National Drug Abuse Treatment
Clinical Trials Network

CTN POLICIES AND PROCEDURES GUIDE

Version 1.7
First released May 12, 2006
Some Sections Added or Revised
Apr 16 09

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1.0 GENERAL

To date, the efficacy of new treatments for drug addiction has been demonstrated primarily in specialized research settings, with somewhat restricted patient populations. To address this problem, the National Institute on Drug Abuse (NIDA) has established the National Drug Abuse Treatment Clinical Trials Network (CTN). Please visit http://www.nida.nih.gov/CTN/Index.htm for detailed information about CTN.

1.1 CTN BY-LAWS (as amended on February 27, 2008)

ARTICLE I - Name

The Name of this organization is the National Drug Abuse Treatment Clinical Trials Network (CTN).

ARTICLE II - Objectives and Purposes

A. To bridge the gap between practice and research by conducting studies of behavioral, pharmacological and integrated behavioral and pharmacological treatment interventions in rigorous, multi-site clinical trials to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations.
B. To facilitate adoption of CTN tested and successful interventions within the CTN and to provide expert support to other components of NIDA and the Public Health Service in the timely transfer of research results to clinicians, providers, their patients and policy makers to improve the quality of drug abuse treatment throughout the country using science as the vehicle.

ARTICLE III - Organization

The CTN operates under cooperative agreements (U10 grants) between academic research institutions and the National Institute on Drug Abuse (NIDA) and is administered by the Center for Clinical Trials Network (CCTN) of NIDA.

Network Structure

Clinical Trials Network (CTN). A collaborative group of clinical research and training Nodes working collaboratively with NIDA to conduct multi-site clinical trials on promising behavioral, pharmacological or integrated treatments, and serve as a platform for clinical research and training.

NIDA CCTN Office. An office reporting directly to the Director, NIDA, responsible for the scientific, administrative, budgetary, and operational management of the CTN.

NODE. A Node is the functional unit within the CTN consisting of the Regional Research and Training Center (RRTC) and its affiliated Community Treatment Programs (CTPs). The RRTC coordinates and arranges a bi-directional research partnership between the RRTC and CTPs.

Regional Research and Training Center (RRTC). The RRTC is the recipient of the cooperative agreement award. It is one of the two components of a Node. The principal investigator(s) at these sites are recognized nationally and internationally as scientific experts in substance addiction treatment. The RRTC provides a core of administrative and study operations services as well as scientific leadership and management of clinical trials.

Community Treatment Programs (CTPs). Drug abuse treatment programs in a community setting that have a history of providing quality treatment to large and diverse patient populations, and have the capability for and interest in participating in controlled clinical trials.

CTN Steering Committee. The Steering Committee (SC) has a major role in setting the scientific agenda of the CTN in conjunction with NIDA; reviews and approves final protocols for implementation; determines and revises, as necessary, the CTN governance; elects members and oversees the operations of the Executive Committee and the Research Development Committee; and oversees the performance of the Publications and Research Utilization Committee. Members of the Steering Committee participate in CTN committees and task forces, as needed, based upon expertise, interest, and Node budget.

NIDA's CTN Protocol Review Board. An expert board appointed by and reporting to the NIDA CCTN Director to review the protocol and informed consent submitted by the CTN for scientific and regulatory review. To minimize delay and provide continuity, this board can be combined with a DSMB (see below) for a study.

Data and Safety Monitoring Board (DSMB). The DSMB is an independent expert board, appointed by and reporting to the Director of CCTN that oversees and monitors the conduct of the clinical trials to ensure the safety of participants and the validity and integrity of data for each study. The DSMB also makes an independent assessment of the interventions under study and whether or not any trial undertaken in the CTN will continue. One or more NIDA staff serves as a non voting administrator of the DSMB. One or more DSMBs may be appointed to oversee clinical trials.

CTN Ad hoc Advisory Panels. The Director of NIDA may appoint expert panels to advise the Institute and CCTN on specific scientific directions or trials.

Clinical Coordinating Center. An organization selected by NIDA to provide centralized support for regulatory functions and requirements, protocol monitoring, training of staff involved in research studies, pharmaceutical supply services, drug testing and analytical laboratory services, and protocol development.

Data and Statistics Center. An organization selected by NIDA to provide centralized support for collecting, managing, and storing study data; designing and performing statistical analyses; reviewing and monitoring data quality; monitoring trial progress; preparing reports for the DSMB and CCTN; and protocol development.

Administrative and Logistical Support. Contract(s) awarded by NIDA to provide centralized support for the administrative and logistical functions of the CTN.

ARTICLE IV – Organizational Leadership of the CTN

SECTION A - The Steering Committee

1. The Steering Committee (SC) comprises the following voting members: (a) the Principal Investigator (PI) of the U10 grant and a CTP representative from each Node, (b) CCTN Director or Deputy Director, and (c) representatives from the NIDA contracted Coordinating Centers, which representatives shall be approved by the Director, CCTN or designee.
2. Each Node shall determine the term of service and rotation policy on the SC for the PI and CTP representatives.
3. The PI and/or the CTP representative may designate alternates to sit and vote at meetings of the SC provided that the individuals are of sufficient stature and leadership in the organization they represent.
4. There shall be a Chair and a Vice-chair elected among the membership of the SC who shall serve for a term of one year. The Chair and/or Vice-chair may serve more than one term. Candidates for the positions shall be self-nominated from the SC. The Chair will be selected from among the PI members and the Vice-chair from among CTP members. Neither the Chair nor the Vice-chair may serve on the EC or RDC.
5. The Steering Committee shall meet face-to-face two times each year, and by conference call, as necessary. The time and/or place of meetings and conference calls shall be at the recommendation of the Chair with the concurrence of the Director, CCTN.
6. Provided that a quorum of the SC members exists, voting may occur through meetings, conference call or mail ballots. Unless otherwise indicated in these Bylaws, a majority vote of those present is required.

SC Roles and Responsibilities:

The roles and responsibilities of the SC are set forth in Article III, Organization.

SECTION B - The Executive Committee (EC)

1. The Executive Committee comprises 5 Principal Investigators (PI's), 5 CTP representatives elected by and from the SC membership, the CCTN Director or Deputy Director, and one member from each Coordinating Center. The members from the Coordinating Centers are non-voting *ex officio*, and will be selected in consultation with the Director, CCTN.
2. SC candidates for the Executive Committee shall be self-nominated. Candidates must commit to the considerable time and energy that service on the EC will require.
3. The term of service on the EC shall be for 2 or 3 years as decided by the EC to ensure orderly rotation depending upon the Node funding cycle and other factors. Vacancies will be filled by special election.
4. The EC shall meet by telephone conference calls on a monthly basis, by face-to-face quarterly meetings at a time and place approved by the Director, CCTN and such other times as the Chair deems necessary.

5. PI and CTP representatives from the same Node shall not serve on the EC.
6. Quorum and voting requirements of the EC shall be the same as for the SC.
7. The CCTN Director or Deputy Director shall serve as the Chair of the EC. If the Chair position is vacated by a NIDA member, EC members shall select a new Chair by two-thirds vote, subject to the approval of the NIDA Director.
8. The EC is delegated authority to act on behalf of and for the SC in order to further the business of the CTN.

EC Roles and Responsibilities

1. Renders decisions on behalf of the SC to advance, in a timely manner the business of the CTN.
2. Through protocol oversight, recommends to CCTN actions necessary to keep protocols on track.
3. Receives and acts upon reports from CCTN and the Coordinating Centers.
4. Provides oversight of the Publications Committee, Research Utilization Committee and the Research Development committee.
5. Reports to SC at meetings and through EC minutes.
6. Ensures effective communication and collaboration among Nodes.

SECTION C – Research Development Committee (RDC)

1. RDC membership will be composed of members from the SC and elected by members of the SC. Candidates shall self-nominate. Members must commit time and energy to the RDC and be knowledgeable about the treatment needs of the field and effective approaches to meet those needs.
2. An RDC member cannot serve on the EC and an EC member cannot serve on the RDC.
3. RDC membership shall be composed of 4 PIs and 4 CTPs, and a designee of the NIDA director. The Chair will be elected among the RDC membership.
4. The RDC may appoint Ad hoc Task forces to address specific areas of investigation.
5. The term of the RDC members shall be approximately 2 years based upon the generation period for new projects.
6. Report to EC quarterly or as needed.

RDC Roles and Responsibilities:

1. Plans jointly with NIDA for a strategic CTN research agenda.
2. Coordinates “brainstorming” workshops with a wide range of experts to formulate research questions that capture the unique scientific opportunities and address critical public health needs.
3. Establishes Ad hoc Task forces to address specific areas of need. These task forces will be time-limited and focused on specific tasks.
4. Prioritizes research projects and establishes protocol project teams for EC and SC consideration and approval.
5. Actively promotes the use of CTN as a research and training platform.

SECTION D – Research Utilization Committee (RUC)

1. Each Node shall select one Node Research Utilization Coordinator (NRUC). The NRUC identifies candidates for membership on the RUC who possess an expertise and interest in dissemination.
2. The NRUC could serve on the RUC but others could serve as well. Members of the RUC can be selected from individuals representing a wide range of interests including the EC, SC (but members need not serve on the SC), and other individuals affiliated with the Node.
3. The RUC shall be composed of 8 members who are elected by the NRUCs and one member from the CCTN. The term of service is 2 years. A chair shall be elected from among the members.
4. The RUC will communicate with NRUCs through e-mail and conference calls.
5. The RUC may establish time limited Ad hoc task forces that bring in expertise not available in the RUC or the NRUCs.

Roles and Responsibilities of the RUC

1. Facilitates adoption of CTN-tested and successful interventions within the CTN.
2. Facilitates sharing of cost effective dissemination strategies among Nodes, Blending Teams, or Federal and State partners.
3. Assists Nodes in developing internal dissemination projects and developing partnerships for internal dissemination.
4. Tracks and describes dissemination activities within the CTN.
5. Promotes dissemination research using CTN as a platform.
6. Report to EC as required.

SECTION E – Publication Committee (PC):

1. Each Node PI shall designate at least one person to be part of a reviewer pool for the Publication Committee. To the extent feasible, the reviewer pool should be balanced between researchers and providers. A reviewer should possess the interest, expertise and willingness/commitment to review, on a timely basis, publication materials, and could include representatives from the CCTN and the SC.
2. The PC shall be composed of 7 members, including one from the CCTN and one from the SC. PC members are self-nominated and elected by the EC, with a service term of 2 years. The Chair of the PC shall be elected by the PC members.
3. The publication reviewers could serve on the PC, but others could serve as well. Members of the PC can be selected from individuals representing a wide range of expertise including the EC and SC.
4. The PC shall determine the number of reviewers who will review each publication draft based upon the complexity of the subject matter and other factors.
5. The PC shall communicate between themselves and the publication reviewers through e-mails and conference calls.
6. The PC can form time limited ad hoc task forces that bring in expertise not available in the reviewers pool.

Roles and Responsibilities of the Publication Committee:

1. Ensures the publication of timely and quality CTN results through:
    a. Reviewing protocol publication plans, including timelines and journal selections.
    b. Arbitrating publication disputes, e.g., ranking of authors on a CTN-related paper.
    c. Reviewing manuscripts to ensure appropriateness and quality of CTN publication.
    d. Interacting with CTN publication authors to facilitate and ensure timely publication of study results.
2. Identify and promote publication opportunities.
3. Identify meetings of professional societies in which the CTN can showcase its research results.
4. Encourage and coach junior researchers and practitioners to publish through:
    a. Facilitating data sharing to generate additional publications with the CTN database.
    b. Conducting workshops to coach junior researchers and practitioners on secondary data analysis and manuscript writing.
5. Report to EC as required.

SECTION F - Ad hoc Task Forces (AHTs)

Principles

1. AHTs are appointed by and report to the CTN committee who establishes the AHT e.g., SC, EC, RDC, RUC, PC.
2. They shall be established for a specified purpose that the appointing committee itself cannot address and are not intended to be an on-going activity.
3. The appointing committee defines AHT goals, work products, and timelines.
4. AHT membership shall be broadly based so that there is an opportunity for full input and the benefit of special expertise by the greater CTN.
5. Communicates to SC and CCTN through the appointing committee.
6. Sunsets at a specifically stated time or upon completion of the task.

ARTICLE V – Procedures

A. For meetings of the SC and EC, a quorum shall consist of 50% plus one of the appointed members. Voting shall be by a simple majority unless otherwise indicated in these Bylaws.
B. The CTN shall be governed by these Bylaws and the Cooperative Agreement award. Should there be an inconsistency between those documents; the terms of the Cooperative Agreement shall govern.

ARTICLE VI – Scientific Misconduct

The CTN complies with Public Health Service regulations and policies for handling misconduct in research as set forth in CFR part 50, subpart A.

ARTICLE VII – Performance Standards

All members supported by the CTN must abide by the policies and procedures of the CTN, including standards for the conduct of clinical trials. Failure to comply with the established performance standards and other policies governing the CTN may result (1) temporary or permanent discontinuation from participation in CTN clinical trials; (2) NIDA action to reduce the level of funding; or (3) termination of funding.

ARTICLE VIII – Conflict of Interest

The CTN members shall comply with the financial disclosure and conflict of interest policy and guidelines of their institutions.

ARTICLE IX - Ratification of and Amendments to the Bylaws

A. A vote of at least two-thirds of the SC members attending a regularly scheduled meeting of the CTN is required to ratify the Bylaws.
B. These Bylaws may be amended at any regularly scheduled meeting of the Steering Committee voting members. Proposed amendments to the Bylaws shall be submitted in writing to the Executive Committee by any voting member of the Steering Committee, within a time that the EC considers reasonable for consideration of the amendment.
C. The Executive Committee will submit the proposed amendment to the SC voting members at least 7 days before their next regularly scheduled meeting, with a statement of the EC's position on the amendment. The Bylaws may be amended by a two-thirds vote of the SC members attending a regularly scheduled meeting of the CTN.

AMENDMENTS

Amendment 1.
To: ARTICLE IV Section A #2. Amend language to read: "Each Node shall determine the term of service and rotation policy on the SC for the CTP representatives." The Amendment removes "PI" from the sentence. Rationale: The PI of the U10 grant is always a member of the SC; the rotations or changes in terms of service apply only to the CTP representatives.

Amendment 2.
To: To: ARTICLE IV Section A #5. Add language to first sentence: "The Steering Committee shall meet face-to-face at least two times each year…." Rationale: The language sets a minimum for face-to-face meetings. In the past, the SC has met more than twice a year, and this minimum contact provides important opportunity for interaction among members of the Network.

Amendment 3.

To: ARTICLE IV Section B #7. Change language to: "EC members shall select a Chair by two-thirds vote, subject to the approval of the NIDA Director. The Chair shall serve a two-year term."

Amendment 4.
To: ARTICLE IV Section C #1. Change language to "Membership will be composed of interested members of the CTN…" Eliminate language restricting membership on RDC to the SC. Rationale: The change provides more flexibility for membership on the RDC and encourages all investigators and CTPs to be involved in development of the research done within the CTN.

Amendment 5.
To: ARTICLE IV Section C #3. Change language to "RDC membership shall be composed of 4 investigators and 4 CTPs, and a designee of the NIDA director." Eliminate "PI". The change is consistent with the above amendment which eliminates that requirement that RDC members be members of the SC.

Amendment 6.
To: ARTICLE IV Section D #4. Change language to read "The RUC will communicate with NRUCs primarily through e-mail and conference calls." Rationale: Allows flexibility for the RUC to meet face-to-face.

1.2 Parliamentary Procedures

1.2.1 Introduction

Parliamentary Procedure is a time-tested method of conducting business at meetings and public gatherings that allows everyone to be heard and to make decisions without confusion. The CTN has adopted Robert's Rules of Order Newly Revised as its basic handbook of operations.

1.2.2 The Basic Rules

1. ***The rights of the Organization supersede rights of individual members.*** The organization has the right to make its own rules, which then must be observed by all members. Should a conflict arise between the rights of a member and the right of the organization to do its business, the rights of the organization prevails.
2. ***All members are equal and their rights are equal.*** Those rights are to 1) attend meetings, 2) make motions and speak in debate, 3) nominate, 4) vote, and 5) hold office.
3. ***A Quorum must be present to do business.*** A quorum is the number of members who must be present to legally transact business. The number is stated in the Bylaws. The purpose of a quorum is to prevent an unrepresentative group from taking action in the name of the organization.
4. ***The majority rules.*** The minority has the right to be heard, but once a decision has been reached by a majority of the members present and voting, the minority must respect and abide by the decision.

5. ***Silence is consent.*** Those members who do not vote agree to go along with the decision of the majority by their silence.
6. ***Two-thirds vote rule.*** A two-thirds vote is necessary whenever you are limiting or taking away the rights of members or whenever you are changing something that has already been decided.
7. ***One question at a time and one speaker at a time.*** No motion is in order that does not directly relate to the question under consideration. In addition, once a member has been recognized, he or she has been granted "the floor" and another member may not interrupt him or her.
8. ***Debatable motions must receive full debate.*** The presiding officer may not put a debatable motion to vote as long as members wish to debate it. Debate can only be suspended by a two-thirds vote of the members present.
9. Once a question is decided, it is not in order to bring up the same motion or one essentially like it at the same meeting. Such motions should be ruled out of order.
10. ***Personal remarks in debate are always out of order.*** The presiding officer must rule all personal remarks out of order. Debate must be directed to motions and not motives, principles, or personalities.

1.3 CTN as a Platform (Revised Mar 20 08)

1.3.1 Introduction

The CTN, with its core of CTPs engaging diverse populations, is also designed to provide a platform for other studies, which would be funded under separate research grants. Important ways to use the CTN are to utilize CTN Node facilities as a platform for investigations; and for Nodes to serve as home bases for NIH Training Centers and individual researchers who have NIH fellowships or career development awards. (Also see section 1.8 of this guide for more information on CTN studies).

1.3.2 Responsibilities

Investigators seeking to use CTN infrastructure, including the participating clinical treatment programs, practitioners, research staff, RRTC resources, or patients are responsible for seeking CTN support and for the implementation and timing of a specific research program in collaboration with the participating Nodes. Investigators must follow and comply with all applicable Human Subjects Protection and clinical research regulations (local, State and Federal), and obtain IRB approval prior to implementing any study.

1.3.3 Request for Support for Platform Studies

1. Investigators requesting permission to access the CTN infrastructure will e-mail NIDA CCTN Director. Requests should include the following:
    a. Brief description of the proposed study
    b. CTN facilities or personnel involved
    c. Funding source(s). Announcement # and title (For Example: RFA-DA XXX from NIDA, titled "…..")
2. NIDA CCTN Director will provide a letter of endorsement to use the CTN as a platform to the requesting investigator within one (1) week of receipt.

3. The externally funded protocol must fully cover all costs associated with the investigation, including expenses (if any) for the CTN staff.
4. Investigators should acknowledge the role of the CTN in any papers prepared for publication. Copies of publications should be sent to the chairs of the Publications Committee.

1.3.4 Research Training Scientists

While the NIDA CCTN encourages and supports the affiliation of individually funded scholars or training centers within the CTN Nodes, it remains the sole prerogative of the Node leadership whether or not to incorporate the individuals or centers. Scientists who are applying for an NIH-funded training award should contact the program director of the Node for information on local review procedures regarding scholars taking up residence and training centers being located at the Node.

If a letter of endorsement to use the CTN as a platform is needed, then the procedures for obtaining the letter are the same as section 1.3.3 above.

1.4 Common Assessment Battery

The Common Assessment Battery (CAB) is optional for studies after January 1, 2006. The battery consists of a series of data gathering instruments that have been used in CTN trials 0001-0029. If a protocol intends to measure a particular construct that is captured by a CAB instrument, it is strongly urged that the CTN CAB instrument be considered over non-CAB assessments. The CTN CAB consists of the following:

Demographics and Study Enrollment (*Some elements are required by NIH*)

- Sex, Age, Ethnicity, Race, Marital Status
- Education, Employment

Recent Drug Use

- Biological – Breathalyzer for alcohol use, saliva probe, urine test cup
- Self-Report – from Addiction Severity Index Lite (ASI-Lite)

Substance Abuse Diagnosis (Drug and Alcohol)

- CIDI (Composite International Diagnostic Interview)

Substance Abuse Associated Problems

- Addiction Severity Index Lite (ASI-Lite)

HIV Risk Behavior

- HIV Risk Behavior Scale (RBS) – self report

1.5 Referencing NIDA and the CTN

Use the following guidance when referencing NIDA or the CTN in materials, newsletters, flyers, websites, and other media. If there are any questions as to the proper language to use, contact Carol Cushing or Ron Dobbins at the CCTN.

Originator	Material	Sample Language
Node or University	Stationery, Promotional Materials, Newsletters, Flyers	A member of NIDA's Clinical Trials Network, Or A member of the Clinical Trials Network of the National Institute on Drug Abuse, NIH, Or This information has not been reviewed by NIDA and does not necessarily reflect the views of the Institute.
	Web Sites	A member of NIDA's Clinical Trials Network, Or The information on this site has not been reviewed by NIDA and do not necessarily reflect the views of the Institute, Or The materials on this site have not been created nor reviewed by NIDA.
Community Treatment Provider	Stationery, Promotional Materials, Newsletters, Flyers	[CTP] is a member of NIDA's Clinical Trials Network through the [university affiliate], Or A member of the [node name] for the Clinical Trials Network of NIDA, Or This information has not been reviewed by NIDA and does not necessarily reflect the views of the Institute.

	Web Sites	[CTP] is a member of NIDA's Clinical Trials Network through the [university affiliate], Or A member of the [node name] for the Clinical Trials Network of NIDA, Or The information on this site has not been reviewed by NIDA and do not necessarily reflect the views of the Institute, Or The materials on this site have not been created nor reviewed by NIDA.

1.6 CTP Participation in Protocols

1.6.1 Introduction:

Decisions about CTP participation in protocols involve communication and decision-making among groups: the study team, the Node PI, the CTP considering participation and NIDA CCTN.

1.6.2 Policy:

1. The CTN should seek to locate protocols in diverse treatment locations so as to evaluate the applicability and effectiveness of interventions across a variety of settings. Such diversity might include: small vs. large program, rural/ urban setting, race/ethnicity of patients, gender of patients, specific drugs of abuse, co-morbid conditions seen in patients, or region of the country.
2. Decisions about CTP participation must take into account the limited resources of both the participating nodes and the lead node, as well as the feasibility of the study at the specific CTP.
3. The study team will set forth the study criteria and requirements for CTP participation. Each node decides, through their own processes, what CTPs to put forward for protocols based on the requirements.
4. While decisions may be made about a CTP's participation based on its prior or current involvement in another protocol, CTPs should not be limited regarding the number of protocols to which they may apply.
5. If conflicts over CTP participation cannot be resolved by the study team and the nodes involved, an ad hoc group composed of one PI from the SC (not the LI and not from an involved node), one CTP SC representative (also from a node not involved), and one SC member from NIDA will be formed by NIDA to make a decision. The CTP, the LI/Protocol Team, or NIDA may initiate this process.
6. The Executive Committee will approve CTP participation.

1.7 CTP Withdrawal

1.7.1 Introduction

Protocol development and implementation within the multi-site trials of the Clinical Trials Network (CTN) involves a cooperative agreement and transparent communications between the

Regional Research and Training Centers (RRTCs), the Community Treatment Programs (CTPs) and the National Institute on Drug Abuse (NIDA). When CTPs withdraw from participation at any stage, there is a significant impact on resources. Formal steps are needed for notification of the necessary responsible parties, documentation of any adjusted recruitment efforts and documentation of the reason(s) for the withdrawal with its impact is outlined.

1.7.2 Responsibility

Site closure due to trial performance is the primary responsibility of the LI, although input from the EC, CCTN, the DSMB, or the study executive team may be factors. Closure of a site for other reasons should be rare. NIDA CCTN may, at their discretion, close a site for regulatory non-compliance or administrative needs. In these cases, the Node Principal Investigator (PI) is responsible for formally notifying the Lead Investigator (LI) and NIDA CCTN staff when officially withdrawing CTPs from any study.

1.7.3 Policy

Whenever a site is withdrawn from a study, the Lead Investigator will report to the Executive Committee at the earliest meeting, addressing the impact on the overall study and the subsequent revised plan. The Lead Investigator will address the reasons for withdrawal, the impact on the budget, study enrollment timeline, any data, quality assurance, or regulatory issues involving the site closure.

If the site had started recruitment and data collection, several steps must be taken to ensure that the collected data is complete and accurate. The LI should consult with the Data and Statistics Coordinating Center on the impact of the changed number of sites and/or number of participants on the analytical plan and the subsequent revised plan for recruiting the appropriate, and potentially adjusted, sample size.

The Node PI must consult and involve the following areas/staff:

1. CTP staff, Data and Statistics Coordinating Center to clarify outstanding data issues.
2. The Clinical Coordinating Center, to ensure a timely, comprehensive close out visit at the site.
3. Node regulatory staff, to ensure appropriate communications to the IRB(s) regarding study closure. The Protocol (or site) PI or their designee is responsible for submitting a final IRB report to their local IRB. This report may be submitted prior to or after database lock according to local IRB policies.
4. NIDA CCTN, indicating future plans for re-allocating the funds.

1.8 Research Conducted in the CTN (NEW April 2, 2008) (Revised July 17 2008)

1.8.1 Definitions

The CTN conducts the following types of studies:

<u>Multi-Site Clinical Trials:</u>

- Large studies involving clinical sites from more than three Nodes.
- Trials are reviewed for implementation in the CTN by the CTN Steering Committee (SC)[1].

[1] In Section 1.8, the "CTN Steering Committee" refers also to any subgroup of the Steering Committee.

- Trials are approved by NIDA based on recommendations by an external review board. The review process for these studies is described in section 2.3 of this Guide.
- In this document, such trials are sometimes referred to as the "parent study".

Ancillary Investigations:
- Studies "attached" to a larger multi-site CTN-approved trial (the parent study).
- May or may not include all participants from the parent study.
- May or may not involve direct contact with participants from the parent study.
- May or may not be funded by the CTN.

Secondary Analyses:
- Single-Study Secondary Analyses
  - Involve only one CTN study
  - Can be part of the protocol, or post-hoc
  - May be conducted before data lock, but only on baseline (pre-randomization) data
  - May or may not be funded by the CTN
- Multi-Study Secondary Analyses
  - Involve more than one CTN study
  - Are conducted after data lock of all studies to be included
  - May or may not be funded by the CTN

Other Studies:
- May be collaborative with other NIDA divisions, NIH ICs or other funding agencies.
- May be "platform" studies, i.e. only use the CTN infrastructure; or "pilot", "feasibility" or "small" studies that involve at least three CTN Nodes.
- May be in response to a specific request from NIH/NIDA (i.e. special populations)

1.8.2 Responsibilities

Investigators wishing to conduct such studies have the primary responsibility for submitting a proposal and, if approved, for the implementation of their study. They must follow and comply with all applicable protections for human subjects, and clinical research regulations (local, state and federal). They must obtain IRB approval and maintain it throughout the study.

NIDA's CCTN is responsible for coordinating the review of proposals (including review by NIDA management if appropriate), for approval of all study proposals, and for informing the CTN SC of final decisions. The CCTN will monitor study progress and, depending on the funding source, may also be responsible for study oversight.

1.8.3 Procedure for Submission, Approval and Coordination of Study Proposals

1.8.3.1 Multi-Site Clinical Trials

See Section 2.3 of this Guide.

1.8.3.2 Ancillary Investigations

1. Investigators must cooperate fully with the Lead Team of the parent trial, and collaborate early on before any ancillary study can be added. The Lead Investigator (LI) of the parent study should agree, in writing, that the integrity of the parent study is not compromised, and that the additional information generated is valuable and cost-effective.
2. Involvement of the CTN coordinating centers will vary. Investigators contemplating ancillary studies should discuss their needs for data, statistical and monitoring support at an early stage with CCTN staff.
3. The proposed ancillary study should be described in detail in a protocol-type document and submitted to the CCTN.
4. If the proposed ancillary study is a genetics study, investigators need to comply with the procedures set forth at http://www.nida.nih.gov/about/organization/genetics/FAQ_CTN.html
5. Once the proposal is approved, the investigator of the ancillary study should coordinate with NIDA's CCTN office to involve the CTN coordinating centers.
6. The DSMB of the parent study will monitor its ancillary studies as well.
7. Investigators must be aware of CTN's guidance of release of study data: "CTN Practice Guidelines on Release of Trial Data Prior to Data Lock" (see section 3.5).
8. Investigators should acknowledge the role of the CTN in papers prepared for publication. Manuscripts of publications should be sent to the CTN Publications Committee for review and approval.
9. Investigators must follow NIH policy for data sharing (http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html). In addition, if the CTN Data and Statistics Center collects the data for the ancillary study, then a de-identified public data set will be posted after the end of the study (see Section 3.2 for CTN's policy on data sharing).

1.8.3.3 Secondary Analyses

The CTN conducts three types of secondary analyses:

- Single-study secondary analyses that are specified a priori in the protocol
- Single-study secondary analyses not specified in the protocol
- Multi-study secondary analyses

Single-study secondary analyses (specified a priori or not) should be developed in close collaboration with the Lead Investigator and the protocol team.

Investigators will submit a brief proposal (up to 3 pages) to the CCTN office. The proposal should include the study title, name of the primary investigator, planned collaborators and co-authors on the final paper, the name of Node PI sponsoring the project, the research question/hypothesis and its importance, the CTN trials to be included, a brief description of the analytic method, and a rough timeline.

Due dates for submission of proposals parallel the NIH R01 receipt dates: February, June and October. The CCTN will coordinate the review, which may include the CTN Steering

Committee, CCTN/NIDA officials, representatives of the CTN coordinating centers, and outside experts.

1.8.3.4 Other Studies

1. The proposal should describe the rationale, design/methodology, data and safety plan (if needed), and CTN resources involved. A tentative budget for the study should also be included.
2. The study may be subject to regular monitoring by an independent group, similar to a DSMB.
3. Investigators should acknowledge the role of the CTN in papers prepared for publication. Manuscripts of publications should be sent to the CTN Publications Committee for review and approval.
4. Investigators must follow NIH policy for data sharing (http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html). In addition, if the CTN Data and Statistics Center collects the data, then a de-identified public data set will be posted after the end of the study (see Section 3.2 for CTN's policy on data sharing).

1.8.4 Numbering (added Sep 2, 2008)

CCTN staff will assign a number to all studies, regardless of size, type of study, or budget. It is expected that each numbered study will provide regular progress reports, a final report and, if at all possible, a publication. The studies will be numbered using the scheme below:

1. Multi Site Clinical Trials – Will assign unique number, following in sequence from the current numbers (i.e., 0001 through 0037) with no suffix.
2. Ancillary Studies – Will assign the same number as the "parent study" with the suffix "A". We will add a number after the suffix, to account for the number of ancillary studies conducted with each "parent" project. (For example, NIDA-CTN-0030-A-1, CTN-0030-A-2, etc. If only a single ancillary study exists for a particular parent study, it will be numbered -A-1)
3. Secondary Analysis – Will assign unique number, in sequence, with the suffix "S" (for example NIDA-CTN-0038-S)
4. Other studies – Will assign unique number, in sequence, with the suffix "Ot" (for example NIDA-CTN-0039-Ot).

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1.9 Financial Conflict of Interest (FCOI): CTN Oversight (Aug 15, 2008)

The CCTN follows the "NIH Oversight of Extramural Financial Conflicts of Interest" procedures, found at http://grants.nih.gov/grants/policy/coi/. NIH policy places the responsibility for determining and reporting financial conflicts of interest on the institution and its investigators. The policy applies to all CTN activities, including ancillary studies, secondary analyses, Health Disparities projects, etc. It is important that key personnel make initial disclosures and update disclosures regularly (usually yearly) with appropriate documentation. Time points for the disclosures may include, but are not limited to, the following:

i. Concept approval

ii. Protocol approval
iii. Site selection
iv. Protocol initiation meeting(s)
v. Site endorsement
vi. Site monitoring visits

Responsibilities

The Node PI is responsible for documenting that key staff complies with all state, local and federal policies and regulations. Key staff include CTP investigators and collaborators.

Documentation of FCOI policy compliance should be maintained in the Regulatory binder at sites.

The CCTN staff will provide periodic reminders to the Nodes about the need to ensure compliance with the institutions' FCOI policies.

2.0 PROTOCOL AND TRIAL MANAGEMENT

The nature and extent of the oversight and implementation structure will be determined by the circumstances of each study with the recognition that hierarchical structures will be limited to the maximum extent possible.

2.1 Study Executive Committee

The organizational structure that is to be deployed to oversee each protocol will depend upon the complexity of the study, its size, and scientific innovation. In more complex studies, the NIDA CCTN (in conjunction with the Steering Committee) will select qualified investigators to compose the Study Executive Committee, and the Chair of this committee will be called the Lead Investigator (LI). The study executive committee is responsible for the oversight of protocol development, implementation, and management. The study executive committee will consist of, at a minimum, the Chair (LI), a participating Node PI and CTP representative, NIDA CCTN, and staff from the Coordinating Centers (one each). The study Executive Committee reports to the CTN Steering Committee (SC) and NIDA CCTN.

The Study Executive Committee could serve as the protocol project team or it may appoint a study team that will lead the implementation and management of the study. This will include representatives from the Nodes, NIDA, Coordinating Centers, and CTPs necessary to coordinate the study. This team will report to the Study Executive Committee.

2.2 Study Executive Committee Chair (Lead Investigator)

2.2.1 Study Executive Committee Chair (Lead Investigator) Qualifications

The Investigator chairing a CTN Study Executive Committee shall meet the following qualifications:

1. The LI shall be qualified by education, training, and experience to assume responsibility for the proper conduct of a multi-site trial, shall meet all the qualifications specified by

the applicable regulatory requirement(s) in the event that the trial is conducted under an IND, and shall provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation upon request.

2. The LI shall be thoroughly familiar with the appropriate use of the investigational product(s) and/or the behavioral intervention that is being evaluated in the trial.
3. The LI, by training and/or experience, shall be fully aware of Good Clinical Practice (GCP), human subject protection and any applicable regulatory requirements and demonstrate a history of compliance with GCP and other regulatory practices.
4. The LI shall have demonstrated communication, organizational, budget management, and leadership skills that are key to the successful and timely conduct of a trial within the CTN.
5. The LI shall be able to devote sufficient time to all phases of the protocol's development and implementation and complete the trial within the agreed trial period.
6. The LI, in conjunction with his or her Node Principal Investigator (PI), shall be able to demonstrate a firm commitment to provide the necessary oversight, mentorship, support services, personnel, and financial resources for developing and conducting the clinical trial.

2.2.2 LI Approval

The selection of an LI shall be approved by the CTN SC. According to the manner in which the research protocol is developed, the recommendation to serve as LI could emanate from the proposed protocol team, by the CCTN, or by the CTN SC.

2.3 Protocol Development and Approval (as Amended on March 20, 2008)

1. Within 4 months of concept approval, the study team will prepare a 12-15 page study proposal for external review. It is imperative that the study team involve the CTN Coordinating Centers in the preparation of the proposal (and specifically in the preparation of the design section). The proposal should include the following:

a) Introduction: List the broad, long-term objectives and the goal of the proposed study, e.g., challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, test a new approach, address a special population, etc. The relevance to public health and potential to change practice should be clearly stated.
b) Background/Significance: Briefly sketch the background leading to the present trial, critically evaluate existing knowledge, and specifically identify the gaps that the trial is intended to fill. State concisely the importance and health relevance of the trial: how will clinical practice be advanced or changed. Describe the effect of the study on the concepts, methods, treatments, services or preventative interventions that drive the drug abuse treatment field. The proposed trial design should be appropriate to the "stage of knowledge".
c) Preliminary studies: provide an account of any preliminary studies pertinent to this application. Preliminary data often aid the reviewers in assessing the likelihood of the success of the proposed project
d) Research Design and Methods:
    a. Include an estimate of sample size, proposed intervention and a description of the assessments planned in the study.

   b. Describe the trial design, procedures, and analyses to be used to accomplish the primary and secondary outcomes of the project.
   c. Include how the data will be collected, analyzed, and interpreted.
   d. Describe any new methodology and its advantage over existing methodologies. Describe any novel approaches, assessments, or tools for the proposed studies.
   e. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. As part of this section, provide a tentative sequence or timetable for the project and a flowchart of the design.

e) Feasibility: Include a budget estimate, plans for human subject protection, potential CTPs settings and projected recruitment plan.
f) Leadership plan: Document the Lead Investigator's (and other critical personnel) experience with the methods, populations, or particular topics of the proposed trial. This information will help to establish the experience and competence of the investigator to lead and implement the proposed project. Areas of expertise to be addressed are: SUD clinical or research expertise, clinical trials experience, and experience within the Clinical Trials Network.
g) References
h) Appendix

2. CCTN will assemble a review panel for the proposal that will provide feedback to the CCTN Director. Minimally, the review panel will consist of individuals with expertise in bio-statistics and scientific or clinical areas relevant to the proposed study (reviewers will include the perspective of treatment clinicians). CCTN will make every effort to recruit these reviewers for a future Data and Safety Monitoring Board (DSMB), (*if the study progresses to that step)*.

   The main review criteria will be:

   a) Significance of the Research Question (not limited to)

   - **Importance of research question/ hypothesis (primary/secondary)**
   - **Background information/preliminary data**

   b) Design of the Study (not limited to)

   - **Intervention and control**
   - **Outcome measures**
   - **Study duration (both active treatment and follow up phases)**
   - **Sample size**
   - **Randomization plan**
   - **Other relevant design issues**

   c) Feasibility

   d) Leadership

3. CCTN will provide feedback to the Lead Investigator and the study team approximately within two weeks of review. Review outcomes will be:
   a) Approved to proceed with current design
   b) Approved to proceed with revisions (will list areas that need revision). See #4 below.
   c) Should not proceed as currently conceived (will list the problem areas)

4. If a resubmission is necessary (when approved to proceed with revisions), the Lead Investigator and the study team will provide the revised study proposal for a second review within a discussed timeline.

5. Once approved to proceed, the study team will develop a complete protocol, data and safety plan and other materials that will be submitted for DSMB review.

6. The study team will prepare the first version of the protocol within four months from the date the study proposal is approved. See Appendix VI for a protocol template and Appendix VII for Adverse Event Reporting guidance.

7. NIDA CCTN will arrange a DSMB meeting for protocol review. The protocol, data and safety monitoring plan, informed consent template and all necessary materials (such as copies of key referenced publications, therapy manuals, relevant checklists, etc.) will be provided to the DSMB members 30 days prior to the meeting. The Chair and other representatives of the study executive committee are expected to attend the open session of the DSMB meeting.

8. The DSMB may recommend (1) approval of the protocol as is; (2) approval with modifications; or (3) disapproval. NIDA CCTN will provide a written summary of DSMB review to the study executive committee chair within two weeks of the meeting. The study executive committee will address DSMB comments, recommendations, and concerns in writing within four weeks of receipt of written summary. NIDA CCTN will arrange subsequent meetings with the DSMB to complete the review process.

9. Once the DSMB recommends approval of the protocol, NIDA CCTN will provide final approval (in writing) to begin the protocol implementation.

2.4 Protocol Data and Safety Monitoring

2.4.1 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

2.4.2 Data and Safety Monitoring Board (DSMB)

The NIH (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) requires the establishment of data and safety monitoring boards for multi-site clinical trials involving interventions that entail potential risk to the participants. In accordance with NIH requirements, NIDA's Center for the CTN (CCTN) has convened DSMBs to provide independent oversight of trials conducted within the CTN. The Director of the CCTN appoints DSMB members for each study. The DSMB monitoring function is in addition to the oversight traditionally provided by IRBs.

The CCTN will communicate in writing with the study Lead Investigator the DSMB recommendations and CCTN decisions based on those recommendations.
See Appendix III for DSMB procedures.

2.5 CCTN Protocol Coordinator (CPC)

NIDA CCTN will assign a staff scientist to serve as CPC for a given study. The CPC will represent NIDA as a member of the Study Executive Committee. As a member of the investigative team, the CPC will participate in all aspects of protocol development, implementation, and management. As determined by the Lead Investigator, the CPC may be included as part of publication teams.

Major activities of the CPC are:

1. Participate in all protocol calls, meetings, and review sessions
2. Work with Study Executive Committee on decisions regarding protocol materials, assistance from Coordinating Centers and deadlines
3. Attend the protocol related training sessions (after approval from CCTN Deputy Director)
4. Report protocol progress to CCTN Director/Deputy Director
5. Sign protocol signature page (designee for sponsor signature)
6. Authorize protocol initiation at participating CTPs by signing the protocol endorsement form

7. Provide final decision regarding proposed changes to the protocol (accept/reject)
8. Encourage and facilitate publication of study results

2.6 Changes to study plans

Usually during the development and implementation of protocols there is a need to revise the protocol and/or implementation plans, which could delay the timeline or interrupt the study. The decision to accept changes to the protocol or the proposed study plan always depends on many factors and should be assessed carefully. In reviewing possible changes, the study team should consider issues of study integrity, impact on outcomes, reasonableness of any delay, and the quality of data collected.

Considerations:

1. Rationale for change/revision
2. Impact on current process:
    a. Data management/data collection system: How long will the change delay the study?
    b. Regulatory: Will the change require IRB review? Does this delay or interrupt the study? Does the change affect data quality or comparability?
    c. Training: Does the change require new training or re-training? How long would this delay the study?
    d. Timeline: How long will it take to process and implement the proposed change? (One delay usually affects other aspects of the time line, and a delay of one week in changing a CRF could actually mean a delay of one month to start the study.
    e. Budget: What will the change cost? Consider time, personnel, supplies, and scheduling.

Procedure for review and decision:

a. LI will provide the CPC with the change request along with answers to the questions above.
b. The Coordinating Centers will provide the CPC with their review regarding the impact of the change on their activities (for example, how long it will take to change a given CRF, what is the impact in the resources needed, training plans, initiation visits, site endorsement).
c. NIDA staff will provide information about the budget impact.
d. CPC will discuss with CCTN Director/Deputy Director, project officers and the study team and come to a decision to accept/reject the proposed change.
e. The CPC will notify the study team and coordinating centers to proceed. The CPC will copy the contract project officers when communicating with the coordinating centers.

CCTN will provide the final approval for protocol revisions and major changes for study directions.

2.7 Training

Appropriately trained and qualified staff is an essential component of any clinical trial. It is especially important in the CTN, because of the use of standardized psychological assessments

and the potential for high turn-over of staff. Fully trained and competent staff are responsible for all data collection and interventions conducted in the course of a trial.

1. All staff active in CTN protocols must receive training in Human Subject Protections and ICH Guidelines for Good Clinical Practice. All other training requirements are determined by the protocol team and will be indicated in the protocol specific training plan.
2. Unless specified in a protocol, each Node is responsible for setting their own criteria to determine that a staff member can be an interviewer and/or a trainer on any specific measure or intervention,
3. The Node PI is responsible for assuring that all appropriate members of the CTP team and RRTC are trained and competent to conduct study procedures. Local Nodes are responsible for providing training to staff in the proper conduct of study procedures, including the use of Common Assessment Battery measures. Where requested, the Clinical Coordinating Center may provide assistance.
4. There is no CTN-wide requirement for certification and re-certification of training in core measures, including the Common Assessment Battery. The Node PI is responsible for ensuring the competency of his or her staff, and that staff complies with all protocol requirements for training.
5. The use of a centralized tracking system for training is not supported by the CTN.

2.7.1 Scheduling Training Sessions

Nodes may schedule training for staff as they deem appropriate. A centralized schedule of trainings on the topics of Good Clinical Practice, Biological Measures and Handling, Demographics, Composite International Diagnostic Interview (CIDI), Addiction Severity Index – CTN (ASI-CTN) and the Risk Behaviors Assessments (RBS) is maintained by the Clinical Coordinating Center (CCC) and is provided to Node personnel and posted on Livelink®. Scheduled Node training sessions should be sent to the CCC via email notice at CTNSupport@emmes.com.

2.7.2 Provision of Training by the Clinical Coordinating Center

The CCC will have standardized training sessions and opportunities available for interviewers and trainers on the following measures: GCP, Biological Measures & Handling, Demographics, and CTN versions of CIDI, ASI, and RBS. These trainings are available to the Node staff if needed.

1. GCP is available on-line; for current URL contact CTNSupport@emmes.com. CTN members who use this training session must register in the on-line system. After each module a quiz is presented. At the end of all the modules, staff must pass with a score of 80% or better to get a certificate of completion. The certificate will be generated by the on-line system and must be printed by the staff member.
2. Biological Measures & Handling and Demographics training sessions are available on CD-Rom from the CCC. Requests for these materials must be sent to the CCC at CTNSupport@emmes.com. All staff within a node or CTP may share the same CD presentation. Instructions for receiving a certificate of completion are sent with the CD(s) along with supplemental materials, where appropriate.

3. CIDI, ASI and RBS training by the CCC may be requested by the nodes. The CCC will develop standard plans on the training that they will provide and the requirements for a certificate of completion. If the Node requires more specific assessments of competency for their staff members, it will be the Node's responsibility to complete these requirements. The CCC training plans will be posted on Livelink®.
4. Training Materials: Standardized materials are available for the CIDI, ASI, and RBS. CCC and Node trainers may use these materials at no cost to the node personnel. Materials for the CIDI and the ASI are provided in paper copies stored in 3-ring binders. Materials for the RBS are provided in electronic format. Copies of all are also available on Livelink®.
5. Requests for standardized training binders should be made at least 3 weeks in advance of the training session. Requests with a shorter turnaround will be evaluated on a case-by-case basis, determined by availability of supplies and resources. Requests should be sent to CTNSupport@emmes.com.

2.8 Data Management Policies/Procedures (from DSC)

2.8.1 Introduction

Data handling, from collection to database lock, must be specified such that the combination of the trial documentation and the trial database is sufficient to reconstruct the original data collected. The CTN operationalizes this policy through the SOPs of the Data and Statistics Coordinating Center (DSC) and the trial-specific documentation for each study (the data management binder).

The DSC will establish procedures that list each major step in the data collection and management process and define the roles and responsibilities of all individuals involved for carrying them out, accountability (whose responsibility is it to see that the task is completed), communication (from whom should the responsible party seek input), and information dissemination (who should be informed about the task, timeline, issues, and completion).

The SOPs are posted in Livelink, in the "DCRI Data SOPs" folder in the DSC area. The link is https://Livelink.nida.nih.gov/Livelink/llisapi.dll?func=ll&objId=1710947&objAction=browse&sort=name. The DSC SOPs apply to all trials and follow an ISO model for documentation. A corresponding set of Work Instructions provides step-by-step system and trial specific information. The trial specific work instructions are written for each trial and are managed in a Data Management Binder for each trial.

Original CTN trials initiated under the CTN DMAS SOPs (CTN 0001-0021) that have not been migrated to the DSC will continue to run under the DMAS SOPs. At the close of the last trial run under the distributed data management model, all of these SOPs that pertain to data collection and processing and data management will be retired.

2.8.2 Site Help Desk

The DSC will maintain a NIDA Site Support Help Desk (SSHD) with an appropriately staffed toll-free telephone service and email address at 1-888-DSC-SSHD (1-888-372-7743) or e-mail at

nidadsc-help@mc.duke.edu. The SSHD will provide support to participating CTN staff in the following areas:

1. Technical support related to the use of data management, randomization, and communications systems.
2. Assignment and maintenance of CTP and staff IDs
3. Maintain user accounts for CTN systems, including but not limited to, the CIDI, InForm, CRIS, and the Learning Management System.

2.8.3 Data Status Reports

Data Status Reports are programmed for each trial. The data status reports are developed and used for the purpose of assuring that all expected "pages" of data are received, and that all data discrepancies are resolved. These reports are used to manage the process of data collection and cleaning for CTN trials. They can be thought of as administrative status reports. There are four levels of reports: Participant level, Site level, Node level and Trial level (Trial Progress Report).

2.8.4 Security and Information Technology (IT)

The Data and Statistics Center (DSC) located at and managed by the Duke Clinical Research Institute (DCRI), is responsible for providing software applications and training to support data collection and management. DCRI developed the "Application Specific Companion to the DCRI Computing Environment System Security Plan (SSP)" to ensure the systems and facilities meet the security requirements. DCRI has provided and implemented the following SOPs and Work Instructions to support the DSC operations. Due to the sensitivity of some information mentioned in these SOPs, some of these SOPs will not be available to the public. The Government Project Officer for the DSC should be consulted if there are any questions.

1. Archiving: IT-S-026.01 – Management of IT Documentation Library
2. Change Management: (a) IT-S-020.00 – Change Control, (b) Managing Website Content
3. Operations: (a) IT-S-023.00 – Managing Problems and Defects in Production Hardware and Software, (b) IT-S-037.01 – Protocol Maintenance Using ClinTrial and ClinTrace Flowchart, (c) IT-S-039.01 – Network Operations, (d) IT-S-041.00 – Computer Management
4. Retrospective Evaluation: IT-S-032.00 – Retrospective Evaluation
5. Security: IT-S-036.00 – IT Systems Security
6. Software Implementation: (a) IT-S-025.00 – Computer Systems Development Life Cycle, (b) IT-S-027.00 – Code Review During Application Development, (c) IT-S-040.00 – Controlling Data Exports and Imports
7. System Backup and Recovery: (a) IT-S-001.00 – Performing and Retaining Enterprise Data Backups, (b) IT-S-035.01 – Recovering Enterprise Data, (c) IT-S-42.00 – Disaster Recovery
8. System Setup and Installation: (a) IT-S-009.00 – Processing Requests for Software, (b) IT-S-010.00 – Server Configuration
9. Training: IT-S-034.00 – Training Standards and Procedures for IT Employees

2.8.5 Data Audits

The audit plan will include drawing a statistically representative sample of the data at each CTP participating in a trial. The sample size will be approximately 7,000 fields per CTP. A larger portion of each sample will be audited early on in the trial. The remainder of the sample will be drawn at several time points throughout the rest of the trial. Spreading the audit effort over the life of each protocol provides critical information to NIDA, the CTPs and to the study teams helping to eliminate issues being perpetuated throughout the life of the trial resulting in time consuming and costly clean-up at the end.

Finally, discrepancies between the source and the database will be identified and resolved by the CTPs during the audit, and an error rate will be calculated for each CTP so that the CTP and study team can track the data quality.

2.9 Trial Implementation: Project Management

The study Executive Committee will prepare all necessary materials for starting enrollment at all participating sites. Because of the complexity of this task and the many people involved, it is recommended that the team use a project management tool to enter all the necessary tasks and track their completion.

Besides a final version of the protocol, there are many interconnected tasks that must be completed before a trial is ready for randomization. A few are listed here for reference. All of these items must be completed before the trial can open.

1. Operations Manual with detailed instructions to complete protocol procedures
2. Training for all staff on study procedures, data entry, human subject protection, etc.
3. Data Dictionaries and case report forms
4. Programmed database ready for data entry
5. Site Selection
6. Study Budget
7. Intervention Manuals
8. Regulatory Binder and regulatory documents (such as protocol signature page, IND/study contract documentation, certificate of confidentiality, etc.)
9. Drug accountability procedures
10. Safety procedures with clear instructions and flowchart
11. Site Management Plan
12. Other as necessary per protocol

The study team must ensure that each participating site performs the following activities:

1. IRB approvals
2. FWA documentation
3. Staff hiring
4. Staff received all necessary training
5. Ordering/receipt of study supplies, drugs, etc.
6. Regulatory binder completion
7. Obtain all appropriate staff licensures
8. Initiation visits by CCC
9. Other per protocol

2.10 Pre-Screening Data

The NIDA CCTN does not require collection of data for any purposes on people who are pre-screened for CTN projects. Participant pre-screening is defined as any activity performed prior to obtaining the participant's consent. Because of this, the CTN Data and Statistics Center (DSC) at the DCRI will not collect in their databases any such information. All Nodes and CTPs should be aware that any pre-screening conducted at a site is subject to the HHS human subject regulations 45 CFR 46 and also CFR 160, 162, and 164 (HIPAA). Sites should contact their local IRB for guidance.

2.11 PI Signature with EDC

In order to streamline operations at the sites, facilitate the development of CRFs, and assure compliance with regulatory requirements, the CTN has standardized the frequency of collecting the site Principal Investigator's signature for CTN trials. CTN trials will require collection of an electronic signature for a site Principal Investigator only once for each participant as the participants completes the trial.

Other signatures may be required. In cases where data are submitted by a clinician independent of the site (e.g. central reading of ECG), the responsible clinician's signature will be required on the data submitted. Data changes and responses to queries require a signature from a site representative, not necessarily the PI, for each data change.

2.12 Node Responsibilities

For each CTP participating in a CTN study, the Node is responsible for the following:

2.12.1 Training

Nodes are responsible for providing training to staff and for assuring that all appropriate members of the CTP team and RRTC are trained and competent to conduct study procedures.

2.12.2 Regulatory and human subjects

1. Nodes are responsible for ensuring CTN protocols are conducted in compliance with all federal, state, and local regulations.
2. Nodes are responsible for ensuring that each CTP engaged in research obtains and maintains a Federal Wide Assurance with OHRP prior to study start and through the life of the studies.
3. Nodes are responsible for obtaining pertinent IRB approvals of the protocol, informed consent, and recruitment procedures, prior to study start and through the life of the studies.
4. Regulatory records will be monitored and collected by the Clinical Coordinating Center (CCC) as needed. All site investigators are responsible for meeting the requirements set forth by ICH Good Clinical Practice and the NIH. Records of regulatory compliance and documentation for Regulatory records will be maintained at the CTP, and duplicates collected by the Clinical Coordinating Center (CCC) for CCTN.

2.12.3 Trial Site Management

1. The Node PI will appoint qualified site investigators and support team members and ensure the site staff is appropriate to conduct all the aspects of a study at each participating CTP. The Node PI takes ultimate responsibility for CTP performance in the studies.
2. The Node is responsible for the management of the site performance according to the protocol and appropriate regulatory bodies, and to report to the study executive committee. Site management of the trial includes (but not limited to) the following: maintaining site regulatory obligations; study participant documentation; identifying and resolving site problems prior to NIDA monitoring visits; assist with necessary training; assist with recruitment; retention and follow up activities; resolution of data queries.
3. The Node is responsible for participant safety, reporting to appropriate regulatory bodies, and reporting to the study executive committee.

2.13 Trial Initiation

The Site Investigator and Study Executive Committee are responsible for assuring site readiness and providing evidence of this to NIDA CCTN. They will prepare and distribute the criteria for site readiness to start the study (endorsement criteria). The CCC is responsible for providing a site initiation visit and report to NIDA CCTN, the site PI, and Lead Investigator which supports site readiness or identifies areas that prevent site readiness. The DSC is responsible for providing an electronic data capture (EDC) system ready for entry of study data and assuring training of site personnel in the EDC system. The NIDA CCTN CPC is responsible for evaluating sites and endorsing them to accrue participants in a study only after assuring that the site is ready, the EDC system is in production, and the CCC's initiation visit report identifies no outstanding criteria.

Once the staff at a participating CTP has completed all protocol and local required tasks, the Clinical Coordinating Center will schedule a site Initiation Visit.

After all endorsement criteria are met, the study team will notify the NIDA CCTN Protocol Coordinator (CPC) to obtain NIDA endorsement to start enrollment at the CTP.

2.14 Initiation for Non-Clinical Trials

Survey and other non-clinical trial studies may involve many CTPs, and could be candidates for exempt or expedited Institutional Review Board (IRB) review. These studies may not be subject to the same initiation requirements established for clinical trials.

The Study Executive Committee will establish the minimal CTP protocol initiation requirements that satisfy the needs of each particular study. This includes, but is not limited to, training of key study personnel, regulatory procedures and documentation, and verification that secure data collection procedures are in place. The study team will coordinate with the Coordinating Centers for implementing necessary procedures for initiation and endorsement.

2.15 Trial Management Responsibilities

The study EC is responsible for study management and oversight at all sites, while the Node is responsible for study management and oversight within the participating site. The study EC will

meet regularly with the participating sites to review study performance and discuss overall timeline, recruitment, retention, training needs, summary of site visits, data issues, participant safety, DSMB review, and other reports.

2.15.1 Coordinating Centers

1. Clinical Coordinating Center (CCC): The CCC is responsible for:
    a. Support and monitor regulatory functions and requirements
    b. Conduct site visits to monitor performance and meet CCTN regulatory responsibility for protocol monitoring
    c. Provide assistance with necessary trainings, in coordination with the study executive committee and the participating site staff
    d. Provide pharmaceutical & clinical supplies, laboratory services and clinical support
    e. Prepare reports as directed by NIDA CCTN
    f. Collecting, adjudicating and reporting, as required, all SAE reports for the study
    g. Prepare safety reports for the DSMB
2. Data and Statistical Center (DSC): The DSC is responsible for:
    a. Provide a system for data collection and will monitor data entry at each CTP
    b. Generating data queries and, along with CCC staff, monitor query response and resolution
    c. Report weekly data status on each trial to the CCTN, CTPs, Nodes and Study and the CCC
    d. Prepare monthly Trial Progress Reports that summarize information by trial and across trials. The Trial Progress Reports will be forwarded to the CCTN monthly. (The CCTN will distribute to the CTN Executive Committee and study LI)
    e. Prepare the DSMB reports, per DSMB requirements, and present the closed section of the report at the DSMB meetings

2.15.2 Sponsor

NIDA is ultimately responsible for:

1. Study performance, including reporting to the FDA on IND studies and the participating sites according to the regulations.
2. Appoint a DSMB and schedule regular meetings for the DSMB to review study performance.
3. Forward summaries of meetings to the Study EC.
4. Make final decisions regarding the scientific, administrative, budgetary, and operational management of the study, collaborating closely with the study EC and the Steering Committee.
5. Monitor clinical trials and to appoint appropriate entities to carry out this task.

As the sponsor of all studies conducted by the CTN, NIDA CCTN has transferred the regulatory responsibility of all study monitoring to the Clinical Coordinating Center (CCC). The Clinical Coordinating Center will follow their internal SOPs to meet the obligations set forth by the transfer of regulatory obligations and the CCC statement of work.

During the course of a clinical trial, monitoring is conducted to assure the rights and well being of participants are protected; the reported trial data are accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements. Other entities may provide review (i.e. local IRB, Node Staff) as part of their site management activities to assure site compliance with other requirements. This does not fulfill the sponsor's regulatory obligation.

NIDA appointed monitors will visit each site after the first two participants are enrolled and approximately every three months thereafter, depending on the rate of enrollment, study conduct problems, and other issues that may arise.

2.16 Protocol Document Maintenance

The most recent version of the protocol will be saved to LiveLink® in the appropriate folder in PDF format by the study team. The original protocol document, in Word format, will continue to be maintained by the study team. The Lead Investigator and the CCTN/designee must approve all changes. Any changes considered for the protocol must be executed by the Clinical Coordinating Center. Changes to a protocol are protocol amendments. A temporary change or one that impacts a single participant may be executed by use of a protocol waiver. All protocol waivers must be forwarded to the appropriate IRB(s). Following a protocol amendment, a new version of the protocol is released to incorporate the amendment's modifications. It will be saved to Livelink® as above, and forwarded to the participating sites for submission to the appropriate IRBs. See Appendix IV for more details.

2.17 Protocol Deviations and Violations

Unapproved departures made from the investigational plan or protocol can cover a wide range of actions (or inaction). In general, a protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. In contrast, protocol violations could do so. The Node PI, study LI and staff must take corrective actions and prevent recurrence.
Certain issues are not under the control of the research personnel and therefore will not be documented as protocol violations or deviations. These include participant non-compliance. Additionally, the site Principal Investigator or Sub-Investigator may deviate from the study protocol when medically indicated. These incidents should be recorded in the source documentation for the particular participant.

2.18 Protocol Waiver

Protocol waivers are used to obtain approval to deviate from the approved protocol prior to the actual event. Any change in the study procedures, which alters or conflicts with the currently approved protocol, will require an approved protocol waiver or an approved protocol amendment, prior to the implementation of the change.
See Appendix VIII for more information.

2.19 CTN Trial Progress Report

The Data and Statistics Center, with assistance from CTN's Clinical Coordinating Center, produces a Trial Progress Report monthly, which is posted on Livelink and available to the CTN community. The main purpose of this report is to provide a trial monitoring tool to study teams, NIDA's CCTN, DSMB, and CTN's Executive Committee. LI and study teams should review the accuracy of the information on their trials and provide comments to Dr. Li-Tzy Wu at the DSC, the CCTN Protocol Coordinator (CPC) for the trial and Dr. Paul Wakim at CCTN.
The Trial Progress Report includes three main parts:

1. Part I: Summary Report on Active Trials
2. Part II: Report on Each Active Trial (protocol-specific sections)
3. Part III: Summary Report on Both Closed and Active Trials (demographics)

The Report is available on the 24th of every month, covering up to the end of the previous month. For example, the February 24, 2006, report will contain information as of January 31, 2006.
Each month:

1. Study teams of active trials receive their protocol-specific section of the report.
2. CCTN forwards an abridged version of the full report to the CTN Executive Committee, highlighting issues for the EC to address.
3. The full report is posted on Livelink, and a notification is sent to the CTN community about the new posting, along with the URL link.

2.20 Protocol Close Out

The study Executive Committee (along with Coordinating Centers) will develop and distribute close out procedures to all participating sites. Close out procedures should include detailed steps for disposition of study supplies & medications, record retention & storage, and data lock. The CCC will provide a listing of all equipment and supplies with instructions for their disposition. The DSC will prepare the final data set after data lock. A copy of the data set will be forwarded to NIDA's repository. The DSC will prepare the data sharing data set and other data sets as necessary for ancillary studies.

Data lock must be completed no later than 4 months after study completion.

2.21 Record Retention and Storage

Each Node is responsible for storing the research records for the studies in which they participate. The RRTC will establish policies and procedures for the archiving of research records at study closure, in compliance with their state, local, institutional and IRB regulations and with the minimum standard for CTN protocols. In all CTN sponsored studies, study records must be maintained for three years (after data lock) or longer if specified by local institutions/agencies or FDA regulations. Clear, written documentation of record location should be forwarded to the study team and NIDA CCTN. The site PI noted in the 1572 and Investigator's Agreement must be notified of the disposition and retrieval process for site records.

Each Node must contact CCTN before records are destroyed.

3.0 PUBLICATIONS AND DISSEMINATION

3.1 Final Study Report

Study teams are required to submit a Final Study Report to NIDA CCTN after all data is collected, the data set is locked, and all closeout procedures are finalized. The Final Study Report is due within 120 days of data lock; please refer to Appendix V for guidance.

3.2 Data Sharing

The NIH expects and supports the timely release and sharing of final research data from NIH-supported studies for use by other researchers to expedite the translation of research results into knowledge, products and procedures to improve human health (see http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html).

Public data sets for CTN protocols will be de-identified and anonymyzed. The datasets will be available after (1) the primary paper has been accepted for publication, or (2) the data is locked for more than 18 months, whichever comes first.

In order to make the CTN data available to as wide an audience as possible, a Data Sharing link has been created on the CTN Homepage (http://www.nida.nih.gov/CTN/Index.htm). As studies are completed and their data become available, this site will be linked to that data.
The following will be posted per protocol:

1. Data set (SAS)
2. Data set (ASCII)
3. Annotated Case Report Forms,
4. Define file (aka data dictionary)
5. Study protocol. The Investigators can provide an abbreviated protocol for sharing purposes, attached with the final study report
6. Reference to study publication of primary outcome

3.3 Publications and Authorship (revised May 13, 2008)

3.3.1 Introduction

CTN investigators are required to present and publish findings of research in the scientific literature. The initial primary outcome paper should be completed and submitted to an appropriate peer reviewed scientific journal within 180 days of data lock of the protocol.
The Publications Committee (PC) will implement procedures to promote publications and ensure the scientific quality and timeliness of CTN publications. Investigators must submit presentations and publications, as defined in the procedures, to the PC for review prior to submission (according to the guidelines specified by the PC). The PC reports to the CTN Executive Committee, which has final authority for approval or disapproval of recommendations.

3.3.2 Protocol Publication Plan

The study team will submit a publications plan to the PC within six months after the study has been implemented at all sites. The publications plan will be updated at least quarterly once the study is completed and the data is locked.

NIH strongly encourages investigators to publish analysis of treatment outcomes for women and racial/ethnic groups. Many times sample sizes are small and analysis will not be statistically meaningful; however, a statement about the results is necessary.

CTN encourages that writing teams involve node investigators and CTP staff who participated in the study. The study team will promptly distribute the data set to all members of the writing teams proposed in the publication plan once the data is locked. All secondary papers listed in the plan should be submitted to appropriate journals within one year after submission of the primary outcome paper.

Study teams must remind all writers that, as stated in the CTN Data Sharing policy, data sets for CTN protocols will be available after (1) the primary paper has been accepted for publication, or (2) the data is locked for more than 18 months, whichever comes first.

Per NIH Policy http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html, investigators are required to submit to the NIH (NLM Pub Med - http://www.pubmedcentral.nih.gov/) an electronic version of the author's final manuscript upon acceptance for publication.

Ancillary studies: Manuscripts of publications from ancillary studies should be sent to the CTN Publications Committee for review and approval.

3.4 Collaboration between Lead Investigators and Participating CTPs

Bi-directionality is a cornerstone of the CTN research endeavor. To ensure the scientific credibility, relevance, and sustainability of treatments investigators and providers work together throughout the protocol concept, development, and implementation stages of CTN clinical trials. Lead Investigators and CTPs who participate in studies are full partners in the conduct of studies and therefore they have an equal stake in products produced. Protocol teams should ensure that the continuity of the bi-directional process is continued beyond the protocol development and implementation stages throughout the analysis, publication, and dissemination of clinical trials results. This continued collaboration is considered essential to appropriate interpretation of the CTN generated data and to maintaining the highest quality of investigator/provider partnerships.

The collaboration between CTPs and Lead Investigators continues throughout the life of a protocol from Concept development to dissemination of results. Each protocol is unique and the collaborative process is likely to differ from protocol to protocol; however, certain principles can be identified. The first addresses limitations on sharing data, which are required to protect study/data integrity. The second addresses the intention of a continued collaboration throughout the research concept development to dissemination of results continuum. The third addresses the sequencing of presentations of CTN Study Research Results.

Results of an analysis of baseline data may be released to CTPs & RRTCs prior to the conclusion of the trial. A formal interim analysis is performed prior to completion of a clinical trial to test for efficacy and/or futility with the intent to stop the trial before study completion if needed. When such an analysis is envisioned, a detailed description of the interim analysis needs to be

included a priori in the protocol, including information on the number of interim looks, the "statistical penalty", and other specifics.

Because conclusions based on this analysis may lead to continuation or discontinuation of a trial with data that are incomplete and preliminary, release of data from this analysis would represent a substantial risk of introducing bias in the outcome of the study or misinterpretation of the data. This may occur by setting up expectancies among treatment staff that might influence the way in which they provide services, or among research staff that might influence the way in which data are collected. Because of the risk of bias and misinterpretation, and the potential to compromise the credibility of inferences from the trial, release of data at this stage of the trial will only be to the Data and Safety Monitoring Board (DSMB).

How does sharing part of the results before study completion affect the design and data integrity of a study? First, the release of data prior to conclusion of the trial at all sites introduces the risk of bias, compromising the ongoing administration of the trial. For example, a site still actively involved in a trial may hear that the experimental treatment did not work well in the closed sites. The staff may then feel less inclined to recruit subjects and perform follow-up visits. Second, the release of "dirty" data introduces the risk of misinterpretation of study findings and false conclusions. Either of these events could undermine the goals of the CTN.

From a design, analysis, and data integrity perspective, the LI should not release any outcome data to any CTP until the trial is completed (including the follow-up phase), the data "cleaned", and the primary analysis completed. Early release of data prior to publication allows for accelerated feedback to CTPs without compromising the integrity of the data. Data should be protected by confidentiality agreements to avoid violation of embargos on prepublication release of data required by some journals.

Future CTN protocols could possibly utilize study designs that make it acceptable to release some findings prior to the conclusion of all study follow-ups. These issues relate to the design and analysis of clinical trials in general and not specifically to the sharing of data with participating CTPs and RRTCs. An example might be trials with very extended follow-up periods (years).

In trials where an analysis of data is planned for the purpose of dissemination of results prior to final lock down and cleaning of all data points, the LI should incorporate this plan into the protocol, describing the steps that will be taken to protect against bias in the final primary analysis, for advanced approval by the DSMB and NIDA.

There is understanding of the desire for the continuation of what appears to be a promising treatment at a CTP following the completion of a clinical trial but before release of the primary outcome results. It is generally not recommended in the scientific community. Decisions may be made to continue a treatment following the conclusion of a trial, based on the CTP's experience with the treatment, independent of design or analysis of the trial. If the intervention is or involves a medication or other test article, the study supply cannot be used.

Clinicians, administrators, and data collection staff who have participated in a trial have useful information for investigators about the feasibility and utility of conducting the intervention and about patient response. This information can be highly useful in interpreting data.

LIs should schedule planned debriefing meetings with CTP clinical and data collection staff shortly after completion of data collection at the CTP. If follow-ups will run quite a bit longer than intervention delivery, this might involve additional debriefing sessions, at the conclusion of intervention delivery and at the conclusion of data collection. The design of these debriefing sessions will differ depending on the design of the protocols, but should be included in study closeout planning.

Providers' feelings of being "dropped" at the conclusion of data collection will be lessened by developing standard mechanisms for informing participating nodes and CTPs of analysis progress, for example, "data from all sites are in, and data cleaning has been completed; the next steps will be…" Mechanisms for transferring such information may be with continued project calls, inclusion of such information in the regular CCTN update, or monthly written updates from the LI to participating nodes. Informing CTPs of data analysis progress will make the process more transparent and may lessen anxiety about what is happening with the data.

Bi-directionality in the CTN suggests an additional step in the pre-publication process, which, though it may lengthen the time to publication, will insure CTPs have a chance to comment on the accuracy of the methods, results, and conclusions from their points of view. A participating CTP comment period should be provided prior to Publications Subcommittee approval of the article for submission. This is not proposed as an opportunity for CTPs to veto any publication but as an opportunity for input. Inclusion of CTP members of the investigative team in authorship of publications is also strongly encouraged.

Release to the Steering Committee can also occur in a variety of formats, but directed at the larger CTN membership and occurring after the release to participating CTPs and RRTCs. Members of the CTN who are presented with results prior to presentation to audiences outside of the CTN are not permitted to present these results at meetings nor are they permitted to include them in publications.

3.5 Practice Guidelines on Release of Trial Data Prior to Data Lock (New, March 24 2008)

1. No post-randomization data will be released prior to data lock. Only pre-randomization data will be considered for release prior to data lock.

2. In general, pre-randomization raw data with no identifiers and no treatment assignment may be released prior to data lock.

3. If requested, pre-randomization raw data will be released only once in the course of the study, and only after all pre-randomization data have been collected, i.e. after all participants have been randomized.

4. The Data and Statistics Center (DSC) does not provide "soft lock" datasets and cannot certify "clean" data until final database lock when all outstanding queries are resolved and closed. Therefore, until that date there may be changes in the final pre-randomization data.

5. Publications based on early release of data should note that "the analyses are based on baseline data as of (*date*)". Publications based on final locked data should note that "the analyses are based on the final database locked on (*date*)".

As in all circumstances, the integrity of the main study will not be compromised. To that end, a document describing the specifics of the data release (what, when and how) should be signed by the data requester and representatives from the Lead Node of the main study, the DSC and the CCTN. The recipient of pre-randomization data obtained before data lock agrees:

1. To use the requested data solely in connection with the proposed research project, and to make another request if substantive changes are made to the proposed research project, or if additional uses of the received data are planned.

2. That the received data will not be used, either alone or in conjunction with any other information, in any effort whatsoever to establish the individual identities of any of the participants from whom the data were obtained.

3. To retain control over the received data, and not to transfer any portion of the received data, with or without charge, to any other entity or any individual.

4. That the proposed research project has been approved by the recipient's Institutional Review Board (IRB) operating under an Assurance approved by the Office of Human Research Protections (OHRP) and in accordance with Department of Health and Human Services regulations at 45 CFR Part 46.

5. To acknowledge the contribution of the Lead Investigator of the original main study in all oral and written presentations and publications resulting from analyses of the received data.

3.6 Public Access Policy (NEW, March 20, 2008)

Effective April 7, 2008 , NIH requires that all investigators funded by the NIH submit to the National Library of Medicine'™s PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication:. Please refer to Notice Number: NOT-OD-08-033 - http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html).

3.7 CTN Practice Guidelines on Release of Long-Term Follow-Up Data before the End of the Study (NEW, April 6, 2009)

These guidelines pertain to CTN studies that are extensions of CTN clinical trials. The goal of such an extension study is to follow up on the participants from the initial trial. In this document, it is assumed that the follow-up study does not involve new randomization or new treatment – only the collection of outcome-related data to extend the duration of a follow-up. It is also given that before any data from the follow-up study are released, the database of the initial trial is locked and the paper with primary results accepted for publication.

CTN's Data and Statistics Center will provide quarterly reports in table format to the Lead Investigator of the long-term follow-up study to allow monitoring of the study's progress. Because these reports are based on raw data that would not yet have gone through a quality assurance process, they are not suitable for public presentations or publication in professional journals.

If the Lead Investigator plans to make presentations and/or write journal articles before the completion of the follow-up study, then the Lead Investigator should:

1. Include in the protocol's statistical plan all analyses to be conducted during and at the end of the study; and,
2. Submit up front to NIDA's CCTN a written plan for presentation and/or publication that includes:
    - A justification as to why it is important to disseminate results prior to the end of the study
    - The time points at which the Lead Investigator would need interim data sets

Based on the submitted plan, CTN's Data and Statistics Center will provide CCTN with an estimate of the resources required to clean and prepare each interim data set.

This information will inform CCTN's decision regarding the release of interim data sets to the Lead Investigator. If data sets are released prior to the end of the long-term follow-up study, the data will be "cleaned" (but not finalized) before they are released. CTN's Data and Statistics Center will keep electronic copies of all interim data sets.

Presentations and/or publications which are based on interim data sets should include the following note: "This information is based on data as of [date of data cut-off]". Any final changes to the data will be noted in subsequent presentations and/or publications." Authors should also note in subsequent publications any discrepancies in the results with earlier publications that are due to subsequent corrections to the earlier data.

All draft publications should be sent to the CTN Publications Committee for review.

Example:
NIDA's CCTN agrees to provide data to the Lead Investigator half-way into a four-year long-term follow-up study. Right after the end of Year 2, CTN's Data and Statistics Center cleans the data for Years 1 & 2, produces an interim data set with the complete data from these first two years, and keeps a copy of that interim data set. At the end of the study, data from all years of the study undergo full quality assurance procedures and are locked as the final data set.
The published paper on Years 1 & 2 should note that the analysis is based on an interim data set that is not final. The article should also indicate the date when the interim data set was created.
After the paper on Years 1 & 2 is published, corrections are made to Year 1's data; and the mean for Year 1 changes from 14.2 (shown in the first publication) to 14.5 (based on the final data set). In such case, authors should note in the second publication that the mean for Year 1 has been corrected. Authors may add some explanation about the corrections that were made.

4.0 APPENDICES

4.1 Appendix I Glossary of Terms in CTN and Research & Tx in Drug Abuse

ADHD	Attention-Deficit/Hyperactivity Disorder
ADR	Adverse Drug Reactions
AE	Adverse Event
ASI	Addiction Severity Index
ATTC	Addiction Technology Transfer Center
BDI	Beck Depression Inventory
BSCS	Brief Substance Craving Scale
BSFT	Brief Strategic Family Therapy
BUP	Buprenorphine
BUP/NX	Buprenorphine/Naloxone
BSI	Brief Symptom Inventory
CAB	Common Assessment Battery
CBC	Complete Blood Count
CCC	Clinical Coordinating Center (NIDA contractor - EMMES)
CCTN	Center for the Clinical Trials Network
CIDI	Composite International Diagnostic Interview
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendment of 1988
CPC	CCTN Project Coordinator
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DB	Diversified Business Consulting Group (NIDA administrative and logistics contractor)
DCRI	Duke Clinical Research Institute (NIDA data and statistics contractor)
DHHS	Department of Health and Human Services
DM	Data Management
DMAS	Data Management and Analysis Subcommittee
DMC	Data Management Center
DSC	Data and Statistics Center (NIDA contractor – Duke Clinical Research Institute)
DSM-IV	Diagnostic & Statistical Manual of Mental Disorders-4th Edition
DSMB	Data and Safety Monitoring Board
EC	CTN Executive Committee
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRBS	HIV Risk Behavior Scale
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug

IRB	Institutional Review Board
LI	Lead Investigator (for a particular protocol)
MET	Motivational Enhancement Therapy
MET/MI	Motivational Enhancement Therapy/Motivational Interviewing
MI	Motivational Incentives
MIEDAR	Motivational Incentives for Enhanced Drug Abuse Recovery
MPA	Multiple Project Assurance
NC	Node Coordinator
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NODE	Combination of RRTC and CTPs:

ATS	Appalachian Tri-State Node
CA/AZ	California and Arizona Node
DV	Delaware Valley Node
FL	Florida Node
GL	Great Lakes Regional Node
LI	Long Island Node
MA	Mid Atlantic Node
NC	North Carolina Node
NE	New England Node
NNE	Northern New England Node
NY	New York Node
OR	Oregon Node
OV	Ohio Valley Node
PR	Pacific Regional Node
RM	Rocky Mountain Regional Node
SC	South Carolina Node
SW	Southwest Node
TX	Texas Node
WA	Washington Node

NPC	Node Protocol Coordinator
NRUC	Node Research Utilization Coordinator
NTC	Node Training Coordinator
NTP	Narcotic Treatment Program
NX	Naloxone
OHRP	Office for Human Research Protections (formerly known as OPRR)
OPRR	Office for Protection from Research Risks (currently known as OHRP)
ORI	Office of Research Integrity
PC	Publications Committee
PCC	Portfolio Coordinating Committee
PI	Principal Investigator (for a node, usually grantee who received award)
PO	Project Officer for a government grant or contract
PRB	Protocol Review Board
PSC	Publications Subcommittee

PTSD	Post Traumatic Stress Disorder
Q&A	Questions and Answers
QA	Quality Assurance
QC	Quality Control
RA	Research Assistant
RBS	Risk Behavior Survey (for HIV risk behaviors)
RDC	Research Development Committee
RFA	Request for Applications (call for grant applications by NIH)
RRTC	Regional Research and Training Center (university associated with award)
RUC	Research Utilization Committee (dissemination within the CTN)
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SAS	Statistical Analysis Software
SC	Steering Committee
SCID	Structured Clinical Interview for DSM-IV
SDSS	Substance Dependence Severity Scale
SF-36	Short Form 36 items (adapted from the Medical Outcomes Study)
SIP-R	Short Inventory of Problems – Revised
SOP	Standard Operating Procedure
V#	Version of protocol

4.2 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? [2]
- 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.

[2] 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

- 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.:
    - 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 http://www.ich.org/pdfICH/e2a.pdf E6: GCP: Consolidated Guideline http://www.ich.org/pdfICH/e6.pdf
6. NIMH Issues to Consider in Intervention Research with Persons at High Risk for Suicidality http://www.nimh.nih.gov/research/highrisksuicide.cfm
7. Jenison, Christopher, Turnbull, Bruce W. (1990). Statistical Approaches to Interim Monitoring of Medical Trials: A review and Commentary. *Statistical Science*, **5**, No.3, 299-317.
8. Friedman, L.M., Furberg, C.D., and DeMets, D.L. (1998). *Fundamentals of Clinical trials, Third Edition.* New York, Springer-Verlag.

4.3 Appendix III Data and Safety Monitoring Board (DSMB) Procedures (Revised March 20, 2008)

The NIH (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) requires the establishment of data and safety monitoring boards for multi-site clinical trials involving interventions that entail potential risk to the participants. In accordance with NIH requirements, NIDA's Center for the CTN (CCTN) will convene DSMBs to provide independent oversight of trials conducted within the CTN. The Director of the CCTN appoints DSMB members for each study. The DSMB monitoring function is in addition to the oversight traditionally provided by IRBs.

The study team is responsible for developing a protocol and a DSMP. The DSMB is charged with (1) reviewing the research protocol and DSMP and (2) monitoring the trial and its ancillary studies on a regular basis.

The CCTN will appoint a DSMB Executive Administrator who will serve as a liaison between the DSMB and other parties (CCTN staff, CTN Coordinating Centers, study teams, CTN Steering Committee, etc.).

Members

DSMB Members will not be associated with CTN trials, will not have conflicts of interests or financial stakes in the research outcome, and will be required to abide by specific written conflict of interest and confidentiality agreements.

DSMB members will be experts in scientific disciplines relevant to the studies conducted within the CTN, such as the medical management and treatment of drug addiction using both pharmacologic and non-pharmacologic interventions, the conduct of clinical trials for addiction disorders, clinical pharmacology and toxicology, including neuropsychopharmacology, statistical analysis of clinical trial data, clinical trial methodology, and clinical trial ethics and human subjects protection.

The DSMB will consist of at least 5 members. The Director of the CCTN will appoint members for a term of 3 years (or for the duration of the study). For trials involving pharmacotherapy, at least 2 members of the Board will be physicians. The Board or CCTN may request the appointment of additional members who can provide the Board with additional expertise required for the effective monitoring of specific trials.

A Chairperson will be selected prior to the first meeting. While the Chair will lead all meetings of the DSMB, the CCTN DSMB Executive Administrator will mainly develop and execute all logistic activities associated with the DSMB including 1) oversight and coordination of all meetings and communications; 2) development of the agenda; 3) identification and review of substantive materials; and 4) production of meeting minutes and reports. In addition, the Executive Administrator ensures that the DSMB complies with all NIH and PHS policies and procedures concerning DSMB activities.

Conflict of Interest

The independence of the DSMB is essential to its mission of protecting subject safety and ensuring study integrity. Members of the DSMB are appointed by, and report to, the Director of the CCTN at NIDA. Members should be completely independent of the trial investigators and should have no financial, scientific, or other conflict of interest with the trial as described in the NIH Grants Policy Statement, Part II, section 12, and in the Combined Federal Register announcement - 45CFR94. Written documentation attesting to absence of conflict of interest is required; potential conflicts that develop during a member's tenure on the board must be disclosed to NIDA in a timely fashion.

Recipients of active CTN grants or contracts and members of any organization directly affiliated with the CTN will not be eligible to serve on the DSMB. Real and perceived conflicts could arise in connection with individuals and organizations who a) are involved in carrying out the study; b) whose products or services will be used or tested in the study; or c) whose products or services would be affected in a significant way by the study outcome.

In addition, members of the Board who are currently receiving or who have received grants, contracts, consulting fees or other financial support from companies (or individuals) for the evaluation of treatments for drug addiction or dependence will be asked to disclose the nature of their financial arrangements. If NIDA determines that the member has a conflict (real or perceived), the individual will be asked to resign from the DSMB.

Confidentiality

All materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in board meetings are expected to maintain confidentiality. Each member of the DSMB, including nonvoting members, must sign a statement of confidentiality confirming their agreement not to disclose data they are asked to review.

Responsibilities

At periodic intervals during the course of the trial, the DSMB responsibilities are to:

1. Review the research protocol, informed consent documents, and plans for data and safety monitoring;
2. Evaluate the progress of intervention trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site(s), and other factors that can affect study outcome;
3. Consider factors external to the study when relevant, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
4. Protect the safety of the study participants;
5. Report on the safety and scientific progress of the trial;
6. Make recommendations to the investigators, CCTN, and, if required, to the FDA concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;

7. If appropriate, conduct interim analysis of efficacy in accordance with stopping rules that are clearly defined in advance of data analysis. In most cases, these stopping rules are proposed by the PI and approved by the DSMB with modification as necessary to ensure patient safety.
8. Ensure the confidentiality of the trial data and the results of monitoring; and
9. Assist CCTN by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

Meetings

The DSMB will meet initially to review the protocol and the DSMP and, at a minimum, have one meeting via conference call and one face-to-face meeting every year.
At any time, the CCTN may request an urgent meeting with DSMB members, either by telephone or face-to-face, to address any significant safety concerns or trial performance concerns that arise during the implementation of a protocol.

The DSMB Executive Administrator will communicate with study teams and appropriate staff regarding meeting dates, timelines and documents required for each meeting.

Initial protocol review meeting: At the initial review meeting, DSMB members will critically review and discuss all aspects of the protocol and the DSMP and will establish guidelines for monitoring the study. Protocols will be reviewed carefully to ensure that investigators will implement appropriate procedures for data and safety monitoring. Materials for the DSMB meetings are required 30 calendar days prior to the meeting. Members will use the form attached in Appendix III A "Protocol Review Guide" to facilitate the review.

Ongoing DSMB monitoring meeting: For ongoing trials, the DSMB will monitor trial performance to ensure that the trial is carried out in accordance with the protocol, that data are reliable, that the scientific goals of the trial will be met, and that participant safety is appropriately protected. The DSMB will review adverse events and outcome data to determine if any study procedures should be altered or discontinued based on indications of clinical benefit or harm to participants attributable to the interventions under evaluation or other aspects of study participation. The DSMB may also recommend early trial termination on the basis of overwhelming efficacy or futility, when such trends are seen in a formal interim analysis of the accumulating data. Interim analyses will be performed according to terms specified *a priori* in the study protocol. The CCTN Data and Statistical Center, along with the Clinical Coordinating Center, will prepare the written report for the meetings and will submit to DSMB 2-4 weeks prior to the meeting.

The DSMB meeting format will consist of (1) open sessions where general information will be discussed. These sessions are open to all individuals who contribute to the study, including the study team; (2) closed session where outcome data are discussed; only members of the Board, Coordinating Centers staff and the DSMB Executive Administrator will attend this session (other CCTN staff may attend when appropriate); (3) if necessary, an executive session attended only by DSMB members and the Executive Administrator; and (4) meeting summary session. At each meeting, the DSMB will determine who should attend this meeting summary session (members of the study team, NIDA CCTN, Coordinating Centers staff, etc.) to receive

recommendations and future action items. Should the Board recommend termination of the trial, a full vote of the Board will be required. In the event of a split vote, a majority vote will rule and a minority report should be appended.

There may be other issues that develop during the course of a trial which lead the DSMB to recommend specific actions, such as suspending a site for its inability to recruit subjects or for continuing poor performance. These issues will be addressed, as they occur, as part of the oversight monitoring role of the DSMB.

After each meeting, DSMB comments and recommendations will be communicated to the study team as required by the NIH "Guidance On Reporting Adverse Events To Institutional Review Boards For NIH-Supported Multimember Clinical Trials" of June 11, 1999. The initial summary report will indicate DSMB recommendations regarding the protocol and DSMP. Subsequent study progress reports will document that a review of data and outcomes across all sites took place on a given date, and provide a summary of the Board's review of the cumulative adverse events reported from all participating sites. It will also provide the Board's conclusion with respect to study progress or the need for modification of the protocol or early termination of the trial. The study team is required to distribute the summary report to all principal investigators (PIs) involved in the study. The PIs in turn submit the report to their local IRBs in accordance with local requirements.

Oversight of DSMB

The DSMB is responsible to the Director of the CCTN for the effective performance of its mission. In fulfilling its mission to ensure the safety and integrity of CTN trials, it is essential that the DSMB function in a manner that exhibits a high degree of competence. The DSMB should function independently of other components of the CTN and of the career and financial interests of its members.

If the Director of the CCTN determines that the functioning of the DSMB is inadequate, s/he will bring the issues to the NIDA Director for discussion and resolution.

Protocol Review Guide

Protocol Number and Title

I. Protocol Review

Research Question (not limited to)

- Importance of research question/ hypothesis
- Background information/preliminary data

Design of the Study (not limited to)

- **Patient eligibility**
- **Intervention and control**
- **Outcome measures**
- **Appropriateness of measures/assessments and participant's burden**
- **Study duration (both active treatment and follow up phases)**
- **Sample size**
- **Randomization**
- **Recruitment plan**
- **Plan for inclusion/perform valid analysis of women and minorities**
- **Other relevant design issues**

Statistical Analysis Plan

Feasibility for Implementation - including, but not limited to:

- **Access to population**
- **Research infrastructure**
- **Leadership Plan**
  - **Lead Investigator credentials**

II. DSM Plan Review

(Is the plan adequate?)

- Safety Monitoring
- Trial Performance Monitoring
- Efficacy Monitoring

III. Questions to the Investigator (If Any)

IV. Other issues that need to be addressed/discussed

Appendix III A

4.4 Appendix IV Protocol Maintenance

Research protocols in the CTN are developed in a collaborative team process. This team is called the Protocol Executive Team and consists of the Lead Node Team, Lead Investigator(s), NIDA CCTN CPC, and representatives from the Data and Statistical Center (DSC) and the Clinical Coordinating Center (CCC). This team continues to guide and manage the protocol throughout its existence.

Once a concept is approved for development by NIDA CCTN, it is given to a Protocol Executive team for development and implementation. After development, an assigned Data and Safety Monitoring Board (DSMB) and the CTN Executive Committee approve it prior to implementation. Once implemented, most protocols require at least one amendment before the study is completed. The Protocol Executive Team will appoint an individual entity (usually the CCC) to act as the administrative office for the protocol and to manage all changes to the protocol.

This document outlines the procedures for protocol maintenance, amendments, administrative changes, and protocol waivers.

Protocol Maintenance

Once a protocol has been approved by the DSMB and CTN EC the protocol should be considered complete. It is then distributed to sites for submission to the local IRB. The disseminated protocol must be saved to Livelink® in the appropriate folder in PDF format by the study team. The original protocol document, in Word format, will continue to be maintained by this same party. Any changes considered for the protocol must be executed by this office. The Lead Investigator and the CCTN/designee must approve all changes. The CCTN may require review and approval of the protocol by the DSMB prior to implementing changes. Changes to a protocol are protocol amendments. A temporary change or one that impacts a single participant may be executed by use of a protocol waiver. All protocol waivers must be forwarded to the participating sites for submission to the appropriate IRB(s). Following a protocol amendment, a new version of the protocol incorporating the amendment modifications is released. It will be saved to Livelink® as above, and submitted to all IRBs.

Protocol Amendments

A protocol amendment is a written description of a change(s) to or formal clarification of a protocol. Changes may affect participant safety, the scope of the investigation, or the scientific quality of the study. The protocol amendment is used to revise the protocol procedures or policies of the study once the study has received initial approval by the IRB (and FDA, OHRP where applicable). All amendments must be approved by the NIDA CCTN and all appropriate IRB(s) prior to implementation. Impact of protocol changes on the EDC must be considered. The timing of implementation of the amendment must coincide with the release of the corresponding version release of the EDC.

All protocol amendments must be submitted to the IRB at the Lead node and the IRBs of all CTPs serving as study sites. The appropriate IRB(s) must approve change(s) in writing before any changes are made to study procedures or parameters, unless participant safety is at risk.

Administrative changes that do not affect participant safety or data integrity will be handled with an administrative change until the next protocol amendment is released. This process is described in section below.

To reduce the number of protocol amendments and other submissions to IRBs for a specific protocol, changes that do not require immediate action should be collected and batched for submission as one protocol amendment. A schedule for regular version changes will be set by the Study Executive, and managed by the protocol administrative office. All changes to a protocol, including administrative changes, must be approved by the appropriate IRB(s) prior to implementation. The process for developing and releasing protocol amendments is as follows:

- All requests for protocol amendment should be sent to the LI and CPC for review and approval (please review policy on protocol changes).
- The LI will forward approved changes to the protocol administrative office.
- At least every 6 months the protocol team will review all amendment requests. If a protocol amendment is required to implement any of these changes, they will be grouped together into one protocol amendment document and distributed for IRB submission. If no changes have been made or the changes do not require action during the upcoming 6-month period, then no protocol amendment will be distributed.
- The protocol administrative office will develop a version of the protocol with track changes, a clean copy of the amended protocol, and, when appropriate, a change table indicating significant changes to the protocol.
- Protocol amendments will be released when an immediate change to the protocol is required, or when a significant number of small changes have been made and the protocol team determines that an amendment is necessary, but at intervals not to exceed 6 months, unless no changes are made.
- The full protocol team, including the lead investigator, protocol executive committee/lead node team, the DSC, CCC, and NIDA CCTN CPC must agree upon the protocol amendment.
- All protocol amendments will be submitted to the DSMB at the discretion of the NIDA CCTN representative.
- Protocol amendments will be distributed to the CTPs with a numbered memo (see section 5.0 below) indicating the new protocol version number and date and that this new version replaces all preceding versions.
- Sites are responsible for submitting the protocol amendment to their IRB upon receipt, and receiving IRB approval prior to the implementation of any change.

Administrative Changes

Administrative changes include those that affect all sites, are sponsor approved, and include changes that do not affect participant safety or data integrity. These changes do not generally require IRB or FDA filing/approval (i.e. typographical errors). Administrative changes will be communicated by protocol clarification memos, sent in numbered format to the protocol teams and will be included in the next amendment.

A protocol clarification memo will be used to revise a protocol procedure or policy at all CTPs participating in the study. The memo will be drafted by the protocol team and approved by the Lead Investigator, any co-investigators, the NIDA CCTN CPC, and the DSC and CCC representatives. To ensure that one office is tracking all changes and memorandum for the protocol, the protocol administrative office will facilitate the process. The protocol administrative office will develop the administrative change memo, including the sequential numbering system, and provide it to the Lead Investigator for final approval and signature. The memo will be distributed by the protocol administrative office.

Protocol Waivers

A protocol waiver will be used to make a single change in a single participant at a specific location or a temporary change at all sites to safeguard the health or safety of a participant. A protocol change that would affect all of the participating sites should be submitted to the IRB and will be followed by a protocol amendment.

Protocol waivers are used to obtain approval to deviate from the approved protocol prior to the actual event. Any change in the study procedures, which alters or conflicts with the currently approved protocol, will require an approved protocol waiver or an approved protocol amendment, prior to the implementation of the change. Changes made after execution will be considered a protocol deviation or violation. A protocol waiver is not required if the change is a clarification of the protocol that does not alter or conflict with the current protocol, but rather operationalizes or further defines elements in the protocol. If the change affects more than one site, an amendment should be made to the protocol.

Protocol waivers may only be granted once the protocol has begun enrolling participants. To request a waiver, the CTP PI should complete the attached form and submit it to the protocol Lead Investigator and the NIDA CCTN CPC for approval. Lead Investigators and the protocol executive committee must carefully consider whether the change alters or conflicts with the protocol or whether it simply clarifies or operationalizes an existing protocol policy or procedure. If the change will potentially affect multiple participants and/or multiple CTPs the protocol team must also amend the protocol at the next available time to implement the change completely.

If the site is frequently outside the limits of the protocol, either by waiver request or protocol violation, the Protocol Executive Team must make a decision regarding the ability of the CTP to continue to participate in the trial, or the need for revisions to the protocol.

The protocol waiver will be documented on the attached NIDA Protocol Waiver Request (Appendix IV A). Only upon signature of the NIDA CCTN Representative or Designee is the waiver fully approved. Without the fully approved form, the change in protocol procedures will be considered a protocol deviation/violation. Sites must keep the application for or fully approved NIDA CCTN Protocol Waiver Request forms in their regulatory binder. Sites should consult their local IRB regarding reporting requirements for the protocol change made in the waiver.

Communication-Distribution of Amendments and Change Memos

It is critical that any and all changes to a protocol are immediately and clearly communicated to all members of the protocol team, including sites collecting data from participants, the coordinating centers, study monitors, and the study sponsor.
To facilitate consistent communications and protocol understanding, the following procedures will be used to release information about protocol amendments and clarifications within the CTN.

Numbered Memorandum

To facilitate the tracking of all "significant communications", as required by regulatory and GCP standards, a numbered memorandum format will be used for the release of all protocol amendments and clarifications/ administrative changes. The protocol administrative office will provide all of the numbered memoranda for that protocol. Each memorandum should be released on letterhead and numbered sequentially, starting with #001. The numbering should contain all of the following information in a similar format:
MEMORANDUM NIDA CTN-XXXX (protocol number) - #YYY (memo number)
For example, the following would be used to release the first numbered memo for protocol 0033.
MEMORANDUM NIDA CTN-0033 - #001

Distribution List:

All protocol clarification memoranda and amendments must be distributed to the following groups/individuals:

- Lead Investigator(s)
- Protocol Executive Committee members
- NIDA CCTN CPC
- CCC Representative
- DSC Representative
- NIDA CCTN Regulatory Office
- CTP Principal Investigators participating in the protocol
- Node Principal Investigators of CTPs participating in the protocol

4.4.1 Appendix IV-A NIDA CTN Protocol Waiver Request

Protocol #:	
Lead Investigator:	
Protocol PI:	
Node Name:	
CTP Name:	
Date of Request:	

Description of Waiver Request:

Rationale for Waiver Request:

Requested by: _____ _____
Signature/Title Date

☐ Approved ☐ Disapproved
☐ Conditions/Revisions Apply (specify):

_____ _____
Signature of LI or Designee Date

☐ Approved ☐ Disapproved
☐ Conditions/Revisions Apply (specify):

_____ _____
Signature NIDA CCTN Representative/Designee Date
Copy of completed form to be sent to the DSC and the CCC

4.5 Appendix V Guidance of Final Study Report Preparation (as amended March 6, 2008)

Introduction and Purpose

Lead investigators submit a *Final Study Report* for presentation to the DSMB and NIDA after all data are collected, the data set is locked, and all closeout procedures are finalized. When all authors sign the *Final Study Report*, and all the DSMB's queries are resolved the study protocol is concluded. The *Final Study Report* will become part of the NIH official file. The *Final Study Report* should be submitted for DSMB review within approximately 120 days of data lock.

This *Guidance* lists the information that is to be included in a *Final Study Report.* The *Final Study Report* will focus on the data collected in the study, utilizing the planned analysis described in the protocol to address the primary endpoint(s). Consultation with CCTN staff prior to preparation of the report is encouraged. While the data tables may generate additional length, it is expected that the text portion of the *Final Study Report* will be approximately 20 pages. The following nine sections must be included.

1. Descriptive Information

- CTN number and CTN title of the protocol. Version number and date of the last protocol
- The name, node, and mailing address of the lead investigator and each co-investigator
- The specific community treatment programs where the study was performed
- Dates for enrollment of the first participant and final evaluations of the last participant
- Date of the *Final Study Report*
- Brief executive summary of the goals and results presented

2. Rationale and aims of the study

- Include critical references
- Include sufficient detail to allow an understanding of the study

3. Clinical trial design

- Overall design including entry criteria, randomization/masking schema, study schedule, clinical and behavioral assessments, outcome measures, target population, inclusion/exclusion criteria

4. Statistical Analysis

- A summary and analysis of the data per the original protocol and a statement of the conclusions drawn from this analyses
- Analyses of study results by sex/gender and race/ethnicity per NIH Policies
- Results from any interim analysis, and any modifications made

5. Summary of results (some information may be presented as tables in the appendix.

- Number of participants with a breakdown of the baseline demographic (age, race, gender, ethnicity) and clinical characteristics of each group assignment

- If applicable, early termination discussion including reasons for early termination and numbers of participants
- Number of participants excluded, and the reasons for exclusion
- Changes in the conduct of the study, if any
- Protocol violations or waivers
- Problems encountered during the trial
- Brief discussion on the implications of the findings (for scientific community, CTP future implementation).

6. Safety monitoring

- Summary of Data Safety Monitoring Plan
- Overall adverse events and adverse reaction data (May use DSMB formats and table shells)
- Summary of all adverse events (May use DSMB formats and table shells)
- Narrative for each Serious Adverse Event
- Key DSMB decisions

7. Plans for archiving and storing the study records and data.

8. Authorship. The authors of the *Final Study Report* should sign and date the report and include in the report a brief statement describing their contributions to the report. Authors of the report should be aware that CCTN views these signatures as an affirmation that all statements are accurate and are complete representations of study activities and results and are fully supported by the data.

9. References

Appendices

1. Statistical tables plus clinical trial results' listings, detailed and summarized
2. Final protocol and summary of protocol amendments since the start of the study
3. Final sample consent form

Any addition, deletion, or correction to the *Final Study Report* should be in the form of an amendment by the authors. The amendment should identify each part of the *Final Study Report* that is being added, deleted, or corrected and the reason(s) for the addition, deletion, or correction, and should be signed and dated by the authors

Adapted from:

- Altman, Douglas G. *et al*. 2001. "The revised CONSORT statement for reporting randomized trials: Explanation and elaboration" *Annals of Internal Medicine* 134(8): 663-694.
- http://www.fda.gov/cvm/guidance/cigfinal.pdf
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, "Structure and Content of Clinical Study Reports" Step 4, 30 November 1995. Published in the *Federal Register* on July 17, 1996 (61 FR 37320).
- Spilker, Bert. 1991. *Guide to Clinical Trials.* New York: Raven Press.

References:

Altman et al., 2001, page 665: Table 2: Checklist of items to include when reporting a randomized trial

International Conference on Harmonization. 1996. "Guidance for Industry E6: Good Clinical Practice Consolidated Guidance." (*Federal Register* Vol. 62, No. 90, May 9, 1997, pp. 25691-25709).

Krzyzanowska MK, Pintilie M, Tannock IF. 2003. "Factors associated with failure to publish large randomized trials presented at an oncology meeting" *JAMA: Journal of the American Medical Association* 290 (4): 495-501 July 23, 2003.

Misakian AL, Bero LA. 1998. "Publication bias and research on passive smoking - Comparison of published and unpublished studies" *JAMA: Journal of the American Medical Association* 280 (3): 250-253 July 15, 1998.

Moher, David et al; The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials; *Lancet*, Volume 357, Issue 9263, 14 April 2001, Pages 1191-1194

4.6 Appendix VI Protocol Template

Title Page:

TITLE
NATIONAL INSTITUTE ON DRUG ABUSE
CLINICAL TRIALS NETWORK
NIDA-CTN-*0000* Version *00 (DATE)*

Lead Investigator (LI):

Co-LI:

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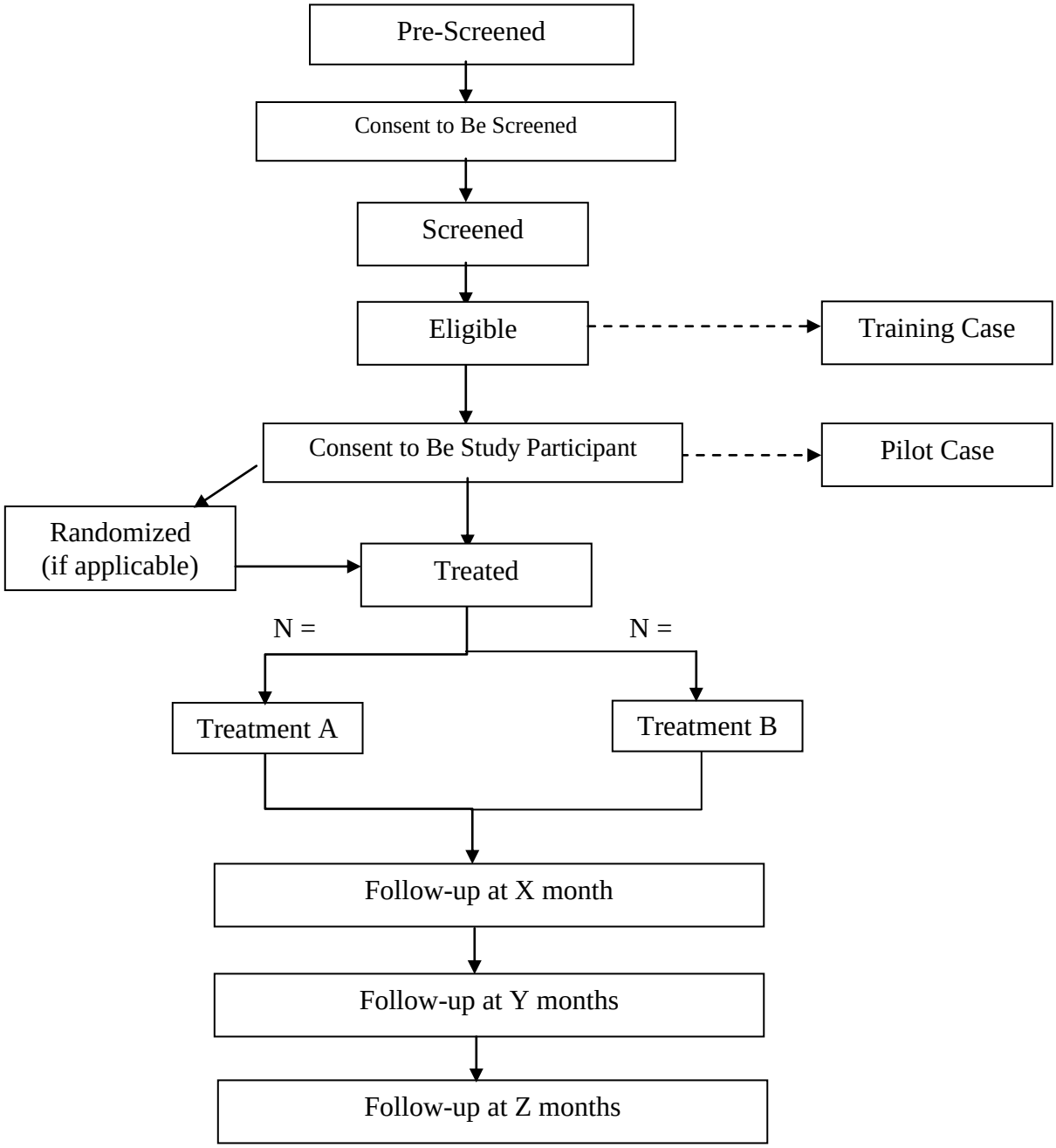
4.6.1 Appendix VI -A Synopsis or Schema (Sample)



4.6.2 Appendix VI-B Time and Event table

Activity	Screening/ Baseline		Treatment A	Treatment B	Follow up X month (± 7 days)	Follow up X months (± 7 days)	Follow up X months (± 7 days)	Follow up
Study Day								
Dosing								
Group 1								
Group 2								
Screening								
Informed Consent								
Audiotape Consent								
Study Eligibility								
Randomization								
Demographics								
DSM-IV Checklist								
Psychiatric Eval								
Medical History								
Prior Medications								
HIV Risk (HBRS)								
Hepatitis Serology								
Safety Assessments								
Physical Exam								
Hematology								
Routine Urinalysis								
12-Lead ECG								
Pregnancy Test								
Adverse Events								
Concomitant Meds								
Efficacy								
Treatment Tracking								
TLFB								
COWS								
ARSW								
ASI Lite								
SF-36								
VAS								
SSR								
CSQ								
Urine Drug Screen								
Ancillary Meds								
Protocol								
Other Assessments								
CIDI								
Participant Satisfac.								
Locator								

RANDOMIZATION

4.7 Appendix VII Adverse Event Reporting

Existing Adverse Event (AE) reporting regulations and guidelines have been developed largely in the context of medication trials. Trials of behavioral interventions, although seemingly low-risk, can pose safety concerns nonetheless. Most regulations do not provide guidance specific to behavioral trials. For CTN trials, there will be a standard template for AE monitoring and reporting. Study teams can develop customized monitoring and reporting plans specific to the study intervention and/or subject population, commensurate with the risks associated with the population/intervention. This means that the plan could exclude certain events, or include additional ones based on the study. The plan should describe the processes and oversight that are in place to assure that AE assessment and reporting requirements are actually met. For multi-center trials, the plan should identify a central reporting entity and outline procedures by which this entity will collect and report AEs to all necessary destinations, including co-investigators at participating institutions.

Adverse events can be elicited via open-ended questions to subjects, query of specific adverse events (i.e. provided in a pre-specified checklist), subject diaries and/or by spontaneous reporting from the subject, the subject's family or staff. The collection of clinical safety information must be harmonized across all sites. The approach for eliciting and collecting adverse event data needs to be detailed in the DSMP with clear instructions on when to start the process (such as any event after initial consent and baseline assessments, or limited to any event after randomization, or any event after first intervention, etc.)

Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (FDA Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting http://www.fda.gov/cder/guidance/iche2a.pdf)
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A pre-existing condition would not be considered an adverse event unless there was an increase in the baseline severity temporally associated with the intervention.

For CTN trials, this definition is expanded to include behavioral interventions, and the events may be medical or non-medical. Non-medical events may include behavioral events (e.g., violence) and/or social events (e.g., arrest, imprisonment). Based on the intervention and the study population, the study team should describe potential risks stemming from the study, as well as the adverse events that can be expected or are likely to be observed in this study population (which could be excluded from reporting, based on the study risks). Furthermore, it is important to document baseline signs and symptoms and their severity for each study subject in order to distinguish what was pre-existing before trial intervention.

Serious Adverse Event (SAE)

The FDA has defined an SAE as any untoward medical occurrence that:

- Results in death

- Is life-threatening (patient was at risk of death at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Furthermore, important medical events that may not result in death, be life-threatening, or require hospitalization may still be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Note that for CTN trials, psychological events are viewed as being relevant as well.

The DSMP additionally, given the nature of the intervention being studied and the condition under study (specific to the study population), may stipulate other AEs (e.g., behavioral/social events) that may not fit the above criteria, but would still be considered serious for the particular study. For example, in a behavioral trial, all suicidal events may be considered SAEs even when the events are not immediately life-threatening and do not result in death or require hospitalization, intervention, etc.

Unexpected Adverse Event
Any adverse experience, the specificity or severity of which is not consistent with the risk information described in the protocol or consent documents.
Unlike medication trials where an investigator's brochure is provided, clinical trials of behavioral interventions may be unlikely to issue an investigator brochure wherein the risks and benefits of the intervention are listed. Nonetheless, for CTN trials, the DSMP should provide at minimum a description of the behavioral intervention, and the adverse events that could be anticipated (e.g. emotional distress from a discussion of HIV risk) or are likely to be seen in the study population.

Severity of AE
Severity is an indication of the intensity of a specific event, as in mild, moderate, or severe chest pain. The term "severe" is *not* the same as "serious," which is based on patient/event *outcome or action criteria* (usually associated with events that pose a threat to a patient's life or functioning). Thus the term "severe" does not convey medical significance. It is important to note the severity of subject reported symptoms and other captured data both at baseline and during the trial in order to monitor their progression. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Severity Grading
One example of a severity grading scale is shown below:

- Mild: Awareness of symptom but easily tolerated; no limitation in usual activity; no intervention required
- Moderate: Discomfort resulting in limitation of usual activity; some intervention required
- Severe: Incapacitation resulting in an inability to perform usual activity; medical intervention required

Causality: Relation to Intervention

An AE is determined to be "related" to the intervention when there is a reasonable possibility that the product or intervention is etiologically related to the adverse event. A causality assessment includes, for example, assessment of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, plausibility, etc. Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Reporting
The monitoring plan should specify the process for reporting adverse events among responsible parties in the study including the study medical monitor, the NIDA medical monitor, and regulatory bodies such as the IRB, and, if appropriate, the FDA. Studies conducted under an IND must comply with the reporting requirements set out by the FDA. The NIH issued guidance in June 1999 regarding the reporting of adverse events to IRBs for multi-center trials. Investigators are responsible for being knowledgeable about the policies of the local IRB and adhering to these policies. An investigator is also responsible for the accurate documentation, investigation, and follow-up of all possible study-related adverse events.
http://grants2.nih.gov/grants/guide/notice-files/not99-107.html

Expedited Reporting
Federal Regulations for IND studies require that the sponsor notify the FDA and all participating PIs of any unexpected SAE associated with the use of the drug (per FDA definitions) within 15 calendar days. When these unexpected and related SAEs are fatal or life-threatening, they must be reported to the FDA, via telephone, fax, or in writing, as soon as possible, but in all cases within seven calendar days. When NIDA holds the IND for CTN studies, initial notification of SAEs must be submitted to NIDA within 24 hours followed by full reports within five working days, so that NIDA can comply with FDA reporting timelines. All available photocopies of any relevant information, including physical examination(s) and laboratory results, should be attached to the SAE summary report. Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above. Follow-up information should be obtained and an amended safety report should be submitted as soon as the relevant information is available.

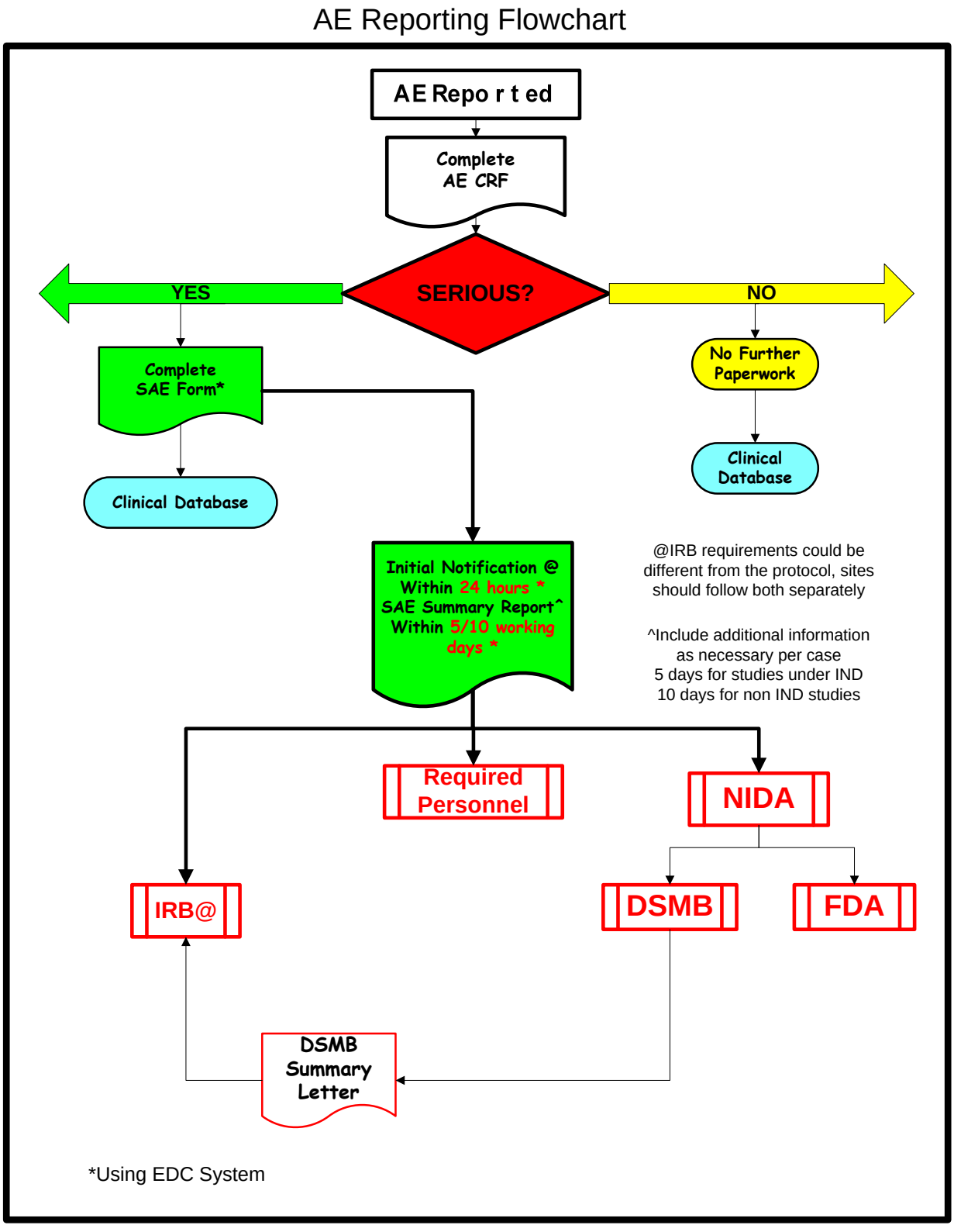
All SAEs must be reported, however the plan could indicate how SAEs will be reported (expedited or not). For expedited SAE reporting: all SAEs are to be reported to NIDA within 24 hours of knowledge of the SAE, to be followed by full reports within ten working days for non-IND studies. Each protocol can also stipulate which SAEs are to be exempt from expedited reporting, along with the rationale for this decision. For example, pre-scheduled elective surgery could be listed as being exempt from expedited reporting. Serious but unrelated events could also be listed as being exempt from expedited reporting. All SAEs exempted from expedited reporting would still need to be documented and submitted to all reporting entities, such as the study team, IRBs, and NIDA, in a timely manner,. The plan should indicate details regarding the preparation of these regular timely reports for SAEs that are exempt from expedited reporting.

A sample flowchart for the monitoring and reporting of adverse events for CTN trials can be found at the end of this Appendix. At various decision-making points in the flowchart, there is provision for the study team to determine what is important and relevant to their study, with regard to the documentation of AEs or SAEs, which AEs/SAEs require further emphasis and attention, and which AEs/SAEs may be exempt from collection and/or expedited reporting. For example, if the study team makes a determination that most of the adverse events reported in a behavioral trial are not relevant to the assessment of risk between treatment groups, then they would forego the documentation of these adverse events, or distinguish that certain adverse events are of particular concern and specify that these will be collected (e.g. episodes of violence, suicidal ideation). As necessary, there can be an AE Log (a source document) that would serve as a worksheet to document adverse events and to enable the Research Assistant (RA) or other study personnel to make an early determination of whether the events are Serious, and require further documentation. It also allows for monitoring of the AE/SAE collection process to ensure that important events are not missed. The AE CRF is used to capture all adverse events (regardless of seriousness) in order to evaluate the risks of the study intervention (such as in a medication trial). All information captured on the AE CRF is destined for the clinical database, and will be available for final analysis. When the AE is determined to be Serious, then the SAE requires documentation in the AE CRF, the SAE Form, and the SAE Summary Report. Regardless of causality, all deaths and life threatening events are to be captured and reported immediately.

Role of the Local IRB

Local IRBs may mandate more stringent requirements for collecting, documenting, and reporting AEs and SAEs. The local Node must always follow these mandates. For example, events meeting the FDA definition of an SAE (e.g. hospitalizations for drug abuse relapse and/or detoxification) may require expedited reporting to the local IRB, even though they may be handled in a routine fashion in the specific CTN protocol. It is always the responsibility of the local PI to comply with all requirements of the reviewing IRB.

AE Reporting Flow Chart



4.8 Appendix VIII Protocol Violations

Exceptions made from the investigational plan or protocol can cover a wide range of actions (or inaction). In general, a protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. On the other hand, protocol violations may be likely to do so, and could be cause for corrective actions if not rectified or at least prevented from occurring again once the cause and effect are understood by the PI and staff.
Additionally, the cumulative effect of many minor deviations can easily reach the level of having a profound effect on the investigation. The study monitoring process makes a significant effort to reveal deviations and violations and to rectify them as quickly as possible.
Protocol deviations may be illustrated with certain examples:

1. Omitting a scheduled blood test, when not directly related to participant safety or study outcomes, at a follow-up visit when it has been measured before and will be measured again at the next visit is considered a protocol deviation.
2. Submitting incomplete data forms or completing forms more than 7 days after a visit is also a protocol deviation.
3. Instances of inaccurate record keeping, inaccurate data entry into the Electronic Data Capture (EDC) system, or other administrative errors that makes data quality auditing difficult is a deviation in each case. The cumulative effect for a number of instances can quickly rise to a more serious level of concern.

Protocol violations are generally more serious. For example:

1. Enrolling an unqualified participant is a protocol violation.
2. Failing to obtain documented informed consent prior to performing protocol specific procedures is a violation.
3. An unreported serious adverse event is another violation of the protocol, one that cannot be tolerated and must be corrected as soon as discovered.
4. Attempts to unblind the treatment assignment are violations, as is failing to report that unblinding has occurred.

Monitoring of a clinical trial often reveals repeated errors (e.g., deviations in data recording) that need to be corrected, and the need to also correct the system (or the training of persons) that permits progress to continue with a lower error rate. How these are handled when discovered requires a lot of interaction with the Quality Assurance Monitor.
When necessary, the Data and Safety Monitoring Board (DSMB) will review protocol violations and deviations, and will make recommendations to NIDA CCTN and the Lead Investigator about necessary actions needed to improve the situation.

Allowable Departures for Protocol and Procedure

Certain issues are not under the control of the research personnel and therefore will not be documented as protocol violations or deviations. These include participant non-compliance. Additionally, the site Principal Investigator or Sub-Investigator may deviate from the study protocol when medically indicated. These incidents should be recorded in the source documentation for the particular participant.
Examples of these events include, but are not limited to:

a) Participant missed visits, such as participant not showing for study visits or coming for visits outside the visit window. (If the participant arrives for a visit outside the visit window and the research personnel do not conduct the visit, this event would not need to be reported as a Protocol Deviation or Violation. This visit would be captured as a missed visit in the database. Study team guidance should be sought for these situations, as the LI may want the visit completed and the data collected for safety purposes.)
   b) Participant medication non-compliance outside the parameters established by the protocol, such as participant not complying with medication schedule or dosing, or participant losing or having medication stolen.
   c) Participant therapy non-compliance, such as participant not showing for some or all therapy sessions, leaving sessions early, or not completing therapy assignments or logs.
d) Early termination, investigator initiated or participant initiated withdrawal from study prior to completing all study requirements. (Early terminations from the study related to SAEs will be captured through SAE reporting).
e) Medical evaluations outside of the scope of the protocol are initiated by site medical staff (i.e. additional ECGs or laboratory work) when medically indicated for the purpose of participant safety and well being.

Deviations from a study Manuals of Procedure or other protocol specific operational documents (monitoring plan, statistical analysis plan, training plan, etc), local SOPs and local IRB approved procedures not specified by the protocol are not considered to be protocol deviations or violations when not specifically encompassed in the protocol itself. Significant deviations by research personnel in protocol related procedures that are not specifically described in the protocol will be reported as appropriate on the monitoring report and will include a corrective action plan and follow-up for resolution.

Protocol Waivers and Deviations

A Protocol Waiver is utilized to request permission to deviate from a study protocol in advance of the event occurring. When a Protocol Waiver is granted the action will not be considered a deviation or a violation. See CCTN Policy on Protocol Maintenance for more information on Protocol Waivers.

Reporting of Protocol Deviations and Violations

Protocol Deviations and Violations will be documented through monitoring visit reports to include a corrective action plan and follow-up for resolution. These documented issues will be followed to satisfactory resolution as soon as possible. In addition to this process, all Protocol Violations will be entered in the study EDC using the standard NIDA CTN Protocol Violations Form eCRF.

The Clinical Coordinating Center and the Data and Statistics Center must be contacted immediately if an unqualified/ ineligible participant is randomized or unblinded.

IRB Reporting for Protocol Violations

All CTN research sites will be knowledgeable of and comply with their local IRB(s) protocol violation reporting policy. The IRB protocol violation reporting documents should be maintained with all IRB correspondence in the site study Regulatory Files.