Generic Data And Safety Monitoring Plan For Clinical Trials *Not Requiring* A Data And Safety Monitoring Board

Note to web designer: make each of these bolded items a link to the appropriate section in the document.

- ***Background***
- ***Decision tree***
- ***Glossary***
- ***Considerations in designing a DSM Plan***;
- ***Designing a Data and Safety Monitoring Plan***
- ***Statistical considerations***
- ***Stopping rules***
- ***Essential Elements*** (for a monitoring plan that can form a checklist):
- ***Data and Safety Monitoring Board link:***

http://www.niddk.nih.gov/patient/Clinical_Trials/PlnwthDSMB.pdf]

BACKGROUND

The National Institute of Nursing Research (NINR) has identified a need to assist grantees conducting clinical trials by providing generic data and safety monitoring plan information. Ongoing study monitoring of outcomes is recognized as the ethical responsibility of study investigators to their participants (Friedman *et al*, 1996; Meinert, 1986; Weiss, 1996). This information will focus on behavioral, biobehavioral, and biological clinical trials, usually phase I and II, that do not require a Data and Safety Monitoring **Board** (DSMB) but that DO require a Data Safety and Monitoring (DSM) **Plan**. All studies that involve more than minimal risk must have a DSM plan.

Phase III clinical trials require a DSMB. Currently, NINR refers applicants to the NIDDK link (see above) for information on DSM Boards. Many other NIH institutes, including NCI, NICHD, and NIAMS, also include DSMB guidance on their websites.

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.

Safety monitoring is carried out to ensure and maintain the scientific integrity of human subjects research and to protect the safety of human participants. Meinert (1986) defines safety monitoring as any process during a clinical trial that involves the review of accumulated outcome data for groups of patients to determine if any of the treatment procedures practiced should be altered or stopped. NIH Guidelines (1998) specify that all clinical trials should have in place a system for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data.

Monitoring activities should be commensurate with the nature, size, and complexity of the trial. For a small, single center study, a statistician in conjunction with a Safety

Monitor usually performs the monitoring. However, for single site, high-risk trials, a monitoring committee called a Data and Safety Monitoring Board (DSMB) may be in order. For larger, single or multi-center, clinical trials, monitoring is usually performed by a DSMB. Ongoing review of the data by an independent individual or committee assures the investigators that the trial can continue without jeopardizing patient safety.

Decision tree to determine the need for a DSM Plan or a DSM Board. (See Glossary below for definitions.)

1. Is the project an intervention study?
    a. Yes – Continue
    b. No – Stop here, unless vulnerable population warrants DSMP or there are invasive procedures
2. Is the study a phase III clinical trial?
    a. No—Continue
    b. Yes – Go to the following sites:
    http://grants.nih.gov/grants/guide/notice-files/not98-084.html
    http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
    and
    http://www.niddk.nih.gov/patient/patient.htm#policy for guidance. [make this a NINR link with NIDDK content?]
3. Is the study a phase I or phase II clinical trial?
    a. Yes – Continue. A DSM Plan is required and a DSMB may be advisable. The scope and elements of a DSM plan are determined by the degree of risk involved and the vulnerability of the population.

Grantee institutions with a large number of clinical trials may develop standard monitoring plans for Phase I and II trials. Thus, individual study investigators may adapt the IRB-approved monitoring plan in their submission to the NIH. However, such plans will always be evaluated for appropriateness to the particular investigation.
As studies progress through Phase II and III, a DSMB is required, as the intensity and frequency of safety monitoring increases, as the number of subjects and sites increase, dosing levels are tested, and subjects are randomized to interventions. The need to document the safety profile of likely adverse events, and to insure data integrity requires more frequent and more rigorous views of the data.

GLOSSARY

ADVERSE EVENT: The notification requirements described in the Common Rule (Federal regulations (45 CFR Part 46, Subpart A)) define adverse events as "unanticipated problems" involving risks to study participants or others. The reporting of adverse events is in addition to, and does not supplant, periodic reports to the IRB at intervals appropriate to the degree of risk in the study, generally, an annual report. Commonly abbreviated as AE.

***BEHAVIORAL CLINICAL TRIALS*:** include interventions whose goals are to increase behaviors (e.g. health promotion, physical activity, disease self-management), eliminate

or reduce behaviors (e.g., smoking, overeating) and/or improve coping and quality of life. Interventions may pertain to any of the science areas listed on the NINR website http://www.nih.gov/ninr/research/dea/function.html, in the Program Announcements or Requests for Applications (http://www.nih.gov/ninr/research/dea/PARFApage.html), or initiated by the investigator.

***CLINICAL RESEARCH**:* In June 2001, NIH adopted the definition of clinical research as consisting of three parts: (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; (2) Epidemiologic and behavioral studies; and (3) Outcomes research and health services research. **Observational, descriptive, methodological, and other studies that do not test interventions are not clinical trials.** http://www.nih.gov/news/crp/97report/execsum.htm.
http://grants1.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

***CLINICAL TRIAL*:** A clinical trial is operationally defined as a prospective behavioral or biomedical research study of human subjects that is designed to answer specific questions about behavioral or biomedical interventions (behavioral, drugs, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new behavioral or biomedical interventions are safe, efficacious and effective. Clinical trials of experimental behavioral, drug, treatment, or device may proceed through four phases. The following briefly describes the four phases of clinical trials (http://grants.nih.gov/grants/guide/notice-files/not98-084.html). Any examples are illustrative only.

Phase I Clinical Trial:
Phase I clinical trials are done to test a new behavioral or biomedical intervention in a small group of people (e.g. 20-80) for the first time to evaluate safety (e.g. determine a safe dosage range, and identify side effects).
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.

Phase II Clinical Trial:
Phase II clinical trials are done to study the behavioral or biomedical intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III Clinical Trial:
Phase III studies are done to study the efficacy of the behavioral or biomedical intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in

health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Phase IV Clinical Trial:
Phase IV studies are done after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

DOSE OR DOSING LEVEL: This refers to the intensity or level of an intervention whether pharmacological, behavioral, or biological.

INTERVENTION OR TREATMENT: These terms are used interchangeably in this document.

SAFETY MONITOR: An individual, external to the study, but who may be affiliated with the institution, who is responsible for reviewing the conduct of the study related to participant (or others) safety issues. The principal investigator may appoint the safety monitor, with attention to the non-affiliation requirement. The Safety Monitor develops or participates in the safety review procedures and:

- Monitors for safety in real time at weekly, biweekly or other appropriate intervals
- Maintains a record of all adverse events or concerns
- Reports events or concerns to the PI and other appropriate officials or agencies
- Insures that the problems or concerns are properly addressed
- Convenes safety committee meetings

See more details under *DESIGNING THE SAFETY MONITORING PLAN*

STATISTICIAN: This individual plays an integral role in data and safety monitoring. The role involves more leadership if the study is blinded. If the study is not blinded, then the PI and statistician work together to develop monitoring plans.

References for the definitions above and additional guidance may be viewed at:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html (phase I and II trials)
http://grants.nih.gov/grants/peer/hs_review_inst.pdf. (human subjects research for all phases of clinical trials)
http://grants.nih.gov/grants/peer/tree_glossary.pdf. (glossary of terms)

CONSIDERATIONS IN DESIGNING A SAFETY MONITORING PLAN

Data monitoring during an intervention study focuses on several areas:

• ***Performance*** - to assess sites' performance with respect to subject recruitment, retention and follow-up, participant risk, participant confidentiality, flow of data forms, protocol adherence and quality of data;

• ***Safety*** - to assess the magnitude of adverse events; and

• ***Treatment*** - to monitor and assess treatment (intervention) effects.

In single-site studies, ***performance monitoring*** should be an ongoing activity performed by the study investigator and statistician, and reviewed by the Safety Monitor.
The investigator and statistician also perform ongoing safety review of the data, and the Safety Monitor reviews safety reports at regularly scheduled intervals.
Treatment monitoring or interim analyses by the statistician is a formal process that is specified in the protocol or by the Safety Monitor. An interim analysis can result in early study termination if continuation will not produce benefit to patients or if the treatment or intervention outcome is known to have benefit. Meinert (1986) points out that ethical questions arise if studies continue beyond where the outcome is known and cites the Tuskegee Syphilis Study as an example. In this study, patients with syphilis were allowed to continue in the study for years even though it was known that the treatment under study, penicillin, was beneficial. ***Stopping rules***, developed and implemented early in a study, specify the conditions under which a study may be stopped.
NINR recognizes that setting up the procedures for study monitoring and for developing reports for the Safety Monitor can be a daunting task for investigators. The DSM **plan**, for all but phase III clinical trials, based on NIH policy and guidance, need not be a long or complex document. This Guide provides a general approach to developing monitoring plans and includes the following:

There is no simple formula for how often data should be reviewed or how frequently relevant parties should meet. These decisions are usually set out in the protocol by the study statistician and/or principal investigator and are reviewed by the Safety Monitor, who may develop a set of bylaws that govern these activities. **Basic considerations for safety monitoring plan components include: size and complexity of the study and appropriateness to the study, population, research environment, and degree of risk involved.** To assist the study team and the Safety Monitor in formulating the safety-monitoring plan, the following considerations should be reviewed.

Study Phase
For many Phase I and Phase II trials, an independent DSMB may not be necessary or appropriate when the intervention is low risk. Continuous, close monitoring by the study investigator in conjunction with a Safety Monitor may be an adequate and appropriate format for monitoring, with prompt reporting of adverse events to the Institutional Review Board (IRB), and/or the NIH awarding institute, and other appropriate federal agencies. **In studies of small numbers of subjects, adverse events 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.**

In situations involving potentially high risks or special populations, investigators must consider additional monitoring safeguards. For example, for studies involving children or other vulnerable populations, investigators may consider the use of a consent monitor to ensure that informed consent or assent is properly administered. In addition, those trials with high risk will require a DSMB.

Trial Design
The design of the trial is, in part, related to the study phase. As studies move from Phase I through Phases II and III, more subjects are required, and again, greater variability in both study implementation and subject population may occur. In addition, adverse events are more likely to emerge as more people are exposed to the intervention. In multi-site or multi-center clinical trials, there is a greater need to examine site-specific data collection and outcomes and inter-site differences.

Disease/Syndrome under Investigation
The nature of the disease being studied may influence the safety-monitoring plan. When the natural history of a disease is known, the investigators and the Safety Monitor are more likely to anticipate the nature and frequency of adverse events. In addition, a monitoring plan should consider the nature of the intervention. The level of scrutiny will depend on the severity of the disease and may require frequently scheduled safety reviews. The same approach may be needed if the disease is serious and/or life threatening and endpoints are anticipated to occur frequently and/or early in the study.

Study Population
The nature of the disease and the trial design will influence the size and characteristics of the subject population. Phase I and II studies have smaller subject populations and treatment studies for diseases are likely to include subjects of similar demographics and health status.
The diversity of a study population can be controlled, to some degree, by the inclusion/exclusion criteria which determine who is eligible to participate in a study. In some studies, eligibility criteria will increase the homogeneity of the patient population. Increased homogeneity may decrease the number of confounding variables that will be considered during analysis. However, stringent inclusion/exclusion criteria may also hinder subject recruitment and accrual to the study. It is therefore important to strike a balance between these two competing demands so that subjects can be recruited to a study in a timely and cost effective manner and that the study yields results that are of high quality and confirm the efficacy of the intervention. This consideration protects the subject's safety in that he/she is not committed to a study that is unduly extended over time or that shows no hope of successfully evaluating the intervention.

Study Intervention
The more that is known about the study intervention, the easier it is to plan for the monitoring of the study. As discussed, interventions that have been studied previously are more likely to have a known safety profile and the frequency and type of adverse events can be anticipated. However, the safety of a treatment is also related to the population being treated, the indication for its use, dosing level and frequency, the presence of co-morbid diseases, and the subject's time in the intervention portion of the study. All of these factors need to be considered in deciding on the frequency and intensity of safety monitoring as well as the types of reports, e.g., number of adverse events per subject.

Endpoints/Outcome Variables

Endpoints that are well defined and immediate are easier to monitor. Acute illnesses are more likely to have these types of outcomes. For example, an intervention with acutely ill subjects in any setting is likely to yield clear-cut results in a relatively short period of time. In contrast, outcomes from chronic illnesses such as diabetes and heart disease may require a longer intervention and follow-up period. Thus, the subject's time on study intervention and in the study from baseline through final follow-up will influence the type and frequency of safety monitoring.

DESIGNING THE SAFETY MONITORING PLAN

Once the study design and population are specified, the investigators can design, with the study statistician, the safety monitoring plans for the study. The monitoring plan should specify the responsibilities of the Safety Monitor, including frequency of data review, triggers for ad hoc reviews, and content and format of the safety reports. In addition, specific instructions as to whom each report will be sent, and what procedures, if any, the PI or recipient(s) should follow (e.g., the institutional Safety Officer will forward the report void of patient-specific information to NINR) to ensure that pertinent parties receive these documents.

A monitoring (or safety) 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 the size and complexity of the study and appropriate to the study, population, research environment, and degree of risk involved.

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.

The safety plan should specify a review of the rate of subject accrual, adherence to inclusion/exclusion criteria and other protocol requirements, and the expected retention rate of the subjects. Studies in which the study requirements are invasive, the intervention causes many adverse events, or the target population is very old, very young, or marginal (e.g., homeless, mentally ill, etc.) may have difficulty accruing and retaining subjects. Careful monitoring of the recruitment, enrollment and retention activities will help to protect the safety of study subjects, integrity of the study and the quality of the data.

If subject accrual is expected to occur quickly, then safety monitoring should take place early and may be tied to a percent of the total population to be accrued. For example, if 60 subjects are to be recruited in six months, safety review can take place after the first month of enrollment or after the first 10% of the subjects are enrolled, whichever comes first.

DSMP components in brief:

- Description of all individuals responsible for safety monitoring and reporting and their roles.
- Due consideration of and description of risks to participants.
- Policies and procedures for adverse event reporting (what, who, when, report recipients) and routine reporting.

See ***Essential Elements*** [**see below**] and ***Special Circumstances*** [**see below**] for more details.

Review Process
The monitoring plan should delineate the review process and the roles of the study coordinator, statistician, and the Safety Monitor in relation to the content, format, and process of the review. Typically, the coordinator produces administrative reports that describe study progress including accrual, demographics, and subjects' status. Reports also describe adherence to inclusion/exclusion criteria and the study protocol. These reports are reviewed internally for ongoing quality control and then presented to the Safety Monitor and NINR.

Safety Reports
Safety reports that list adverse events, serious adverse events, deaths, and disease or treatment specific events are required for Safety Monitor review in order to ensure good clinical care and identify any potential trends. The statistician may review data routinely and will alert NINR and the Safety Monitor if event rates are of statistical concern, occur in a disproportionate number in one of the treatment groups, or fall out of a pre-determined set of boundaries. The study statistician may distribute interim reports to the Safety Monitor between meetings to allow for special sessions when necessary. If individual participants are monitored, rather than statistical group analysis, the reporting process is the same as for statistical analysis results. ***The review plan should specify the process for reporting safety concerns among the IRB, the Safety Monitor, NINR and, if appropriate, other agencies.***

Typically, the Safety Monitor reviews the safety reports in aggregate fashion and by blinded treatment group. If there are a significant number of adverse events, the Safety Monitor may request that the treatment groups be unblinded to ensure that there are not untoward treatment effects. The review plan should specify how data are to be presented and triggers for presenting safety data in an unblinded manner.

Interim Analysis
The study coordinator also prepares the data for the study statistician to analyze in conformance with an interim analysis. The coordinator must have procedures in place for preparing the data for the analyses and for "freezing" the data set so that additional analyses may be performed or the analyses recreated, if necessary. The schedule for interim analyses can be a fixed time frame (e.g., every six months), after a certain number or percentage of subjects are enrolled (e.g., 25%, 50%, 75%, 100%), or in response to a specific number of occurrences of an event (e.g., *n* deaths or other critical events).

Independence of Review
The Safety Monitor should be separate and independent from the clinical staff or anyone responsible for patient care. The Safety Monitor should not have scientific, financial, or other conflict of interest related to the trial. Current collaborators or associates of the PI

(i.e., same institution) are not eligible. Clinicians should be blinded to the safety monitoring data, as exposure to emerging trends may influence enrollment and care, thus biasing the study.

Steps Emanating from Review

Statistical considerations, such as alpha spending and early stopping are discussed below in the section on statistical issues. The review may result in an amendment to the protocol, which must be approved by the IRB, NINR, Safety Monitor, and/or FDA. If the review causes changes to the data collection plan or study forms, then there should be a set of procedures for documenting and implementing these changes since the study data sets and analyses may also be affected. The monitoring plan should also specify what steps will be taken as a result of the review and should consider the impact of the review on the study.

STATISTICAL CONSIDERATIONS

Statistical issues arise with ongoing data monitoring such as the "multiple testing" problem, spending the study "alpha", and powering the study for "multiple looks." These issues and associated methods are addressed in the monitoring plan and are briefly discussed. References provide more robust discussion of these issues. "Multiple looks" at the data during interim analyses can reduce the power of a study. Thus, there is an inverse relationship between the number of interim analyses and the interim p-values for significance. Pocock (1977) recommends that the significance levels for all interim analyses be the same. For example, assuming five interim analyses, a significance level of 1.6% achieves an overall 5% significance. O'Brien and Fleming (1979) modify this rule so that the significance levels begin lower and end at the final analysis closer to the desired overall significance level. The adjustment of the analytic plan and significance level(s) for interim analysis is referred to as the 'alpha spending' function. The 'boundary conditions' described by the interim and final significance levels are symmetrically 2-sided if it is important to measure both the potential positive and negative effects of a treatment vis-à-vis the placebo.

STOPPING RULES

A 'stopping rule' specifies the outcome differences detected between groups during an interim analysis that can stop a clinical trial. The stopping rules reflect one of the following conditions:

- There is clear evidence of harm or harmful side effects of the treatment;
- There is no likelihood of demonstrating treatment benefit; or
- There is overwhelming evidence of the benefit of the treatment.

One of the benefits of stopping rules is that they can prevent over-reaction to random highs or lows in treatment response rates and adverse events since they generally require very low threshold p-values in interim analyses to indicate significance. However, stopping rules, also called 'discontinuation guidelines,' are not sufficient to justify stopping a trial for several reasons:

• ***New Information*** **-** There may be new information available such as the results of other trials, a change in the understanding of the underlying science or outside evidence of unacceptable adverse effects.

• ***Limits of Assumptions* -** Assumptions in the trial design regarding sample size and power, subject recruitment, the adverse event profile, and anticipated treatment affect differences may prove to be false when the trial is underway.
• ***Limits of Rules* -** Rules cannot be developed for all potential study scenarios and contingencies.
Stopping a trial early, even if justified, has consequences. The scientific purpose behind clinical trials is to calculate with some assurance the size of the differences between treatment outcomes. With less than a full complement of events recorded, the confidence intervals associated with estimates of treatment effects are larger. Another consequence of early stopping is to bias the estimates of treatment effect upward. This bias occurs because random high values in treatment effect may be used to justify early stopping, but rarely would random low values be so used.
Stopping rules should be defined in the statistical plan or early in a study and require realistic estimates of sample size to be effective. Optimistic subject accrual projections often mean that the trial is unable to show the test effect with the necessary assurance.
Stopping rules are no more reliable than the data on which they are based. Thus, the quality of the data must be ascertained for the interim analyses.
Before employing stopping rules, there are a host of issues that should be considered, according to Friedman (1996):
• ***Group Differences*** - Possible differences in baseline characteristics and prognostic factors between the two groups should be explored and necessary adjustments made in the analysis.
• ***Response Variables* -** Potential bias in the assessment of response variables must be considered, especially when the trial is not double-blinded.
• ***Missing Data* -** Possible impact of missing data should be evaluated. For example, could the conclusions be reversed if the experience of participants with missing data form one group were different from the experience with missing data from the other group?
• ***Protocol Compliance* -** Different participant protocol compliance should be evaluated for possible impact.
• ***Side Effects* -** Potential side effects and outcomes of secondary response variables should be considered in addition to the outcome of the primary response variable.
• ***Subgroup Consistency* -** Internal consistency across subgroups and various outcome measures should be examined.
Relevant statistical methods used in monitoring include classical or group sequential methods, flexible group sequential procedures, applications of group sequential boundaries, asymmetric boundaries, curtailed sampling procedures, and other approaches. These methods are discussed in numerous statistical methods books for clinical trials, a few of which are included in the bibliography.

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-site or 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 participants. Monitoring entities may include, but are not limited to:

- Principal Investigator
- Independent individual/Safety Monitor
- Designated medical monitor
- Internal Committee or Board with explicit guidelines
- DSMB (required for multi-site NIH-defined Phase III Clinical Trials)
- IRB (required)

2. **Plans for assuring compliance with requirements regarding the reporting of adverse events (AE).** 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-site or 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 AE to all necessary destinations, including co-investigators at participating institutions.

   The requirements for proper reporting of AE on clinical trials are complex (see **http://grants.nih.gov/grants/guide/notice-files/not99-107.html**). Note that current federal regulations almost always require reporting of AE in all categories of clinical trial to the institutional IRB, in addition to what is specified in NIH policy (***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).**
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   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 NINR-funded clinical trial is reported to the NINR grant Program Director responsible for the grant.** These actions include, for example, any FDA actions that affect NINR-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 NINR-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 NINR.

Special Circumstances

A. Behavioral Studies

For behavioral Phase I-III trials, the NINR 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.

B. Training Grants

Certain types of NINR career and training awards may support clinical trials, directly or indirectly. NINR'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 NINR'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 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 NINR 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.

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