emergency DSMB meeting).

Access to Interim Data

Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB relieves the investigators of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

Confidentiality

All materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.