

Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute

Summary

This document outlines the essential elements of an adequate plan for data and safety monitoring (DSM) of clinical trials. It is intended to assist investigators and institutions in the formulation of DSM plans for all phases of cancer clinical trials, in accordance with National Institutes of Health (NIH) requirements. We suggest that institutions sponsoring a significant number of clinical trials formulate institutional DSM plans that can be broadly applied to the individual trials in their portfolio. Investigators from institutions or organizations without institutional DSM policies may also find this document useful as a guide in fashioning suitable DSM plans for their individual trials.

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 DSM of clinical trials. This is to insure 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. DSM plans must be in place before grants supporting such studies can be funded. Applicants must submit a general description of the DSM plan for peer review as part of the grant application and, subsequently, a more detailed plan for review and approval by NCI staff prior to issuing a Notice of Grant Award.

Operational Definition of a Clinical Trial

For purposes of this document, we define a *clinical trial* operationally 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. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.

- In the area of molecular or imaging *diagnostics*, we consider a study 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.
- *Behavioral clinical trials* include interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not clinical trials.

Requirements for a DSMB

For some time now NCI policy has required that Data Safety Monitoring Boards (DSMB) be in place for *all* Phase III randomized clinical trials (<http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm>). The present document modifies this policy, in that there is no longer a blanket requirement for DSMB in the cases of low-risk behavioral and nutritional trials. As discussed further below, all such trials should include a DSM plan, but this may or may not include a DSMB, depending chiefly on the anticipated level of risk to participants.

Nor does NIH or NCI policy require that formal DSMB's be constituted for clinical trials other than Phase III, though investigators or institutions may wish to do so for certain non-Phase III trials involving particular risk, complexity, likely decisions about early stopping, or the need to obviate conflict of interest.

The Role of Institutional DSM Plans

Cancer clinical trials funded by the NCI are conducted in thousands of institutions nationwide. Many of these institutions – notably the comprehensive and clinical cancer centers – have particularly intensive clinical research portfolios that include dozens or hundreds of trials. It makes sense for such institutions to have in place *institutional* plans for an effective DSM process. An effectively formulated and executed institutional plan should improve both participant protection and trials conduct and should greatly reduce the need to set up new policies *ad hoc* on a trial-by-trial basis. For most investigator-initiated grant applications supporting clinical trials in an institution with an already approved institutional plan, the investigator should only have to supply the approved institutional plan in the human subjects section of the grant application and describe how it applies to the specific trials.

Tailoring Institutional DSM Plans to Specific Studies

The NCI clinical trials portfolio encompasses a vast array of investigation; examples range across early feasibility studies in treatment, prevention, or diagnosis; nutritional interventions to modulate risk of cancer; gene transfer; and behavioral research relating to cessation of tobacco use. Accordingly, the essential elements for DSM outlined below are described in general terms, and we do not stipulate details of how this process should be carried out. We have used general language to describe the essential content of such plans, leaving to individual institutions and investigators wide discretion in how to carry out these activities in an effective manner.

Clearly, a sensible DSM plan for a particular clinical trial must be based on the medical or health-related context of the particular study and, in particular, the degree of risk to which participants in the trial are exposed. In applying an institutional plan to a particular trial, therefore, the principal investigator will consider whether the institutional plan is sufficiently specific or whether it needs some further tailoring to the conditions of the particular trial. An institution might choose to have one general plan, which investigators tailor to individual trials. Alternatively, the institution might choose to have a plan that is essentially formulated in modules, each of which describes in adequate detail how monitoring will be accomplished for a major *class* of trials that the institution supports (e.g., early-phase studies in treatment, behavioral studies, bone-marrow transplantation, chemoprevention studies in healthy populations, etc.). Investigators can then apply these plans to particular protocols with little or no change in the description. For purposes of NCI review, as noted above, investigators may append the institutional plan to the human subjects section of their own grant applications and use these institutional documents in their interactions with NCI staff reviewing their plan. Under most circumstances NCI anticipates that a properly prepared institutional plan should suffice both for peer review and for NCI staff review.

Review of DSM Plans by NCI Staff

NCI staff review of institutional or individual DSM plans prior to grant award will focus on the adequacy with which the plan covers the essential elements outlined below. It is not necessary that submitted plans (whether they are institutional or individual) cover all possible aspects of each element down to the last detail. Rather, the plan should describe processes for dealing with these elements such that a reasonable reviewer would conclude that the institution or investigator has a serious, robust process in place for assuring the safety of research participants and the oversight of data integrity.

ESSENTIAL ELEMENTS

- 1. 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 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?

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 (or a direct report of the PI) as the only monitor of trials that pose significant risk to study subjects.

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

The requirements for proper reporting of AEs on clinical trials are complex (summarized in the Appendix). Possible destinations for AE reports include the institutional IRB, the sponsor (if an IND is involved), the FDA (for AEs from commercially available agents), and, if gene transfer is involved, the NIH Office of Biotechnology Activities (OBA). Note that current federal regulations almost always require reporting of AEs in all categories of clinical trials to the institutional IRB, in addition to what is specified in the Appendix.

Note also that there is *no* requirement that individual AEs be reported in real time to the NCI, unless NCI is also the IND sponsor of the study (see the Appendix). Where appropriate, investigators should summarize toxicities or adverse consequences of interventions as part of the progress reports in their non-competitive (Type 5) or competitive (Type 2) renewal applications.

- 3. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant.** These actions include, for example, any FDA actions that affect NCI-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 him/herself, if an NCI-funded trial is involved.
- 4. 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 NCI.

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 institution 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 principal investigator, to a formal external data-audit process by an agent external to the institution.

Special Circumstances

1. Behavioral and Nutritional Studies

For behavioral and nutritional Phase I-III trials, the NCI requires that a DSM plan be in place appropriate to the anticipated level of risk involved in the particular study. A DSMB can be constituted at the investigator's discretion and seems particularly appropriate when investigators anticipate the possibility of early stopping based on emerging differences in either risk or benefit.

2. Training Grants

Certain types of NCI career and training awards may support clinical trials, directly or indirectly. NCI's DSM policy covers those career and training awards in which the trainee has direct responsibility for conduct of the clinical trial or in which award funds directly support the trial. Responsibility for compliance with NCI's DSM policies rests with the grant recipient; this may be either the trainee or the training program director, depending on the award (individual versus institutional). Trainees in a mentored career program should consult with their mentors about adapting or designing suitable DSM plans for their clinical trials. In most cases the trainees will be in a mentored stage of their career and will lack the experience needed to provide appropriate oversight of the trial. The DSM plan must therefore clearly identify the senior individual responsible for monitoring the trial and the function of the trainee in this process.

- For institutional career development programs (e.g., K12, R25T) in which clinical trials are an integral part, applicants should provide with their application documentation that either (a) the sponsoring institution has an institutional DSM plan in place that covers all trials supported by the grant, or (b) the trials are covered by individualized DSM plans, included in the application submission, that apply to the trials directly.
- For individual career development awards in which the trainee has direct responsibility for trial conduct or in which award funds directly support the trial, the DSM plan covering the trial may be either institutional or individual at the discretion of the grant recipient.
- If the clinical trial is not to be started immediately upon award but will follow after a considerable lapse of time (years), submission of a DSM plan to NCI for approval may be delayed until the nature of the trial is clear and its initiation is in the near future. This will insure that the DSM plan, whether institutional or individual, suits the needs of the trial.

Appendix: Summary of Reporting Requirements for Adverse Events on NCI Trials Supported by Grant or Contract Funding

A. Trials for which NCI is also the IND sponsor (for details, see the NCI Investigator Handbook, available on-line at <http://ctep.info.nih.gov/handbook/handbook/HandBookIEPF.htm>)

TABLE A: Expedited Reporting for Phase I Studies (including hospitalization*)

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 2 - 3 Attribution of Possible, Probable or Definite	GRADES 4 - 5 Regardless of Attribution	GRADES 1 - 3	GRADES 4 - 5 Regardless of Attribution
<p>Grade 2 - Expedited report within 10 working days Grade 3 - Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</p> <p>(Grade 1 - Adverse Event Expedited Reporting NOT required.)</p>	<p>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>	<p>Adverse Event Expedited Reporting NOT required.</p>	<p>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>

TABLE B: Expedited Reporting for Phase II and II Studies (including hospitalization*)

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 2 - 3 Attribution of Possible, Probable or Definite	GRADES 4 - 5 Regardless of Attribution	GRADES 1 - 3	GRADES 4 - 5 Regardless of Attribution
<p>Expedited report within 10 working days</p> <p>(Grade 1 - Adverse Event Expedited Reporting NOT required.)</p>	<p>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>	<p>Adverse Event Expedited Reporting NOT required.</p>	<p>Expedited report, including Grade 5 Aplasia in leukemia patients, within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p> <p>Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.</p>

* **For Hospitalization Only** – Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for Phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later Phase II and Phase III protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is definitely related to the investigational agent is only to be reported if the patient is hospitalized using the generic reporting criteria, for instance. In a trial of an investigational agent where Grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

B. Trials of an investigational agent for which NCI is not the IND holder

The controlling regulations are those of the Food and Drug Administration (21 CFR, Part 312.32: Expedited Safety Reporting Requirements for Human Drug and Biological Products) and are available at <http://www.fda.gov/cder/aers/fr07oc97.htm>. They describe the responsibilities of the investigator and the IND holder. Additional sponsor or institutional requirements may be appropriate for specific agents and included in the pertinent protocol sections.

C. Trials involving commercially available agents only (no INDs involved)

Serious adverse events that occur with commercially available agents/devices are reported through Food and Drug Administration Medwatch (<http://www.fda.gov/medwatch/index.html>).

D. Trials involving recombinant DNA molecules (gene transfer)

In addition to the reporting requirements for investigational agents (see A or B above, as appropriate), investigators should adhere to NIH Guidelines for Research Involving Recombinant DNA Molecules (Gene Transfer) (<http://www4.od.nih.gov/oba/guidelines.html>).

E. Food and Drug Administration reporting requirements of serious adverse events for postmarketing trials of vaccines (no cancer vaccines yet in this category)

Serious adverse events must be reported according to applicable FDA regulations (<http://www.fda.gov/cber/vaers/vaers.htm>).

F. Trials involving behavioral or nutritional interventions that do not use an investigational agent

Since there are no standard grading scales for adverse events, defining suitable grades for adverse events is the responsibility of individual investigators for each protocol. Adverse events of a psychological nature can occur with behavioral trials and should be specified for the particular intervention in question.