Guide for Developing a Monitoring Plan for Studies Sponsored by NIAMS

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GUIDELINES FOR DEVELOPING A MONITORING PLAN FOR CLINICAL STUDIES SPONSORED BY NIAMS

INTRODUCTION

Since1998, NIH has required that all intervention studies have sufficient oversight and monitoring to assure participant safety and the validity of the study data (http://grants.nih.gov/grants/guide/notice-files/not98-084.html). The NIH Institutes/Centers are responsible for oversight of the monitoring of the clinical studies they sponsor. "Further Guidance on [a] Data and Safety Monitoring for Phase I and Phase II Trials" was issued on June 5, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). The guidance includes the following points:

- ***Application -*** As *part of a research application for a Phase I or II clinical trial, Investigators must submit a plan for data and safety monitoring.*
- ***Review -*** *The Scientific Review Group will review the plan and provide comments, as necessary, as an administrative note in the summary statement.*
- ***Monitoring Plan –*** *A Monitoring Plan must be included as part of the protocol and submitted to the Institutional Review Board (IRB) for review. The Monitoring Plan will also be submitted to the Institute/Center (IC) for review and approval before the study commences*.

The study risks, whether from the intervention, tests, or study population, determine the type of monitoring required. The NIH 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. Small, single site studies with low risk interventions and populations are typically monitored by an independent Safety Officer. However, Phase I and II clinical trials with multiple clinical sites, masked design, high-risk intervention or vulnerable population require a Data and Safety Monitoring Board (DSMB).

Observational studies with large (i.e. greater than 1000 participants) or vulnerable populations, or with risks associated with tests and/or standard of care are likely to require monitoring oversight either through the Observational Study Monitoring Board (OSMB) or Safety Officer[1].

A study's Principal Investigator and staff are responsible for the safety of study participants and the data credibility and validity. However, ongoing, independent review of the data and the study helps to assure the Institute that a trial can continue without jeopardizing patient safety.

NIAMS recognizes that setting up the procedures, reports, and descriptive tables for study monitoring can be a daunting task for Investigators. This Guide provides a general approach to developing monitoring plans and incorporates the following:

- ***A list of issues*** to consider when developing a study Safety Monitoring Plan that can form a checklist;
- A discussion of ***statistical issues and stopping rules*** along with examples and references;

[1] *Note: henceforth, reference to a DSMB may also include an Observational Study Monitoring Board (OSMB).*

- ***An outline of a Safety Monitoring Report*** along with sample data presentations, their rationale and general data elements to be included. Template reports can be located at http://niams.nih.gov/Funding/Clinical_Research/NIAMS_sample_documents.asp.

CONSIDERATIONS IN DESIGNING A SAFETY MONITORING PLAN

The goals of clinical study monitoring are to ensure the safety of study participants, data integrity and validity of the study results. Study data and safety monitoring focuses on several areas:

- *Safety* - to assess the mechanisms used to protect the safety and privacy of the study participants as well as the magnitude of adverse events;
- *Performance* - to assess sites' performance with respect to participant recruitment, retention and follow-up, Case Report Form (CRF) tracking, protocol adherence and quality of data;
- *Intervention Effects* – to assess whether the study should continue based on safety and efficacy data (if applicable).

The Principal Investigator and study team should consider the protocol, phase, intervention, target population and risk when formulating the Safety Monitoring Plan. These items are each discussed in the following section.

Protocol

A good monitoring plan begins with a comprehensive, well-written protocol (Dixon et al, 2006). Elements of a well-written protocol include the following:

- ***Study Design –*** The study design must be feasible to answer the research question using the study hypotheses and should be doable in the "real world."
- ***Eligibility Criteria –*** The inclusion and exclusion criteria must be clearly defined, rigorous enough to allow accrual of a defined population, and yet not so restrictive as to deter enrollment. Issues such as severity of disease, concomitant medications, language comprehension, ability to comply with the study regimen and confounding factors should be considered when formulating inclusion and exclusion criteria.
- ***Assessments and Timeline --*** Study assessments and clinical labs must have collection times and visits specified to facilitate safety review and identify potential issues in a timely manner.
- ***Statistical Plan --*** The protocol should justify sample size, describe and define the study endpoints, analytic procedures, and any plans for interim analyses.
- ***Treatment Modification or Discontinuation –*** For dose escalating studies, procedures for modifying or discontinuing treatment must be specified.
- ***Study Termination –*** Procedures for reviewing enrollment, safety events, and outcomes must be specified to allow for early stopping or suspension of the study.
- ***Ongoing Adverse Event Review -*** Procedures must be specified for identification and reporting to all appropriate organizations and staff of adverse events.
- ***Data Management –*** Procedures for data capture, cleaning, summarization, and quality assurance should be specified.

Study Phase

DSMBs are required for Phase III studies and multi-center Phase I and II studies. Additionally, Phase I or II studies with high risk interventions, vulnerable populations, complex design, or large number of participants may warrant a DSMB. For example, stem cell studies or studies with children will require a DSMB.

Single site Phase I and II clinical trials with low risk and small numbers of participants may be monitored by a Safety Officer, rather than a DSMB, who is independent of the study staff. Final approval of the monitoring plan and level of oversight will be made by NIAMS.

Study Type

A large number of study participants and sites may warrant more intense and frequent safety monitoring procedures. Increased exposure to an intervention will require ongoing assessments of the study's safety profile.

Typically, dosing studies accrue small numbers of study participants, and drug toxicity is assessed through review of individual participant data, as well as in aggregate. Larger studies utilize statistical comparisons among treatment groups.

Clinical studies with no intervention may still warrant monitoring if the study has a large or vulnerable population, or there are risks associated with the tests and/or standard of care. If monitoring for an observational study is determined necessary, NIAMS will appoint an OSMB or Safety Officer.

Study Population

Accrual and retention difficulties may arise in studies utilizing interventions or assessments with greater than minimal risk. Additionally, some populations (i.e., elderly or pediatric) may have trouble understanding an informed consent form, and others may encounter difficulty accruing and retaining participants (i.e., such as the very ill). Thus, careful monitoring of the recruitment, enrollment and retention activities will help to protect the safety of participants, integrity of the study and the quality of the data.

Patients with an acute illness are more likely to reach an endpoint in a short period of time. In contrast, chronic diseases may require a longer treatment intervention and follow-up period. Thus, the length of treatment and follow-up as well as the study enrollment period will influence the type and frequency of safety monitoring.

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

The Safety Monitoring Plan should specify a schedule for review of the rate of screening, enrollment, completion, withdrawal and early termination by site; adherence to inclusion and exclusion criteria and other protocol requirements; treatment compliance and Adverse Events.

Study Intervention

The more that is known about the intervention, the easier it is to develop the Safety Monitoring Plan. Interventions that have been studied previously by other Investigators are more likely to have a known safety profile, which can help predict the frequency and type of adverse events for new studies.

However, the safety of an intervention is also related to the population under study, the indication for its use, dosing level and frequency, the presence of comorbid diseases, and the time on an intervention. New treatments are generally considered to have more risk, since there is less information available, than treatments approved for another indication. These are other factors which influence the frequency and intensity of safety monitoring.

Regulatory Considerations

Studies that require an Investigational New Drug (IND) submission to the Food and Drug Administration (FDA) are subject to compliance with FDA regulations. IND submissions are generally required when an approved drug is being tested for a new indication. Additional information on IND submissions can be found at the following location:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

DESIGNING THE SAFETY MONITORING PLAN

Once the target population and study design are specified, the clinical Investigators and study statistician can design the Safety Monitoring Plan. The Safety Monitoring Plan should specify the following:

- Type of monitoring body (e.g. DSMB, OSMB or Safety Officer)
- Responsibilities of study staff and monitoring body
- Procedures for data review and reporting for adverse events
- Contents and format of the safety reports

Monitoring Body

The type of monitoring body, as discussed above, depends on the type of study, its complexity, intervention, and study population. The monitoring body must be separate and independent from the clinical staff or anyone responsible for patient care. The monitoring body should not have scientific, financial, or other conflict of interest related to the trial. Current or past collaborators or associates of the Principal Investigator should not be a part of the monitoring body.

Responsibilities

The Safety Monitoring Plan should specify the roles of the study staff and study statistician with respect to safety monitoring. The roles and responsibilities of a DSMB and Safety Officer are described in the NIAMS “Data and Safety Monitoring Guidelines” located at:
http://niams.cit.nih.gov/Funding/Clinical_Research/data_safety_monitoring_guidelines.doc

Typically, the Principal Investigator provides a study summary and identifies any problems or issues. The study staff produces administrative reports that describe study progress to date, summarizing participant status (numbers screened, enrolled, completed, withdrawn, and discontinued treatment). In addition, CRF tracking, data quality, and protocol deviations are noted. These reports are reviewed internally for ongoing quality control and included in the report to the monitoring body through the Executive Secretary. Report templates can be located at
http://niams.nih.gov/Funding/Clinical_Research/NIAMS_sample_documents.asp (Please note: report templates must be customized to each study, and additional or fewer reports may be appropriate.)

The Principal Investigator is responsible for reporting serious adverse events to their IRB, NIAMS and the monitoring body (through the Executive Secretary), and FDA as required.

The study statistician prepares reports that list adverse events, serious adverse events, deaths, and disease or treatment specific events required for monitoring body review in order to ensure good clinical care and identify any emerging trends. A schedule for proposed reports to be submitted to the monitoring body is specified in the monitoring plan.

The statistician should review the data routinely and should alert NIAMS and the monitoring body (through the Executive Secretary) if event rates are of statistical concern, occur in a disproportionate number in one of the treatment groups, or fall out of a predetermined set of boundaries. The study statistician may distribute interim reports to the monitoring body between meetings to allow for special sessions when necessary.

Procedures for Data Review and Reporting

The Safety Monitoring Plan should specify the process for data and safety review. Procedures should be described for the following:

- Frequency of reports and reporting of concerns to the IRB, monitoring body and NIAMS through the Executive Secretary and, if appropriate, the FDA.
- Routine review of adverse events to the monitoring body, NIAMS, etc.
- Specific triggers for ad hoc review (e.g., deaths, threshold for serious adverse events) as well as the process for ad hoc review.
- Interim analysis, as necessary, along with its schedule (i.e., after half of the patients are enrolled).
- "Stopping rules", as necessary, especially with high risk interventions or populations. The stopping rules should be defined in the statistical plan.

OUTLINE OF TYPICAL SAFETY MONITORING REPORT

The following provides an outline for a typical Safety Monitoring Report that is prepared by the study statistician or data management staff:

- Brief narrative introduction that describes the status of the study, progress or findings to-date, issues, and the procedures that produced the report (e.g., data obtained by a specific date).
- Brief study description along with current organization chart and updated study timeline.
- Administrative tables that describe study status, including participant status (i.e., screened, enrolled, completed, lost-to-follow-up, etc.), expected versus actual enrollment, CRF tracking, quality of the data
- Data tables that summarize demographic and baseline clinical characteristics
- Aggregate tables of adverse events and serious adverse events
- Aggregate tables of clinical laboratory values
- Listings of serious adverse events

The specifics of the study will guide requirements for additional tables and listings. Multicenter studies will have the tables presented by site as well as in aggregate.

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