

**Guide for Developing a Data and Safety Monitoring Plan for Clinical Studies  
Funded by the National Institute of Arthritis and Musculoskeletal and Skin  
Diseases (NIAMS)**

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# GUIDE FOR DEVELOPING A DATA AND SAFETY MONITORING PLAN FOR CLINICAL STUDIES FUNDED BY THE NIAMS

## INTRODUCTION

Since 1998, the National Institutes of Health (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 policy states that data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); and efficacy, effectiveness and comparative trials (phase III); The NIH Institutes/Centers are responsible for oversight and 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, but is not limited to, the following points:

- **Application** - *As part of a research application for clinical trials, 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 risks to participant safety, whether from the study intervention, tests, or population involved in the research, 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 phase 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 involve vulnerable populations. Small, single site studies with low risk interventions and populations are typically monitored by a single individual, usually a Physician, referred to as an independent Safety Officer. However, Phase I or II clinical trials with certain characteristics such as multiple clinical sites, masked design, high-risk intervention or a vulnerable population require a Data and Safety Monitoring Board (DSMB).

Observational studies with large (e.g., 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 an Observational Study Monitoring Board (OSMB) or Safety Officer.<sup>1</sup>

Most clinical trials supported by the NIAMS must have a Safety Officer or a Data and Safety Monitoring Board (DSMB) that is independent of the study and advisory to the NIAMS. The type of independent safety monitoring is guided by the risk, size and/or complexity of the study. Applicants must submit a data and safety monitoring plan as part of the research application-based risk evaluation, NIAMS guidance documents and NIH policy. Applicants may consult with the NIAMS during the pre-submission phase to discuss monitoring needs, but the final data and safety monitoring determination will be made by the NIAMS at the award phase. Small, single-site studies usually have a Safety Officer, while multi-site studies typically require a DSMB. However, if a small, single-site study is determined to be high risk (e.g., a gene therapy trial of six participants), a DSMB may be required. In addition, the NIAMS may require an Observational Study Monitoring Board (OSMB) for a large, multi-site, observational study that entails risk or burden to participants.

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<sup>1</sup> Note: henceforth, reference to a DSMB may also include an Observational Study Monitoring Board (OSMB).

Safety monitoring activities performed by an independent monitoring body appointed by the NIAMS include reviewing the protocol with emphasis on data integrity and participant risk and safety issues, monitoring adverse events, ensuring practices are in place to safeguard the confidentiality of the data and results, and making recommendations to the NIAMS and Principal Investigator to continue, modify or conclude the study. Since the independent monitoring body is advisory to the NIAMS, the NIAMS must provide final approval of the study materials and initiation of recruitment, participant treatment, or any clinical procedures. The NIAMS reserves the right to accept or reject the recommendations made by the monitoring body.

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;
- **A discussion of statistical issues and stopping rules** along with examples and references;
- **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\\_guidelines.asp](http://niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.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 analysis plan should justify sample size, describe and define the study endpoints, analytic procedures, and any plans for interim analyses.
- **Treatment Modification or Discontinuation** – Procedures for modifying or discontinuing treatment must be pre-specified (e.g., for studies with adaptive designs, dose escalation, or those that may require a modification of concomitant medications due to exacerbation of symptoms or insufficient therapeutic effect).
- **Study Termination** – Procedures for reviewing enrollment, safety events, and outcomes must be specified to allow for early stopping or suspension of the study. These are generally referred to as Stopping Rules.
- **Ongoing Adverse Event Review** - Procedures must be specified for identification and reporting of adverse events to all appropriate study staff and organizations (i.e. the NIAMS, independent DSMB or Safety Officer, IRB, the FDA, etc.) .
- **Data Management** – Procedures for data capture, cleaning, summarization, and quality assurance should be specified.

## Study Phase

DSMBs are required for all NIH-supported, Phase III clinical trials. Additionally, Phase I or II studies with high risk interventions, multiple clinical sites, 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. The NIAMS will make the final determination for the level of oversight required for its clinical trials.

Single site Phase I and II clinical trials with low risk and small numbers of participants may be monitored by an independent Safety Officer, rather than a DSMB. The NIAMS will make the final determination for the level of oversight required for its clinical trials.

## 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 (such as the very ill or those with rare diseases) may be difficult to accrue and retain. 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 10 percent of the participants are enrolled, whichever comes first. Dose escalation studies may require review of safety data at specified intervals and/or before escalation can occur.

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 and/or are marketed are more likely to have a known safety profile, which can help predict the frequency and type of adverse events for new studies. The Investigator Brochure or Device Manual should be developed to capture what is known about the intervention. It can be updated as new information arises.

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 duration of an intervention. New treatments which are unapproved are generally considered to have more risk, since there is less information available, than treatments already approved for another indication or population. 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 or population. Additional information on IND submissions can be found at the following location:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=312>

## DESIGNING THE SAFETY MONITORING PLAN

Once the target population, intervention 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 (unblinded, as appropriate) 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://www.niams.nih.gov/Funding/Clinical\\_Research/NIAMS\\_guidelines.asp#2](http://www.niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.asp#2)

Typically, the Principal Investigator provides a study summary and identifies any problems or issues with study conduct. The study staff produces administrative reports that describe study progress to date, summarizing participant status (numbers screened, enrolled, randomized, 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\\_guidelines.asp](http://niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.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 his or her 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 (e.g. biannually).

## 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 (e.g., after half of the patients are enrolled).
- Process for unblinding when it is clinically indicated. This process should be delineated in the study Manual of Operations and Procedures (MOOP).
- “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. In addition, the NIAMS has created report templates for multi-site and single-site clinical trials that Investigators can use to guide them in their reporting process. Please refer to report templates posted here

[http://www.niams.nih.gov/Funding/Clinical\\_Research/NIAMS\\_guidelines.asp#2](http://www.niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.asp#2)

- 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 (e.g., 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 and the requests of the independent monitoring body will guide requirements for additional tables and listings. Multi-site studies will have the tables presented by site as well as in aggregate.

## BIBLIOGRAPHY

- Baigent C, Harrell FE, Buyse M, Emberson JR, Altman DG. Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clin Trials*. 2008;5(1):49-55.
- Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, Heels-Ansdell D, Walter SD, Guyatt GH; STOPIT-2 Study Group. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA*. 2010 Mar 24;303(12):1180-7.
- Cassell, EJ. Consent or Obedience? Power and Authority in Medicine, *NEJM*. 2005 Jan27;352:4328-330.
- DAMOCLES Study Group, NHS Health Technology Assessment Programme. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*. 2005 Feb 19-25;365(9460):711-22.
- Demets DL. Futility approaches to interim monitoring by data monitoring committees. *Clin Trials*. 2006;3(6):522-9.
- DeMets D, Califf R, Dixon D, Ellenberg S, Fleming T, Held P, Julian D, Kaplan R, Levine R, Neaton J, Packer M, Pocock S, Rockhold F, Seto B, Siegel J, Snapinn S, Stump D, Temple R, Whitley R. Issues in regulatory guidelines for data monitoring committees. *Clin Trials*. 2004;1(2):162-9.
- DeMets DL, Fleming TR. The independent statistician for data monitoring committees. *Stat Med*. 2004 May 30;23(10):1513-7.
- DeMets DL, Fleming TR, Rockhold F, Massie B, Merchant T, Meisel A, Mishkin B, Wittes J, Stump D, Califf R. Liability issues for data monitoring committee members. *Clin Trials*. 2004;1(6):525-31.
- DeMets DL, Califf RM. Lessons Learned from Recent Cardiovascular Clinical Trials: Part I. *Circulation*. 2002;106:746-751.
- DeMets DL and Califf RM. Lessons Learned from Recent Cardiovascular Clinical Trials: Part II. *Circulation*. 2002;106:880-886.
- Fontanarosa PB. Reporting Conflicts of Interest, Financial Aspects of Research, and Role of Sponsors in Funded Studies, *JAMA*. 2005 Jul 6;294(1):110-111.
- Hibberd PL and Weiner DL. Monitoring Participant Safety in Phase I and II Interventional Trials: Options and Controversies. *Journal of Investigative Medicine*. 2004 Nov;52(7):446-452.
- Knottnerus JA, Spigt MG. When should an interim analysis be unblinded to the data monitoring committee? *J Clin Epidemiol*. 2010 Apr;63(4):350-2. Epub 2009 Sep 17.
- Meinert CL. *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York: 1986.
- National Institutes of Health NIH Policy for Data Safety Monitoring [Online]. Available at <http://www.nih.gov/grants/guide/notice-files/not98-084.html> 1998Jun10.
- Nebeker JR, Barach P, and Samore MH. Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting. *Ann Intern Med*. 2004;140:7905-801.
- O'Brien PC; Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-556.

Otte A, Maier-Lenz H, Dierckx RA. Good clinical practice: historical background and key aspects. *Nucl Med Commun*. 2005 Jul;26(7):563-74.

Ottevanger PB, Therasse P, van de Velde C, Bernier J, van Krieken H, Grol R, De Mulder P. Quality assurance in clinical trials. *Crit Rev Oncol Hematol*. 2003 Sep;47(3):213-35.

Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 1977;64:191-199.

Rosa C, Campbell A, Kleppinger C, Sampson R, Tyson C, Mamay-Gentilin S. Quality assurance of research protocols conducted in the community: the National Institute on Drug Abuse Clinical Trials Network experience. *Clin Trials*. 2009 Apr;6(2):151-61.

Rosen DH, Johnson S, Kebaabetswe P, Thigpen M, Smith DK. Process maps in clinical trial quality assurance. *Clin Trials*. 2009 Aug;6(4):373-7. Epub 2009 Jul 22.

Sather MR, Raisch DW, Haakenson CM, Buckelew JM, Feussner JR; Department of Veterans Affairs Cooperative Studies Program. Promoting good clinical practices in the conduct of clinical trials: experiences in the Department of Veterans Affairs Cooperative Studies Program. *Control Clin Trials*. 2003 Oct;24(5):570-84.

Shaughnessy M, Beidler SM, Gibbs K, Michael K. Confidentiality challenges and good clinical practices in human subjects research: striking a balance. *Top Stroke Rehabil*. 2007 Mar-Apr;14(2):1-4.

Sydes MR, Altman DG, Babiker AB, Parmar MK, Spiegelhalter DJ; DAMOCLES Group. Reported use of data monitoring committees in the main published reports of randomized controlled trials: a cross-sectional study. *Clin Trials*. 2004 Feb;1(1):48-59.

Sydes MR, Spiegelhalter DJ, Altman DG, Babiker AB, Parmar MK; DAMOCLES Group. Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. *Clin Trials*. 2004 Feb;1(1):60-79.

Williams GW. The other side of clinical trial monitoring; assuring data quality and procedural adherence. *Clin Trials*. 2006;3(6):530-7.