Protocol Data and Safety Monitoring

(From CTN Policies and Procedures Guide, V1.3, Rev May 13 08)

I. Data and Safety Monitoring Plan

All CTN studies must include a Data and Safety Monitoring Plan (DSMP) as a distinct, separate document, which will be reviewed by the study Data and Safety Monitoring Board (DSMB) and approved by NIDA prior to trial implementation. (Appendix II) The purpose of the DSMP is to ensure the safety of participants, as well as the integrity of the data for the trial; and to provide the DSMB with a plan regarding the information they will receive for review. It is the responsibility of the study team to prepare the DSMP in close collaboration with the CCC and the DSC. The DSMP should address three areas:

1. Safety Monitoring—The goals of safety monitoring in trials are to ensure the safety of participants and to assess the risks of the study intervention. The Data and Safety Monitoring Plan should address two general areas:
    a. Protection of subjects (including administrative aspects of trial conduct directly relevant to subject safety and well-being), and
    b. Monitoring of adverse events that occur during the trial.

2. Trial Performance Monitoring—This component of the DSMP seeks to identify the aspects of trial implementation that are key to the successful execution of the study, and the preservation of the scientific rigor expected in a randomized clinical trial. The study team will consider the most likely threats to the trial's internal validity posed by potential problems in trial execution.

3. Efficacy Monitoring—The DSMP should include the procedures and methodological approaches for any planned interim analysis or analyses (efficacy monitoring). A formal interim analysis provides statistical guidelines for terminating the trial because of definitive evidence for benefit, harm, or futility. This section must include:
    a. rationale for conducting or not conducting an interim analysis, including statistical methods to be used
    b. proposed methodology to limit the Type I error rate to not more than 5%
    c. considerations for futility analysis

Appendix II Data and Safety Plan Guidance

Introduction

It is the responsibility of the study team to prepare the Data and Safety Monitoring Plan (DSMP) in close collaboration with the CTN Coordinating Centers. This guidance is specific to the CTN and is provided to assist our grantees with developing their protocol DSMP, in accordance with NIH requirements.

NIH policy on Data and Safety Monitoring requires that all NIH-supported clinical trials have appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data. http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The procedures outlined herein are in addition to (and not in lieu of) Institutional Review Board (IRB), Office for Human Research Protections (OHRP) and Food and Drug Administration (FDA) requirements, and any additional applicable state laws and National Institutes of Health (NIH) guidelines.

Background

All clinical trials supported or conducted by the federal government must adhere to the Federal Policy for the Protection of Human Subjects found in the Code of Federal Regulations (45 CFR 46). This policy requires that the research plan make adequate provision, when appropriate, for monitoring the data collected to ensure the safety of subjects. The research plan must include written procedures and policies for reporting "unanticipated problems" involving risks to participants. http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

Clinical trials regulated by the Food and Drug Administration (FDA) must adhere to additional requirements found in Title 21 of the Code of Federal Regulations, which contains a number of provisions concerning safety monitoring.

Data and safety monitoring of a clinical trial should be commensurate with risks; the method and degree of monitoring needed is related to the degree of risk involved. Monitoring of a given trial should be commensurate with the size and complexity of the trial. Monitoring may be conducted in various ways, 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. Monitoring must be performed on a regular basis, and conclusions of the monitoring reported to the NIH Institute/Center (IC).

Oversight of monitoring activities is distinct from the monitoring itself. Oversight of monitoring must be done to ensure that Data and Safety Monitoring Plans (DSM Plan) are in place for all interventional trials; that the quality of these monitoring activities is appropriate to the trial(s), and that the sponsor has been informed of recommendations that emanate from monitoring activities.
The NIH requires the establishment of data and safety monitoring boards for multi-site clinical trials involving interventions that entail potential risk to the participants. Further guidance

provided in October 2000 states that 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.
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

In accordance with NIH requirements, the CCTN has established Data and Safety Monitoring Boards [DSMB(s)] to provide independent oversight of trials conducted within the CTN. The DSMB(s) are appointed by NIDA CCTN Director, usually specific to a study. The DSMB monitoring function is in addition to the oversight traditionally provided by Investigational Review Boards (IRBs). A DSM Plan must be developed for each protocol, and will focus the DSMB monitoring and oversight function. The DSMB will review the DSM Plan prior to NIDA approval of the study. The DSMB can make recommendations regarding appropriate changes to the protocol and DSM Plan.

ESSENTIAL ELEMENTS OF A DATA AND SAFETY MONITORING PLAN

A DSMP for a clinical trial must be based on the medical or health-related context of the particular study and the degree of risk to which participants in the trial are exposed. The overall elements of the DSMP may vary depending on the potential risks, complexity, and nature of the trial. In situations involving potentially high risks or vulnerable populations, the study team must consider additional monitoring safeguards. Submitted plans should not cover all possible aspects of each element down to the last detail, the details should be provided in other study specific documents. Rather, plans should describe processes for dealing with these elements such that a reasonable reviewer would conclude that the study team has a robust process in place for assuring the safety of research participants, and oversight of study validity and data integrity. The DSMP should address three areas: (1) safety monitoring for human subject protection, (2) trial performance monitoring to assure that the results yielded by the trial will be scientifically valid, and (3) monitoring to assess the efficacy of the intervention during the course of the trial.

SAFETY MONITORING

The goals of safety monitoring in trials are to ensure the safety of participants and to assess the risks of the study intervention. Study teams will need to develop safety monitoring plans commensurate with the potential risks of the intervention, specific to the population being studied, the indication for the intervention's use, dosing level, and frequency, and the presence of co-occurring conditions.
The safety monitoring plan should address two general areas: the protection of subjects (including administrative aspects of trial conduct directly relevant to subject safety and well-being), and the monitoring of adverse events that occur during the trial.

I. Subject Protection

The description of the trial's safety monitoring processes should include a number of elements, including:

- Identification of the study medical monitor (or clinical monitor)
- Identification of specific safety assessments to be performed, the timing and frequency of such assessments, and the qualifications required to perform the assessments.
- Identification of procedures to ensure that:

- Only subjects of appropriate medical risk (per inclusion/exclusion criteria) are enrolled in the study and can continue in the study. For example, if suicidal ideation is a risk, then the protocol should include provisions for identifying this risk at screening and throughout the study, and procedures to assure that the subject will receive appropriate attention and medical care to minimize and alleviate the risk.
- Acute medical conditions, if not excluded, are adequately treated or cleared for study participation and that subjects temporarily absent from the study for medical reasons are medically cleared to return to the study in accordance with protocol specifications
- Subjects requiring discontinuation are appropriately withdrawn from the study for medical reasons. Criteria for withdrawal for medical reasons should be specified a priori
- Any medical/mental health condition/complication occurring during the course of the trial will be appropriately handled, e.g., suicidal ideation, other signs of clinical deterioration, adverse events

Any clinical conditions (or adverse events) that are known to be associated with the intervention or the patient population should be identified in the protocol. For example, study teams should consider additional procedures necessary to monitor for:

- Possible laboratory abnormalities known to occur with a study drug;
- Possible problems known to occur when the study drug is ingested with other agents; e.g., potential for life-threatening events with use of buprenorphine and benzodiazepines;
- Suicidal ideation or attempts in a population particularly at risk for such events;
- An increase in violent behavior during a particular behavioral intervention.

There can be other non-medical risks arising simply from participation in a clinical trial. Study teams should attempt to address ways to minimize these risks in the protocol, such as the following:

- Violation of confidentiality, and its attendant consequences;
- Discomfort due to assessment procedures;
- Embarrassment in disclosing sensitive personal information;
- Disclosure of information about intended physical harm to victims or abuse of children that would need to be reported to the child welfare agency and any investigation of the allegation(s) and further action, as indicated.

II. Adverse Event Monitoring

This section should provide:

- Statistical methodology to detect harm from the interventions being tested
- Considerations for stopping rules

AE and SAE data collection:

Definitions of AEs and SAEs:

The CTN has adopted the standard FDA definitions for AEs and SAEs as a starting point. It is the responsibility of the study teams to further refine these definitions (expand or limit), to reflect what is clinically and scientifically appropriate to their particular study. This section should be followed by the specific safety plan for that trial, where the study team may choose to subtract from, or expand upon, these FDA definitions. The safety plan should then describe and specify the extent of the data to be recorded (the forms to be used), and the procedures for adverse event reporting to all relevant parties, including the timeframes for reporting. The extent of the data captured should be commensurate with:

- The risks inherent to the particular interventions used in that protocol - what is already known and may be expected (akin to the information provided in the investigator's brochure in a pharmacologic trial).
- The risks inherent to the study population. For example, what types of events are expected in this population with this condition? Are these events that would normally be expected in this particular population (e.g. detoxification treatment, suicidality)? Would the intervention increase these events, or cause others not usually expected? [1]
- The risks inherent to participation in the particular study, and the conditions under which the study is being conducted. Considering these, the study team may ask what could occur as a result of study participation, which may or may not be a result of the intervention? For example, the risk of loss of confidentiality.

The DSMP should provide an overall summary flowchart of the procedures to be followed in the event an AE/SAE is reported. It should include an assessment timetable for when information will be elicited, by whom, how it is to be recorded (the forms to be used), and the timeframes for expedited and non-expedited reporting (as applicable) in that particular protocol. The duration of AE monitoring should also be specified; for example, will AE monitoring occur only during the active intervention period, or until a set duration post intervention, or throughout the entire duration of the study until the participant completes the study, or until the last participant completes active treatment or follow-up, or until final study closure.
The plan should also specify the person(s) who will determine whether the AE meets the criteria for being a serious event (an SAE). The plan should identify who will determine event severity, relatedness to the intervention(s), outcome of the event, and any action to be taken regarding study status. Regardless of the recording and reporting requirements, it is the responsibility of all study personnel to assure that subject well-being and protection is given priority.

The AE Section of the DSMP

The AE section should provide details specific to that study on the following:

- The definition of AEs in that specific protocol.
- Determination of which AEs will be collected - The plan may exclude collection of any AEs, or specify that only certain named AEs will be collected, e.g.:

[1] As an example, some CTN investigators consider that residential admission for drug treatment is expected in this population, and therefore would not consider it to be an adverse event. (Information about residential admissions may be important for other considerations, and can be captured in other study records) Others have expressed that residential drug abuse treatment facilities should not be considered on a par with hospitals, and therefore have made the case that residential admissions do not meet the criteria for considering an adverse event as being serious on the basis of requiring hospitalization

    - The plan may propose that only designated AEs (e.g. specific list of AEs) will be collected. As an example, the team may decide that withdrawal symptoms, increased drug use, or admission for detoxification only are relevant to the whole substance abusing population, but are not situations which would be caused by this specific protocol or its interventions. Therefore, the team may decide that these events will not be captured as AEs in this study.
    - If a list of AEs is compiled, the plan should specify how they would be elicited - via open-ended questions, by specifically probing for them, only collecting them if volunteered by the participant, etc.
    - Indicate in what kind of source documentation would be necessary regarding collection/reporting of AEs.
- All designated AEs are to be recorded on the AE CRF (which will be sent to the data management center and included in the study safety database).
- All AEs should be followed to resolution or stabilization or until some predetermined cut off time point. The plan should clearly indicate the cut off time point for follow-up of AEs.

The SAE Section of the DSMP

The SAE section should provide details specific to that study on the following:

- The definition of SAEs. There should be language stating whether the protocol modifies the FDA criteria for determining an SAE. The plan should specify any exemptions from normal SAE collection/reporting, such as pre-scheduled hospitalizations, admissions to residential detoxification programs, normal child birth, etc.
- Once an adverse event is recorded, and the event has been determined to meet criteria for seriousness, an AE CRF, an SAE Form and a summary report must be completed on each of these events.
    - A summary flowchart. The flowchart should include the process of notification for all personnel expected to receive notice of SAEs, and the notification timeframes (expedited vs. non-expedited).
    - For CTN trials, the time frame for notification of expedited SAEs to NIDA is within 24 hours of learning of the event. Subsequent follow-up information should be submitted within 5 days for studies under an IND, and within 10 working days for all other studies. The initial report may be very brief, stating only the information known at the time, with further information to follow as soon as it can be obtained.
    - The study teams retain the option to further qualify these reporting timeframes. For example, reporting only related SAEs within 24 hours, and all other SAEs will be submitted in a regular (such as quarterly) report, or in some other time frame consistent with local IRB requirements, and agreed to by the DSMB (and FDA if the study is under an IND). The DSMP should clearly state the agreed upon reporting requirements.
- All participant deaths must be reported to NIDA within 24 hours of (the CTP) first learning of the event.
- All SAEs should be followed until resolution or stabilization. The determination of the length of follow-up for the SAE must ultimately be made within the clinical context of that particular event. It is up to a qualified clinician to determine whether the SAE is

resolved, or when the condition has stabilized. There should be written documentation to support that determination. Once the SAE report (event resolution or stabilization) is submitted, no further follow-up is necessary for that particular event.

Using Electronic Data Capture (EDC) Systems

Please confer with the DSC and data manager when using an electronic data capture system for reporting SAEs. Such systems may develop electronic processes for submitting the SAE forms and summary reports. Also, the system will provide processes for submission when the EDC is not functional, in order to meet the necessary timeframes.

TRIAL PERFORMANCE MONITORING

This component of the DSM Plan seeks to identify the aspects of trial implementation that are key to the successful execution of the study, and the preservation of the scientific rigor expected in a randomized clinical trial. The study team needs to consider the most likely threats to the trial's internal validity posed by potential problems in trial execution. The internal validity of a trial is the degree to which it establishes the cause and effect relationship between the experimental manipulation and the observed outcome. A trial's internal validity has been compromised if something other than the manipulation of the experimental intervention can readily explain treatment group differences in outcome measures. It has also been compromised if the lack of an experimental effect could be explained by something other than the experimental manipulation. Some of these threats will undoubtedly be very similar across all trials, while others will be specific to the particular intervention being studied.

Study teams should include in this section of the DSMP their strategies to minimize these factors.

Potential Threats to Internal Validity

This section discusses selected aspects of trial execution, which can often threaten the internal validity of trials investigating either behavioral or pharmaceutical interventions for drug addiction. This is not an exhaustive list, and there will be aspects that are pertinent only to specific trials that are not listed here. It is up to the study team to specify for their particular study what all the aspects may be.

Recruitment and Enrollment

It is important to every trial that the study subjects are recruited to reflect the target population, and enrolled in accordance to the inclusion/exclusion criteria specified in the protocol. Determining subject eligibility for participation in any study is of critical importance. Attention should be paid to ensure that subjects are screened, and enrolled appropriately. Study teams should describe how inclusion/exclusion determinations will be checked for accuracy; address the verification of data upon which eligibility determinations are made; the cross-checking of these data across different screening and baseline assessment instruments; how to accomplish prompt resolution of any questions or inconsistencies that are identified; and ways to ensure diagnostic reliability.

Randomization

The randomization process is absolutely crucial to a clinical trial's internal validity. Failures in randomization destroy the equivalence of participants across treatment arms. This, in turn, allows for the possibility that resulting differences in trial outcome may be due to the different compositions of the treatment groups rather than the experimental manipulation. Thus, there should be checks on the randomization procedure, and assurances that site staff cannot predict treatment assignment. Complex procedures incorporating stratification factors need additional monitoring throughout the life of the trial.

Participant Attrition

Participant attrition threatens the equivalence of subjects across treatment arms established by randomization. CTN trials are especially vulnerable to this threat, because of the difficulties in retaining drug-using participants in any treatment program. Consideration should be given to how subjects can be motivated to remain in the study and to remove barriers to continued participation over the duration of the study. Procedures for keeping subjects in the study, and for contacting subjects if they fail to return for study visits, should be specified in the DSMP. Throughout the trial, subject attrition should be monitored closely. If attrition is seen to be a problem, investigators should attempt to identify factors contributing to attrition and expeditiously implement procedures to mitigate these factors.

Staff, Participant and/or Assessor Bias

This is an extremely important source of confounding that must be addressed in all open trials. There are many situations in CTN trials where staff delivering the interventions cannot be blinded to the treatment assignment of subjects. As much as possible, other study-related staff must be kept blinded to the actual treatment arm of the subject. For example, staff collecting data for the primary outcome measures must be blinded to the subject's treatment assignment. Ongoing assessment of whether the blind is being maintained needs to occur throughout the trial, and the monitoring plan should outline these procedures.

Treatment Fidelity

In any clinical trial, attribution of observed outcomes to the trial intervention rests on the assumption that the intervention is delivered in a standardized manner to all participants. For behavioral trials in particular, the consistent delivery of interventions is critical to the validity of study results. The DSMP should specifically address monitoring of treatment fidelity, including the following issues:

- *Competency in the specific intervention* - There should be measures to demonstrate that the staff delivering the intervention has mastered the intervention.
- *Standardization of intervention delivery* - There should be periodic assessments to demonstrate that the interventions are delivered in a standardized manner within and across all sites. This may be accomplished directly by on-site supervision, or by an examination of videotaped therapy sessions. The DSMP should describe who will review tapes, the qualifications of reviewers, the frequency of review, and review criteria. The DSMP should state how the review results will be used to determine whether the intervention has been delivered appropriately, and, if not, what steps will be taken to ensure the standardization of intervention delivery.

- *Re-Training* - There should be built-in provisions for corrective actions when the bounds of consistency and or quality have been breached. If re-training is called for, the DSMP should specify who would do the re-training, how will it be done (e.g. locally vs. centrally), and what checks will be in place to assure that re-training is successful.
- *Staff Turnover* - The training of new therapists needs to conform to the training provided at the start of the study. Due to logistical considerations, new therapists replacing those who left may be trained by the on-site team, whereas the original therapists may have been trained centrally. In trials where some sites have high turnover rates, or where the study is expected to run for an extended period of time, the training of new staff needs to be monitored closely for adequacy and consistency.

Reliability of the Primary Endpoint

Methods of assessing the reliability of the primary endpoint depend on the level of objectivity of the measurements. With a biological measure, such as urine testing for presence of certain drugs, the precision of the measure is dependent on the adherence to the window of time specified for urine collection. With a psychometric measure, the precision of the measure is subject to many influences including fluctuations in participant response and interviewer variability. Inter-rater differences can compromise reliability and diminish the ability of the trial to demonstrate efficacy. Monitoring procedures must be in place that can assure the reliability of the primary endpoint(s). All systems must be coordinated to protect this aspect of the trial, and checks on these systems must be carried out systematically and in accordance with a specified schedule, and corrective actions taken as soon as a problem is identified.

Errors in the Collection and Transmission of Clinical Data

Assurance of accurate data is an extremely important task in any multi-site trial. Procedures must be in place for accuracy checks of the clinical data throughout the trial, in real time as the trial is occurring. Errors should be identified in a timely manner and corrective actions applied immediately, with subsequent checks that the errors are fixed. Accuracy of the clinical data must be assessed on an ongoing basis, and should not be left to the end when the trial is being closed out. The DSC will provide information on this process.

Summary

For each of the areas considered to be crucial to the internal validity of the trial, the study team should provide an overview of the way in which these areas of trial execution will be monitored. The overview should include what information is examined, at what frequency, and the responsibilities of the participating CTP, the participating node, and the study team. It is suggested that the plans for each aspect of trial performance be summarized in tables. This set of tables can outline the priorities for monitoring. As an example, an overview of one aspect of trial execution (participant attrition monitoring) is shown below.

Responsibilities:	**Participant Attrition**
Study Team	State the study team responsibilities with respect to participant attrition

	monitoring; identify staff responsible for monitoring, (necessary qualifications if relevant)
Participating Nodes	State the participating Nodes' responsibilities with respect to participant attrition; identify staff responsible
Site Staff	State the site staff's responsibilities with respect to tracking participant attrition; identify staff responsible
Attrition Assessment	List the measures or instruments to be used
Action	State actions that may be taken to mitigate excessive attrition, if and when it is identified
Follow-up	State the process for confirming that mitigating actions are successful; identify staff responsible for follow-up; state the schedule for follow-up checks

EFFICACY MONITORING

A formal interim analysis (efficacy monitoring) provides statistical guidelines for terminating the trial because of overwhelming evidence for either benefit or futility. Efficacy monitoring is distinguished from trial performance and safety monitoring because it provides statistical stopping rules for trial termination as a result of a planned analysis at an interim stopping point. It should be noted that these stopping rules serve only as guidelines, and that the decision to terminate a trial at an interim stopping point may depend on factors beyond the results of statistical hypothesis testing. Efficacy monitoring must also be distinguished from mid-trial analyses to re-estimate required sample sizes. Mid-trial analyses focused on re-designing the trial are not discussed in this document.

The procedures and methodological approaches for the interim analysis should be specified a-priori. There are logistical issues to consider since interim analyses are conducted on datasets that are frozen at the specified interim analysis time point. The data coordinator must have procedures in place for preparing the data for the analyses. If group sequential methods are considered, the schedule for interim analyses must be specified, which can be a fixed time frame (e.g., every six months), or after a certain number or percentage of subjects are enrolled (e.g., 25%, 50%, 75%, 100%), or after a certain number of sites have completed enrollment. Study teams should work with the DSC to design appropriate interim analyses. In such design the following should be considered:

1. **Rationale -** Generally, a formal interim analysis is justified by the overriding ethical concern that subjects should not be exposed to an inferior or harmful treatment longer than necessary. A trial should not be continued once it is established that equipoise is unlikely to be disturbed, both for subject protection and for needless expenditure of public funds.
2. **Methodological Approaches** - The Problem of Controlling for Type I Error Rates in Interim Analyses. A type I error refers to the situation where the null hypothesis is rejected in error; claiming a difference in the two treatments when in fact, there is no difference.

3. **Early Detection of Benefit** - To detect early benefit the most extensively used statistical approaches are group sequential methods. These methodologies are designed to provide the study team with a way to examine efficacy (a test of the null hypothesis as stated in the protocol) before the end of the trial while preserving the pre-specified Type I error rate.
4. **Early Test for Futility** - In this situation, a statistical (or probabilistic) assessment is made regarding whether the collection of more data will result in an acceptance or rejection of the null hypothesis at the end of the trial.
5. **Other Approaches** - There are many other approaches and issues related to the statistical analyses of mid-trial clinical data, the scope of which is beyond this guidance document.

CONCLUSION

This document summarizes NIDA's Clinical Trial Network's requirements for Data Safety and Monitoring Plans (DSMP) in CTN-sponsored clinical trials. A DSMP that addresses safety monitoring, trial performance monitoring and efficacy monitoring is an essential element of all CTN protocols. The study team is responsible for developing a DSMP and complying with the approved Plan; the DSMB provides oversight of these tasks. The study team must be thoroughly familiar with the DSMP, and ensure that the study will be carried out in accordance with all aspects of the protocol and the DSMP. All elements of the DSMP and all training of study personnel must be in place before the study begins.

REFERENCES

1. NIH Policy For Data and Safety Monitoring
   http://grants1.nih.gov/grants/guide/notice-files/not98-084.html
2. Further Guidance on Data and Safety Monitoring for Phase I and II Trials
   http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

NIDA Guidelines for Developing a Data and Safety Monitoring Plan
   http://www.drugabuse.gov/Funding/DSMBSOP.html

3. NIAMS Generic Monitoring Plan for Trials Requiring a Data and Safety Monitoring Board http://www.niams.nih.gov/rtac/clinical/dsmb3.html
4. NIH Guidance on Reporting Adverse Events to IRBs for NIH-supported Multimember Clinical Trials http://grants.nih.gov/grants/guide/notice-files/not99-107.html
5. International Conference on Harmonization http://www.ich.org/
   E2A: Definitions and Standards for Expedited Reporting
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