



National Drug Abuse Treatment
Clinical Trials Network

CTN POLICIES AND PROCEDURES GUIDE

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V6.0

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1.0 INTRODUCTION

The National Drug Abuse Treatment Clinical Trials Network (CTN) provides a means by which the National Institute on Drug Abuse (NIDA), treatment researchers, and community-based service providers can cooperatively develop, validate, refine, and deliver intervention options for use with anyone with a substance use disorder. The CTN operates via cooperative agreement awards (UG1 grants) with research institutions, research and development contracts to coordinating centers, and NIDA. The awards, contracts, and research conducted within the CTN are administered by the Center for the Clinical Trials Network (CCTN) of NIDA.

The main objectives of the CTN are:

- To bridge the gap between practice and research by conducting studies of behavioral, pharmacological and integrated behavioral and pharmacological treatment and/or prevention interventions in rigorous, multi-site clinical trials to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations.
- 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 and prevention throughout the country using science as the vehicle.

Additional information, available online, includes:

- CTN overview -- www.drugabuse.gov/about-nida/organization/cctn/ctn
- CTN By-Laws – http://ctndsc2.com/Reports/WebOut/Documents/CTN_ByLaws.pdf
- CTN Investigator Toolbox – <http://ctndsc2.com/Reports/WebOut/Toolbox/Resources.htm>

1.1 The Clinical Trials Network Structure: Definitions and Acronyms

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

CCTN Protocol Coordinator (CPC): A Scientific Officer from the CCTN appointed to serve as NIDA's liaison and member of the Lead Team (LT) for a given study. The CPC participates in all aspects of protocol development, planning, implementation, management, and study analysis. The CPC may be included as an author on publications.

Center for the Clinical Trials Network (CCTN): An office within NIDA responsible for the scientific, administrative, budgetary, and operational management of the CTN.

Clinical Coordinating Center (CCC): An organization contracted by NIDA to provide centralized support for safety and regulatory functions and requirements, protocol development and

monitoring, training of staff involved in research studies, pharmaceutical products and supply/equipment services, and drug testing and analytical laboratory services. As members of the protocol LT(s), individuals from the CCC assist in protocol development, planning, implementation, and close-out of studies.

Clinical Trials Network (CTN): A collaborative group of grantees (e.g. Nodes) and contracted coordinating centers (e.g. Data and Statistics Center and Clinical Coordinating Center), that serves as a platform for conducting clinical research and training in diverse settings.

CTN Steering Committee (SC): A committee that constitutes the primary governing body of the CTN, with representation by each of the CTN Nodes, CCTN, the CTN Clinical Coordinating Center, and the CTN Data and Statistics Center. The SC works in conjunction with NIDA to set the scientific agenda of the CTN. The committee reviews concepts and protocols for implementation in the CTN; determines and revises, as necessary, the CTN governance; elects members and oversees the operations of the subcommittees. Members of the Steering Committee participate in CTN committees, task forces and special interest groups, as needed, based upon expertise and interest.

Data and Safety Monitoring Board (DSMB): An independent board of experts, appointed by and reporting to the CCTN Director to oversee and monitor the conduct of CTN studies, which protects the safety of participants and the validity of data for each study. The DSMB makes an independent assessment of the interventions under study and advises the CCTN on whether or not any trial undertaken in the CTN should continue. One or more CCTN staff serves as a non-voting administrator of the DSMB. One or more DSMBs may be appointed to oversee CTN studies.

Data and Statistics Center (DSC): An organization contracted 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, CCTN, Lead Investigative Team and site staff. As members of the protocol LT(s), individuals from the DSC will assist in protocol development, planning, implementation and close-out of studies.

Healthcare Organization: An organization affiliated with a CTN Node that may represent specialty care settings (e.g., substance use disorder treatment), general medical settings (e.g., primary care, emergency care, etc.), or a network (e.g., Federally Qualified Healthcare Centers, Health Maintenance Organization Network, Practice-based Research Networks, etc.).

Lead Investigator (LI): An expert investigator appointed by CCTN to conduct a research project within the CTN. The LI chairs a Lead Team that includes representatives of the coordinating centers (CCC and DSC) and CCTN to ensure that protocol development and overall study conduct as well as publication of the primary outcome(s) is achieved.

Lead Team (LT): Group of individuals assigned to assist the LI with protocol development and the day-to-day activities associated with protocol implementation and study conduct. The LT will include the LI, additional Lead Node staff and other designated individuals and representatives from the CTN, CCTN, CCC, and DSC.

NIDA Oversight Board: An independent expert board, appointed and reporting to NIDA, that oversees all activities conducted under the CTN and advises NIDA regarding the programmatic

advisability of proceeding with studies proposed by the CTN and assists the Institute in prioritizing and approving protocols for implementation in the CTN.

Node PI: The grant awardee for the Node who has an academic position at the university or Node organization.

Node: The functional unit within the CTN consisting of the grant awardee organization and its affiliated research partners.

PI of Record: This is the PI for the study site that is recorded in the IRB application. Several Node IRBs require that the PI listed on the study IRB application is a member of the university faculty/staff and so may be the Node PI who may be 100s or thousands of miles away from a research site.

Principal Investigator (PI): The term PI refers to (1) the grant awardee for the Node (i.e., Node PI) or (2) the person responsible for the study conduct for a given site (i.e., site PI).

Protocol Review Board (PRB): An independent committee of experts appointed by and reporting to the CCTN Director to provide scientific review of protocols (including data safety monitoring plans and associated informed consents) submitted by researchers within the CTN. To maximize resources, the Data and Safety Monitoring Board (DSMB) Charter could include the role of scientific review. One or more CCTN staff serves as a non-voting administrator of the PRB.

Publications Committee (PC): A committee charged, on behalf of the CTN SC, to ensure the publication of timely and quality CTN results, the review of protocol publication plans, and the identification of dissemination opportunities.

Research Development Committee (RDC): A committee charged, on behalf of the CTN SC, to collaborate with the CCTN to develop a strategic CTN research agenda, conduct review of CTN concepts, and promote the use of CTN as a research and training platform.

Site PI: The term Site PI refers to the principal investigator for the study who is on site where the research is being conducted and is responsible for the oversight of research study staffing and the assignment of appropriately qualified and trained staff to conduct the study.

2.0 FEDERAL POLICIES GOVERNING CONDUCT OF RESEARCH WITHIN THE CTN

Investigators and key personnel are expected to comply with the terms and conditions of the grant and all applicable policies included in the National Institutes of Health (NIH) Grant Policy Statement (available at <http://grants.nih.gov/grants/policy/nihgps/HTML5/introduction.htm>). The Node Principal Investigator (PI) and NIDA CCTN staff may be consulted for questions regarding NIH policies. The NIDA website is also useful for information regarding clinical trials (<http://www.drugabuse.gov/funding/clinical-research/regulations-policies-guidance>).

Below are some of the main policies included in the NIH Grant Policy Statement; however, investigators must comply with all applicable federal, state, and local regulatory requirements. If studies are implemented outside of the U.S., individuals should also comply with all international sites' regulatory requirements. The CTN Investigator Toolbox contains additional details and procedures at <http://www.ctndsc2.com/>.

2.1 Certificates of Confidentiality (CoC)

Certificates of Confidentiality are issued by the Department of Health and Human Services (DHHS) and serve to protect identifiable research information from forced disclosure. A CoC allows the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

Lead Investigators must obtain a CoC for each study and distribute a copy of the certificate to the CCC and each participating site prior to beginning enrollment. There is further information on applying for a CoC contained in the Investigator Toolbox found at: <http://ctndsc2.com/Reports/WebOut/Toolbox/Resources.htm>.

2.2 Clinical Research Misconduct

Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, reviewing research, or in reporting research results. All NIH grantee institutions are responsible for having written policies and procedures for addressing allegations of research misconduct. For information from the NIH Grants Policy Statement, visit: http://grants.nih.gov/grants/research_integrity/research_misconduct.htm.

Investigators and key personnel are responsible for providing education on research misconduct to their Node research staff as well as staff at any of the participating sites. They are also responsible for ensuring that all staff members are in compliance with their respective institution's policies and procedures regarding research misconduct.

2.3 Clinical Trials Registration and Maintenance

All CTN studies must be registered (and updated appropriately) on the clinicaltrials.gov website at <http://prsinfo.clinicaltrials.gov/>. LIs are responsible for registering and updating their studies. At the end of a trial, the LI must provide results via this website.

2.4 Conducting Research with Prisoners

Individuals participating in research on substance use often have interactions with the criminal justice system. While study teams may choose not to recruit or follow-up with study participants who are incarcerated, there may be situations in which study participants, while not incarcerated, could be defined as prisoners by their state. Regulations indicate that research is not to be conducted on any individual who may be considered a prisoner unless appropriate Institutional Review Board (IRB) and other regulatory approvals have been obtained.

The CCTN strongly recommends that all CTN study teams plan to have all research sites for their study obtain an Office of Human Research Protection (OHRP) Prisoner Certification to decrease site staff and study participant burden in evaluating at each visit if a study participant is considered a prisoner. Please see the Investigator Toolbox for more specific information on applying for and obtaining OHRP Prisoner Certification for CTN studies.

2.5 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 (<http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>). See Section 9.5 for CTN policy on data sharing.

2.6 Federalwide Assurance (FWA)

All sites must obtain an FWA and provide the number and expiration dating to the CCC prior to study start. This is required of all federally funded research sites. Information about FWA is found at: <http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html>.

2.7 Financial Conflict of Interest (FCOI)/Financial Disclosure

All investigators are responsible for complying with the NIH policy regarding FCOI, found at <http://grants.nih.gov/grants/policy/coi/>. NIH policy places the responsibility for determining and reporting financial conflicts of interest on the grantee institution and its investigators. The policy applies to all CTN staff, including collaborating sites, and for all types of studies (including ancillary studies, secondary analyses, health disparities projects, etc.). It is important that key personnel (who are listed on either the Form FDA 1572 or the Investigator's Agreement) make initial disclosures and update disclosures with appropriate documentation if any changes occur. Regulations issued in 2011 require that institutions ensure participation in training programs on FCOI.

For all IND studies conducted within the CTN, CCTN requires collection of financial disclosure documentation from investigators and key personnel (as defined above) prior to commencing enrollment. Key personnel conducting non-IND studies must confirm with the CCC annually that they are following their institutional requirements regarding financial disclosures. Investigators are required to update the sponsor (via the CCC) if there are any changes related to financial disclosure agreements for up to one year following the completion of the study (21CFR 312.53).

Key personnel should receive FCOI training as required in the NIH policy <http://grants.nih.gov/grants/policy/coi/>.

2.8 Grant Acknowledgement

Investigators must acknowledge funding received from NIDA in any document describing the project(s) funded in whole or in part with the CTN grant. For each presentation and/or publication, grantees must include an acknowledgment of NIH grant support and a disclaimer stating the following:

“This publication was made possible by Grant Number UG1 DA 012345 from the National Institute on Drug Abuse (NIDA).”

-or-

“The project described was supported by Grant Number UG1 DA012345 from the National Institute on Drug Abuse (NIDA).”

-and-

“Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIDA or NIH.”

2.9 Inclusion and Valid Analyses for Sex Differences and Minorities

Investigators are required to include women and minority groups in the studies conducted in the CTN. Investigators are also required to conduct valid analyses for these groups and include these analyses in the final study report and publications. For more information, please visit http://grants.nih.gov/grants/funding/women_min/women_min.htm. CTN investigators and study teams should discuss the primary outcome and/or other valid analyses during study design and provide a section in the protocol regarding inclusion and analysis for sex differences and minorities in the proposed study.

2.10 Informed Consent (IC)

All CTN studies must comply with federal, state, and local regulatory laws and policies regarding informed consent. All sites must obtain IC from all participants (or request a waiver of informed consent from IRB) prior to engaging them in research activities.

The CCC will review the initial and all subsequent ICs for basic/additional elements of informed consent prior to submission to any IRB for review and may include additional language as required by federal agencies or requested by the CCTN.

For training on the elements of an effective informed consent, please visit <http://www.nimh.nih.gov/funding/grant-writing-and-application-process/elements-of-a-successful-informed-consent-video.shtml>.

2.11 Institutional Review Board (IRB) Oversight

All CTN studies must comply with federal, state and local regulatory laws and policies regarding IRB review and oversight. All sites must obtain approval(s) from the IRB(s) of record prior to study start. The IRB(s) must review and approve the protocol, informed consent, recruitment materials, and any other necessary documents.

In order to reduce the burden on local IRBs and to standardize the oversight for human subjects protection in the trials, the use of a single IRB for CTN research studies is strongly encouraged.

2.12 Protection of Human Subjects

All clinical trials in the CTN must comply with the appropriate local, state and federal policies regarding research with human subjects. All sites must comply with HHS human subjects protection regulations compiled in [Title 45 CFR Part 46](#).

In addition, for trials involving investigational drugs and devices, or other products regulated by the FDA, sites must comply with all applicable FDA requirements, including those for INDs, Investigational Device Exemptions (IDEs), and human subject protection. Among other provisions, FDA policies for the protection of human subjects are published in 21 CFR parts 50 and 56 with additional standards found in parts 312 and 812. Consult with the Node PI, the study LI, the CCC, and NIDA CCTN staff for questions regarding these and other applicable regulations.

2.13 Public Access

Investigators are required to submit to the NIH (National Library of Medicine [NLM]) PubMed <http://www.pubmedcentral.nih.gov/> an electronic version of the author's final manuscript upon acceptance for publication (<http://publicaccess.nih.gov/>).

2.14 Training

All personnel engaged in research activities must receive training in Human Subjects Protection (HSP), Good Clinical Practice (GCP) guidelines, and the proper conduct of clinical trials (see Section 5.5 Training). All research study staff also receives study-specific training and retain all documentation of training completion. This training information is collected by the CCC and retained for all CTN study personnel who are engaged in research.

3.0 RESEARCH CONDUCTED IN THE CTN

3.1 Types of Studies Conducted in the CTN

3.1.1 Clinical Trials/Multi-Site Research

The CTN conducts research in Substance Use Disorder (SUD) specialty care settings, general medical settings, networks and other health care settings. The majority of studies conducted within the NIDA CTN are multi-site clinical trials of treatment and prevention interventions to answer important SUD health research questions. The CTN may also conduct implementation trials as well. These multi-site clinical trials are also referred to within this document as “parent studies.”

3.1.2 Ancillary Studies

Ancillary studies are studies associated with a parent study conducted within the CTN. These ancillary studies may or may not include all participants or all sites from the parent study, and they may or may not involve direct contact with participants from the parent study. Ancillary studies may or may not be funded by the NIDA CCTN.

Ancillary studies are subject to all regulatory requirements as the parent study, as needed. See Section 10.0 for more information on ancillary studies.

3.1.3 Secondary Analyses

Secondary analyses may be conducted on data collected from one or more CTN parent studies and may involve public data sets or final data sets obtained directly from CTN investigators.

3.1.4 Other Studies

The CTN conducts other, usually small, projects to target a specific area. These could include health care data science, health services, epidemiological, or observational studies that may lead to a future larger study. See Section 10.0 for more information on other studies.

3.2 Numbering of CTN Studies

Once a protocol is approved for implementation by NIDA, CCTN staff will assign a unique identifying number regardless of size, type of study, or budget.

3.3 CTN as a Platform for Other Studies

The CTN, with its core linkage to Healthcare Organizations engaging diverse populations, is designed to provide a platform for other studies, which would be funded under separate research grants, such as:

- to conduct ancillary studies in connection with CTN protocols;
- to utilize CTN Node facilities as a platform for investigations; and
- to serve as the home base for recipients of NIH fellowships or career development awards.

4.0 PROTOCOL DEVELOPMENT AND APPROVAL

This section provides overall policy regarding submission, review, and approval of studies in the CTN. Please refer to the Investigator Toolbox at <http://www.ctndsc2.com/> for templates, examples and more details on these topics mentioned below.

4.1 Protocol Concept Submission and Review

Investigators interested in conducting research in the CTN, must submit a study concept and initial budget estimate to the Research Development Committee (RDC).

- CTN study concepts should be no more than three pages long (excluding references and budget).
- The RDC will review all types of study concepts and provide recommendations to the CCTN accordingly.
- CCTN Director (or designee) will review RDC recommendations and study budgets, make final approval decisions, and communicate with investigators as decisions occur.
- Once a concept is approved, a protocol number is assigned and investigators will proceed with protocol development procedures with the CCC, DSC, and CCTN representatives.

4.2 Study Leadership

Each protocol must include a team of qualified and appropriate staff that will be charged to develop and conduct a protocol in the CTN. The study team includes:

- Lead Investigator (LI): The LI is the Investigator appointed to oversee a protocol conducted in the CTN. The study LI is responsible for protocol development and overall study conduct as well as publication of the primary outcome(s).
- Lead Team (LT): The LI will convene a team of qualified individuals (including staff from the CCTN, CCC, and DSC) called the Lead Team (LT) to achieve the goals of a successful study, assisting with the daily activities regarding study development and implementation. Members of the LT usually include the LI, a Project Director, the NIDA CPC, staff from CCC and DSC, and other key personnel at the Lead Node. Representatives from the CCC and DSC should be involved with study development as early in the process as possible to ensure successful and timely development and implementation of the protocol.
- Study Leadership Plan: The LI will prepare a study leadership plan that will include the names, affiliations, expertise, and qualifications of the key personnel involved in the protocol development and implementation. The LI will include this plan in the materials submitted to the PRB/DSMB for review.

4.3 Timeline

The LI will complete a study timeline with key activities in collaboration with the coordinating centers. The final protocol should be approved for implementation within 8 months of concept approval. The study should be open for enrollment within 7 months of protocol approval.

4.4 Protocol Document

After a concept has been approved for protocol development, the Lead Team will prepare the protocol for independent review. This first version of the protocol is due within four months of the concept approval date.

Investigators will develop a protocol in collaboration with the Lead Team using the protocol template. The investigator will also develop with the Lead Team members other key documents such as the Informed Consent, Manual of Operations, Quality Assurance Monitoring Plan, Training Plan, Site Selection Plan, etc.

CTN common assessments and instruments: The LI should visit the Investigator Toolbox for information regarding the primary outcome measures and common assessments used in CTN studies.

Inclusion of women and minorities: The protocol will include a separate section regarding inclusion and analysis of outcome(s) for women and minorities, and the analysis should be part of the study statistical analysis plan.

4.4.1 Data and Safety Monitoring Plan (DSMP)

The LT will prepare a DSMP that addresses safety monitoring, trial performance monitoring, and efficacy monitoring as an appendix to the protocol. A template is available in the Investigator Toolbox. See Section 6.1 for more about the DSMP.

4.5 Version Control of Protocol and Other Study Documents

Staff from the CCC will assist the LI with version control of the protocol from early protocol development (starting with version 0.1) through study implementation and study closure. The CCC will also assist with version control of other key documents. For more details on document management, including version control and formatting, as well as distribution, storage and use of the protocol and other key study documents visit the Investigator Toolbox.

4.6 Protocol Review

The CCTN will arrange a meeting for initial scientific review of the protocol. In most cases the CTN Data and Safety Monitoring Board (DSMB) will serve as the review board. This board will review the protocol and related study materials (e.g., Informed Consent, DSMP, plans, etc.) and provide recommendations to the CCTN Director. The CCTN Director will consider the recommendations and make final decisions.

4.6.1 Materials for Review

The LI will submit the following materials 30 days prior to the scheduled protocol review date:

- Full protocol
- Data and Safety Monitoring Plan (usually submitted as an appendix to the protocol)
- Informed consent form(s)
- Leadership plan (with CVs of the key personnel)
- Timeline for the proposed trial
- Recruitment and retention plan
- Site Selection Plan: Recruitment and retention of diverse participants are a critical part of site selection, including determination of staffing needs and research site requirements determined by the details of the study. These elements should be included in the Site Selection Plan.
- Estimated study budget, including estimated site budgets
- Any additional, relevant materials, such as key reference papers, etc.
- Cover letter with any additional useful information regarding study design/scientific question/rationale for the study

Long-Term Follow-Up Studies: If the protocol is for a Long-Term Follow-Up (LTF) study of a completed CTN trial, then the LI must also submit the statistical plan for all analyses to be conducted during and at the end of the LTF study. The LI will also submit a written plan for presentation and/or publication to the CCTN in advance of study implementation that includes:

- A justification for disseminating results prior to the end of the LTF study.
- Specific time points at which the LI would need interim data sets.

4.6.2 Review Meeting

The LI is expected to prepare a presentation in collaboration with the coordinating centers and participate in the open session of the review meeting. Other members of the Lead Node may attend if deemed necessary. The meeting may be held in person or by teleconference.

4.6.3 Review Outcome/Protocol Approval

The CCTN will consider the reviewers' recommendations and provide feedback to the LI approximately two weeks from the date of the review meeting. Review outcomes will be one of the following:

- a) May proceed with current design.
- b) May proceed with few or minor revisions.
- c) May proceed, but major revisions are needed.
- d) May not proceed.

If the protocol is approved with revisions, a re-submission of the protocol and response to the original review will be necessary for a second review. The CCTN will consult with the LI for a timeline for re-submission and arrange a re-review of the protocol. CTN investigators should not contact the review board members directly.

4.7 Final Protocol Approval by NIDA CCTN

The CCTN Director will communicate with the LI when the protocol is approved for implementation.

5.0 PROTOCOL IMPLEMENTATION AND TRIAL MANAGEMENT

5.1 Study Timeline

The approved study should be open for enrollment within 7 months of protocol approval. Delaying the study implementation may result in cancelling the protocol implementation, given that priorities may change in the CTN.

5.2 Responsibilities of the Lead Investigator (LI)

The study LI is responsible for the overall study conduct, working closely with the coordinating center(s), NIDA CCTN and the Node PIs to achieve the goals of a successful study. The LI responsibility during protocol implementation includes oversight of recruitment, retention, and follow-up of study participants as well as providing leadership for proper study conduct at each site. In addition, the LI will work with CCTN to prepare and monitor the budget for the study, including budgets for the participating sites.

The LI (in collaboration with coordinating centers, NIDA CCTN staff, and Node PIs) must:

- Prepare the final study budget.
- Follow and comply with all applicable protections for human subjects and clinical research regulations (local, state, and federal).
- Obtain IRB approval for their respective protocol and maintain it throughout the conduct of the clinical trial.
- Select qualified sites, per the Site Selection Plan, with sufficient staff that is adequately and appropriately trained to implement the clinical trial.
- Provide/coordinate necessary training of the research staff, as specified in the training plan and documented on each individual's training documentation form (TDF).
- Provide evidence of adequate and appropriate oversight throughout the conduct of the clinical trial.
- Report as needed to the study DSMB.
- Submit a publication plan to the Publications Committee when 50% of the target sample is reached (see Section 9.3).
- Provide regular progress reports to the SC and CCTN.
- Provide the final study report to the CCTN.
- Prepare the manuscript of the primary outcome measure(s) and submit for publication.

5.3 Responsibilities of Participating Node PIs:

- Provide oversight and study management throughout the conduct of the clinical trial, for the participating site(s).
- Maintaining regulatory records at the research site and, if required by local IRB, at the Node. Ensuring that each research site affiliated with their Node is aware of their regulatory responsibilities associated with each study.
- Ensuring that each research site affiliated with their Node obtains, and maintains, a Federalwide Assurance (FWA) from OHRP prior to enrollment of study participants at that site. If the site is deferring to another IRB then a written agreement should be in place to outline their relationship and include a commitment that the IRB will adhere to the requirements of the Institution's FWA.
- Obtaining IRB approvals on behalf of their associated research sites for the protocol, informed consent, recruitment materials and all documents meant for distribution to research participants; and for sharing this information immediately with the research sites and the CCC.
- Ensure personnel received and documented appropriate training and to conduct the study at the participating site.

5.4 Site Selection

Decisions about site participation in protocols involve communication and collaboration among the Lead Team (LT), the Node PI, and the site considering participation according to the Site Selection Plan.

Following the Site Selection Plan, the LI or designee will communicate with each Node and provide the materials needed by the site selection team (i.e., surveys, checklists, questionnaires, etc.). Node staff will facilitate the process, collect information from sites, and communicate with the LI or site selection team for the protocol. More detailed information about the Site Selection Plan, survey and interviews can be found in the Investigator Toolbox under "Site Selection."

All sites interested in participating in the study must provide budget estimates to the site selection team as well as an estimate of the number of women and minorities they expect to recruit as part of the site selection process.

The Lead Team will evaluate information from potential sites and develop a list of sites to be considered. The LI will present the list of potential research sites to NIDA CCTN staff for approval, then to the SC prior to study start.

5.5 Training

5.5.1 Protocol-Specific Training

The LT will prepare and maintain a current Training Plan for each individual protocol and distribute it to the participating Nodes and sites. The Training Plan describes all of the necessary training required for research staff and back-up personnel at the selected sites to implement the protocol. The study sites will each maintain documentation that all members of its research team have completed the necessary training. Each site staff member engaged in research activities

will complete and provide to the coordinating centers a training documentation form, verifying completion of all training as prescribed for their assigned study role(s).

It is the responsibility of the Node and/or site PI or designee to ensure that each study team member within their Node is appropriately trained and qualified to conduct study procedures before carrying out their assigned role in the study.

5.5.2 Training Requirements Summary

Individuals engaged in research procedures will receive necessary training, per the protocol specific Training Plan and documented on the training documentation form (TDF). In addition to protocol-specific training, training in Human Subjects Protection and Good Clinical Practice is required and is renewed every three years unless required more frequently by your IRB.

1. Individuals who are doing any of the following activities are considered “engaged in research” and need documentation of HSP and GCP training:
 - collecting and/or entering study data into the data capture system;
 - interviewing, consenting, assessing or examining potential study participants;
 - deciding on eligibility for potential study participants;
 - counseling or providing the intervention for the study; or
 - reviewing AEs/SAEs.
2. Node PIs are responsible for providing adequate training (according to institutional policy) to their respective research site staff members on research misconduct and financial conflict of interest (FCOI). Training in FCOI must be updated every 4 years.
3. The Lead Team will conduct protocol-specific training via a national training meeting prior to study initiation.

5.6 Protocol Manual of Operations (MOP)

The Lead Investigative team is responsible for preparing a study MOP in collaboration with coordinating centers. The MOP will contain specific, detailed procedures for all aspects of the study protocol and the first draft should be complete 12-14 weeks before study launch.

5.7 Protocol Deviations (PDs)

All departures from protocol procedures are considered a protocol deviation (PD). The CCC will review PDs on a regular basis and communicate with the participating site and the full LT regarding corrective actions and prevention of recurrence. The DSMB will review a summary of PDs at regularly scheduled meetings.

The CCC/LT will also conduct anonymous PD discussions with the research sites on periodic national calls to share across all study sites recommendations and corrective actions to prevent occurrence at other sites. The LT will provide appropriate training regarding the documentation, reporting, and assessment of PDs. When PDs occur, staff at the participating sites should complete the appropriate case report form(s), and report to their local IRB(s), as required.

5.8 Site Performance Monitoring

The LT will prepare a study Quality Assurance (QA) plan specific to each protocol focused on site management. This plan will provide guidance for Node personnel to conduct local activities for site management, as well as general schedules for DSC and CCC site monitoring and data auditing which will be provided by the coordinating centers. The CCTN has contracted with the CCC to provide quality assurance monitoring for all CTN studies.

The Node PI has responsibility for study performance at each participating site.

The CCC will monitor the performance at each participating site for most CTN studies as determined before study launch by the CCC, CCTN and the QA plan. Site monitoring visits will include monitoring tasks related to study procedures and processes as well as to initiation, interim and close-out activities; they will occur as needed. Remote monitoring will complement on-site visits to review performance.

5.9 Site Staff Delegation of Responsibilities and Signature Log

During the implementation of a study, the study staff will maintain a site staff delegation of responsibilities and signature log for all personnel on site who are engaged in research. There should be only one PI for the study at each site.

The earliest study start date for each individual staff member will be the date the training documentation form (TDF) is signed. The latest end date will be the database lock date. The Node staff will not be included on this site log unless they are engaged in research activities at that site (as defined in Section 5.5.1 above). The Node PI will be entered as the "PI of Record" on a specific line on the log if required by local IRB, and there is only one PI listed and that is the PI at the site.

5.10 Trial Progress Report

The DSC, with input from the CCC, produces Trial Progress Reports (TPRs) for each study conducted within the CTN. The TPRs are updated daily and are available to authorized users on The NIDA CTN Clinical Trial Reports website (www.ctndsc2.com). The main purpose of these reports are to provide a trial monitoring tool to study LTs, CCTN and the CTN SC. Portions of TPRs may be shared with the reviewing DSMB. Information in the TPR is confidential and should not be shared outside of the CTN.

Investigators should not include information from the TPR or protocol-specific Data Status Reports (DSRs; see Section 7.3) in posters, abstracts, or publications.

5.11 Recruitment, Retention, and Follow-Up

Recruitment and retention are a critical part of all clinical trials. The LI will prepare a recruitment, retention, and follow-up plan and submit along with the protocol for NIDA approval early in the protocol development cycle. Once approved, they should distribute the plan to each site for implementation.

The LT will monitor the recruitment, retention, and follow-up performance at each site closely throughout the duration of the study and work with the sites to improve when necessary. Non-performing sites may be discontinued from the study at the discretion of the LI, CCTN, and the LT.

5.12 Statistical Analysis Plan (SAP)

The LI and DSC will prepare a detailed SAP prior to study completion. Version 1 of the SAP must be finalized prior to final database lock. Minor changes may be made after database lock if necessary; however, it is strongly recommended that no changes be made to the analytic plan for the primary outcome. In general, the SAP should cover the analyses, tables, figures, and listings for the final study report. The SAP will also cover analyses by sex and race/ethnicity groups. If interim analyses are planned *a priori*, then the SAP must describe the methodologies for those analyses.

5.13 Collaboration between Lead Investigators and Participating Sites

Two-way communication and collaboration are cornerstones of the CTN research endeavor. To ensure the scientific credibility, relevance, and sustainability of interventions, investigators and providers are encouraged to work together throughout the conception, development, implementation, closeout and data reporting/publication stages of CTN studies.

LIs and research sites who participate in clinical trials are full partners and therefore have an equal stake in the knowledge produced as a result of the trial. Protocol teams must ensure that two-way communication continues throughout the analysis, publication, and dissemination of results. This continued collaboration is considered essential to appropriate interpretation of the information generated by the CTN and to maintaining the highest quality of investigator/provider partnerships.

6.0 PROTOCOL DATA AND SAFETY MONITORING

6.1 Data and Safety Monitoring Plan

All CTN studies must include a specific Data and Safety Monitoring Plan (DSMP) as an appendix to the protocol. The purpose of this plan is to ensure the safety of participants as well as the integrity of the data for the trial. It is the responsibility of the study LT (LI, CCTN, CCC, and DSC) to prepare the DSMP (see Section 4.4.1). The Investigator Toolbox has an example of a DSMP as an appendix in the Protocol Template, which includes standard language that can be modified to fit any particular study.

This DSM Plan is also submitted to the NIDA grants management office as part of funding requirements.

6.2 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 DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants. In accordance with NIH requirements, NIDA's CCTN has convened DSMBs to provide independent oversight of the clinical trials conducted within the CTN. The Director of the CCTN appoints DSMB members. The DSMB monitoring function is in addition to the oversight traditionally provided by IRBs (see Section 4.6).

After each DSMB meeting, the CCTN will communicate the DSMB recommendation(s) and its decisions based on those recommendations in writing to the study LI along with a letter to participating IRBs detailing study safety information. See Investigator Toolbox for more DSMB information (<http://ctndsc2.com/Reports/WebOut/Toolbox.htm>).

6.3 Safety Monitoring

The protocol template has both a safety section within the protocol and a safety appendix. The safety section within the protocol will be updated by the LT with items which need to be carefully monitored during study implementation. Each protocol may have specific items of interest or occurrences, which will be followed as adverse events or serious adverse events or captured on other specialized data forms. The safety appendix (usually Appendix A) will provide standard definitions for adverse events and serious adverse events, their identification, characterization regarding severity and relationship to therapy and processing.

Most CTN study sites will provide a Study Clinician (e.g., MD, DO, PA, NP, or RN) for the study, who will review or provide consultation for each serious adverse event as needed. These reviews will include an assessment of the severity and causal relationship with the study drug, if any, or study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required.

In addition, NIDA will assign a Medical Monitor to this protocol to independently review the safety data, and present it to the DSMB for periodic review. The medical monitor will determine which adverse events require expedited reporting to NIDA, the DSMB, pharmaceutical/distributors, if any and regulatory authorities. This will include all suspected adverse reactions that are serious and unexpected. The study staff will be trained to monitor for and report adverse events and including serious adverse events.

Each of the participating research sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Study medical clinicians at each research site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

7.0 DATA MANAGEMENT

7.1 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 Standard Operating Procedures of the CTN DSC and the trial-specific documentation for each study.

7.2 Data Audits

The CCC will conduct data audits during interim site monitoring visits throughout the duration of a study when it has been determined that on site QA monitoring visits will occur for the protocol. The scope of the data audit, including the frequency of audits and the quantity of data to be reviewed, may be defined in the study-specific Monitoring Plans. Discrepancies between the source and the database will be identified and resolved by the sites during or immediately after the audit, and an error rate will be calculated for each site so that the site and LT can track data quality.

7.3 Data Status Reports (DSRs)

The DSC programs DSRs for each study. There are four levels of reports: participant-level, site-level, node-level, and trial-level (Trial Progress Report). The DSRs are developed and used for the purpose of monitoring accuracy, completeness, and quality of data submitted, and to provide the study LI with summary data to manage the day-to-day operations of the study. Investigators should not include information from Data Status Reports in posters, abstracts, or publications.

7.4 Electronic Data Capture (EDC) System

With limited exceptions, the DSC is responsible for providing software applications and training to support data collection and management for most CTN studies. For these studies, the DSC is responsible for ensuring the security of the data collected in the EDC system. In addition, the EDC system complies with 21 CFR Part 11. CCTN officials should be consulted if there are any questions.

7.5 Signatures within EDC

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

In some cases, other signatures may be required, such as when data are submitted by a clinician independent of the site (e.g., central reading of ECG). The responsible site clinician's signature will be required on the data submitted.

7.6 Help Desk

The DSC will maintain a NIDA Help Desk (HD) with an appropriately staffed toll-free telephone service and email address.

The DSC Help Desk will provide support to participating CTN staff in the following areas:

1. Technical support related to data management, randomization, and communications systems.
2. Assignment and maintenance of user accounts for CTN systems, such as the document management system and the electronic data capture system.
3. Assignment and maintenance of site and staff ID numbers.

8.0 STUDY TERMINATION

The milestones listed below are in the order in which they occur for study termination:

- Last participant, last visit. This entry defines the date at which the last participant that was enrolled in the trial completes their trial participation. This event signifies the conclusion of data collection.
- Last participant, last visit—primary outcome (LPLV-PO). This date is when the last participant that was enrolled in the trial has primary outcome data collected. Study results are due in the clinicaltrials.gov website 12 months from this LPLV-PO date.
- Database lock. After the last participant, last visit date has occurred the database system will automatically calculate the estimated date of database lock. Once the coordinating centers have certified that the study dataset is final, no queries will be circulated and no data discrepancies will be generated. The DSC will be responsible for providing the LI and the CCTN with the actual date of database lock.
- Study datasets. These files contain all raw data collected in the study. The DSC provides the files to the LI or designee for data analysis. A copy is maintained by the DSC and will be transferred to NIDA or other entities, as requested by the CCTN.
- Final study report. The LI will provide a report to the CCTN that contains the final analysis of the primary outcome measure(s), along with other important secondary analyses (such as evaluating the primary outcome for gender and ethnic differences).

The CCTN considers the study completed once the final study report is accepted.

8.1 Guidelines on Release of Long-term Follow-Up (LTF) Data before the End of the Study

These guidelines pertain to CTN studies that are independent extensions of previously completed CTN clinical trials. The goal of an extension study is to continue to follow the participants from the initial study to gain further insight into their longer-term clinical outcomes. It is assumed that the follow-up study does not involve new randomization or new treatment – only the collection of outcome-related data for an extended period of time. The LI for the LTF study will prepare a protocol, which will be reviewed by an appropriate PRB/DSMB, and contain all information expected of a CTN multi-site protocol. Before any data from the follow-up study are released, the database of the parent trial should be locked, and the paper with primary results from the trial accepted for publication.

The DSC will provide progress reports in table format to the LI of the LTF study in order to allow for monitoring. These reports will be based on raw data that have not gone through a complete quality assurance process; therefore, 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, s/he must include these plans in the protocol, and prepare and follow an approved publication/presentation plan. The DSC will prepare interim datasets, as

described in the LTF protocol. Data will be “cleaned” (but not finalized) before datasets are released. The DSC will keep electronic copies of all interim datasets.

Presentations and/or publications based on interim data sets should include the following note:

“This information is based on data collected as of [date of data cut-off].
Any changes to the data, results, or conclusions will be noted in subsequent presentations and/or publications.”

All draft publications, posters, and presentations should be sent to the CTN Publication Committee Chair or designee prior to submission to journals or meetings to allow for review, feedback, and changes if necessary.

8.2 Protocol Close-Out and Database Lock

The LT, including staff from the coordinating centers, will develop and distribute close-out procedures and materials to all participating sites. The supply of study medications, equipment, and/or other test materials must be returned, destroyed, or donated per LT instruction, once the study is closed at the site and may not be used outside the study, unless expressly authorized by the LT. Close-out procedures will include detailed steps for disposition of study supplies and medications, record retention plans and storage, and database lock. The CCC will provide a listing of all CCC provided equipment, medication, and supplies with instructions for their disposition.

Before database lock, the CCC will perform a close-out site visit, review site-specific regulatory documents and resolve gaps in regulatory documentation, conduct source document to data verification, review query resolution, action item completion and site process reviews. Database lock will be completed no later than 2 months after the conclusion of data collection (last participant, last visit). The DSC will prepare the final dataset after database lock.

8.3 Record Retention and Storage

Each Node is responsible for ensuring the appropriate and adequate storage of paper and electronic research records associated with the clinical trials at their research sites. The Node will establish policies and procedures for the archiving of research records, in compliance with their state, local, institutional and IRB regulations, and meeting the minimum standard for CTN protocols. In all CTN studies, study records must be maintained for at least three years after database lock, or longer if specified by local institutions/agencies or FDA regulations.

The Node PI will prepare clear, written documentation of record location and the retrieval process for research records for a given site, and forward the information to the study LT and to the CCC at study close-out. Node PIs are responsible for alerting the LT and the CCC in writing if there are changes to the record retention/storage plans.

Each Node must contact the LI, the CCTN, and CCC in writing prior to the destruction of any protocol-related records at least 30 days prior to the intent to destroy date.

8.4 Release of Trial Data Prior to Database Lock

1. The study LI will provide a written request for data release (what, when, and how) to the CCTN, who will forward it, as appropriate, to the DSC.

2. For non-LTF studies, a limited dataset will be considered for release prior to database lock (for example, a dataset containing demographic/baseline characteristics once all participants have been enrolled). The study team will prepare a document prior to study start defining which data will be in this dataset, and DSC/CCTN staff will approve language.
3. If requested, this limited dataset will be prepared and released (only once) after all participants have been enrolled in the study.
4. The DSC can provide “soft lock” data sets and will not certify “clean” data until final database lock when all queries have been resolved and closed.
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*).”

9.0 PUBLICATIONS AND DISSEMINATION

9.1 Presentation of Research Results

The LI should present the study primary outcome and other results to the participating sites as soon after the analyses are completed as possible to ensure that participating sites have a chance to comment on the results and conclusions of the trial from their respective point(s) of view. This presentation serves as a collaborative exchange. Inclusion of site staff in authorship of publications related to the trial's results and conclusions is strongly encouraged.

The LI should present the primary outcome results to the Steering Committee after the presentation to participating sites, at the next scheduled meeting. The LI will present the final results to the DSMB before submitting the primary outcome manuscript to a journal (before or after presenting to sites). Members of the CTN who may receive results prior to presentation to outside audiences are not permitted to present these results at meetings or include them in publications.

The LI or any member of the study team may not release any outcome data to any sites until the trial is completed, the database locked and the primary analysis performed.

9.2 Final Study Report

The LI in collaboration with the CCC and DSC will submit a final study report to the NIDA CCTN within four months of database lock. CCTN staff will review the final study report and respond to the LI. The LI or his/her representative will sign the final study report only when it has been determined that all data discrepancies and queries noted have been resolved.

Investigators should include analysis of outcomes by sex and race/ethnicity. The CTN DSMB will review the final study report and provide recommendations regarding appropriateness of study conclusions.

This final study report will become part of the NIH official file. If a study is conducted under an IND, then the final clinical study report will also be submitted to the FDA. The final study report is also shared with any pharmaceutical companies which may have collaborated on the project by providing donated study medication and when applicable with the Research Advisory Panel of California (RAP-C) group in California.

For more information about creating and submitting a final study report, refer to the Investigator Toolbox (<http://ctndsc2.com/Reports/WebOut/Toolbox.htm>).

9.3 Publications and Authorship

The CTN Publications Committee (PC) will implement procedures to promote publications and ensure their scientific quality and timeliness. The PC reports to the CTN SC, which has final authority for approval or disapproval of recommendations.

The LI will submit a publication plan to the PC when 50% of the target sample is reached. The publication plan is a comprehensive list, often prepared as a spreadsheet, which indicates all the planned papers that the study team would like to pursue, and includes the general research question(s), data source, lead author, proposed co-authors, and the target journal. Within six

months after database lock, the LI will review and revise the publication plan and resubmit the plan to the PC. Thereafter, the publication plan will be reviewed and revised semi-annually.

CTN LIs are expected to present the main outcome research findings at scientific and clinical meetings and to publish findings of their research in the scientific literature. The primary outcome paper should be completed and submitted to an appropriate peer-reviewed scientific journal within six months of database lock.

Investigators should publish analysis of 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.

Writing teams should involve investigators and site staff who participated in the study. Once the datasets have been received, the LT should promptly communicate with all members of the writing teams proposed in the publication plan. All secondary papers listed in the plan should be submitted to appropriate journals within one year after submission of the primary outcome paper. Publication of secondary analyses prior to publication of the primary study results is not permitted without prior SC approval.

Study teams must remind all authors that, as stated in the CTN Data Sharing Policy, datasets for CTN protocols will be available after (1) the primary paper has been accepted for publication, or (2) the study database has been locked for 18 months, whichever comes first.

Per NIH Policy (<http://publicaccess.nih.gov/>), investigators are required to submit an electronic version of the author's final manuscript upon acceptance for publication to the NIH (NLM Pub Med - <http://www.pubmedcentral.nih.gov/>).

9.4 Submission of Materials to the Publication Committee

Lead authors will submit to the CTN Publication Committee (PC) all manuscripts for publication, abstracts, presentations, posters and other CTN materials based on data collected as part of the CTN studies or describing scientific methodology of these studies. Specifically, authors should provide materials to the PC-designated individuals for review and approval at least one month prior to the anticipated submission or presentation date.

Lead authors will inform the PC of decisions by journals or meeting organizers, and provide the PC with the final published papers or poster/presentations.

9.5 Data Sharing

With DSC assistance and consultation, de-identified public datasets for CTN protocols will be made available on a designated website after (1) the primary paper has been accepted for publication, or (2) the final trial database has been locked for 18 months, whichever comes first. In most cases, the DSC will prepare the data for sharing. Study teams must include a plan with their protocol.

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 (<https://datashare.nida.nih.gov/>).

The following information about the protocol will be posted:

1. Dataset
2. Descriptive metadata – including annotated case report forms; overall descriptive data, and data dictionaries;
3. Definition file (also known as a data dictionary, if available);
4. Study protocol;
5. Reference to primary outcome paper;
6. De-identification notes which describe the de-identification process; and
7. Website links integrated into the website to reference study summaries provided on the CTN website and the study description on clinicaltrials.gov.

9.6 Dissemination Library

The CTN Dissemination Library is a source for many journal articles, protocol manuals, reports, conference and workshop presentations training materials, and other documents emanating from CTN activities. Only those items that are open to public viewing are posted. The Library provides free and open access to all such CTN-related documents.

It is requested that authors submit relevant materials electronically to the CTN Dissemination librarians as soon as possible after publication and/or presentation. The email address for submission to the library is: info@ctndisseminationlibrary.org.

9.7 Continued Collaboration

Research sites may wish to continue using an intervention following completion of a trial, but before release of the primary outcome results. This practice is not recommended in the scientific community or by CCTN.

Clinicians, administrators, and data collection staff members who have participated in a clinical trial often have information for investigators about the feasibility and utility of conducting the intervention and about overall participant response to the intervention. This information can be useful to the LI when interpreting trial data. The LI should schedule planned debriefing meetings with research site staff shortly after completion of data collection. The design of these debriefing sessions will differ depending on the design of the protocols.

10.0 PROCEDURES FOR OTHER TYPES OF STUDIES CONDUCTED IN THE CTN

In addition to clinical trials, the CTN conducts other type of studies (see Section 1.1 for definitions). This section provides policies and procedures for submission, approval, and coordination of these studies.

The majority of these studies are considered small projects, and study teams should discuss with CCTN the need for CCC/DSC resources and support.

These studies must follow all the applicable policies and procedures described in this document (i.e., data and safety monitoring, data sharing, submission of a final study report, publication of results, etc).

Involvement of the CTN coordinating centers (CCC and DSC) for these studies will vary according to the complexity of the study design and availability of resources. Investigators contemplating these studies should discuss needs for the data, statistical, and monitoring support with the CCTN staff prior to the DSMB review of the parent study. If the coordinating center(s) are not involved in data collection, the investigators must provide the CCTN with a plan to share data in as open and unrestricted a manner as possible. Investigators are expected to provide a final study report to CCTN on a timeline similar to that for the parent study.

10.1 Ancillary Studies

All concepts for ancillary studies will be reviewed by the SC, or designee, who will make recommendations to NIDA. Investigators of ancillary studies must provide a letter of support from their Node PI and the LI of the parent study, along with the concept and budget of the proposed ancillary study. The LI of the parent study must agree that the integrity of the parent study will not be compromised by conducting any proposed ancillary study, and that the additional information generated is valuable. The Node PI must agree to provide necessary support for the ancillary study.

For many ancillary studies, it is essential that planning begin early in the protocol development process for the parent trial so that required data can be incorporated into the case report forms. Failure to consider these issues will affect assessment of the proposed ancillary study.

If the concept for an ancillary study is approved by NIDA, the investigators will submit to CCTN a completed protocol that includes the rationale, design/methodology, data and safety monitoring plan (if applicable), informed consent, required staffing needs and a timeline, and detailed budget for the study. The CCTN staff will coordinate an independent review by the PRB/DSMB of the parent study or other reviewers as appropriate.

Investigators of ancillary studies are expected to prepare and submit to CCTN written documentation detailing major milestones, expectations, timelines and individual responsibilities, and must follow CTN policies regarding release of study data, publication, and data sharing.

The DSMB of the parent study will monitor all related ancillary studies. The ancillary study PI will present progress to the DSMB during the scheduled meeting for the final report from the parent study.

Investigators must prepare a final report for the ancillary study, or include as addendum in the parent final study report. It is expected that the final results are presented to the participating sites, the SC and DSMB per described in Section 9.0 of this document.

Ancillary studies will maintain the same clinical trial number as the parent study but will contain the suffix “A” for ancillary (CTN-00XXA).

10.1.1 Examples of Ancillary Studies

- a. Genetic studies: NIDA supports a variety of genetics protocols through The NIDA Center for Genetics Studies (NCGS). For many parent studies, a blood sample may be collected from participants for the purpose of future genetic research.
- b. Organizational surveys
- c. Economic analyses
- d. Long term follow-up of participants

10.2 Secondary Analyses

The CTN conducts three types of secondary analyses:

- Single-study secondary analyses that are specified *a priori* in the protocol (these should be developed in close collaboration with the LI and the protocol team).
- Single-study secondary analyses not specified in the protocol.
- Multi-study secondary analyses.

Investigators seeking CCTN funding for conducting secondary analyses must submit a concept and budget for review and recommendation. In addition to the routine requirements for concepts, the proposal for a secondary analysis should include the PI of the secondary analysis study, the names of planned collaborators in the study and co-authors on the final paper, the name of the Node PI sponsoring the project, the research question/hypothesis and its importance, the CTN trial(s) to be included, a brief description of the analytic method, and a preliminary timeline.

Following the review, the CCTN will make a final decision and communicate accordingly with the involved investigators.

Investigators are encouraged to conduct secondary analyses using the public data sets available at: <http://www.ctndatashare.org/>.

Secondary analyses studies will contain the suffix “S” when numbered (CTN-00XXS).

10.3 Other Studies

Investigators interested in conducting other studies are to submit an initial concept and budget for review and recommendation. If the concept is approved, the investigators will need to submit a more detailed proposal in the form of a protocol that describes the rationale,

design/methodology, data and safety plan (if needed), informed consent and CTN resources involved. A timeline and detailed budget for the study should also be included.

CCTN staff will coordinate an independent review, similar to a PRB/DSMB and the study may be subject to regular monitoring by the DSMB or other independent group similar in structure to a DSMB.

These studies will contain the suffix “Ot” when numbered (CTN-00XXOt).

10.4 Platform Studies

Investigators wishing to use the CTN infrastructure should contact the most relevant PI of a CTN Node (<http://www.nida.nih.gov/ctn/network.php>) to discuss the project and the best way to engage the network.

Investigators requesting permission to access the CTN infrastructure are to contact the Director of the CCTN requesting a letter of support. The request will include information about the specific grant application, the title of their project and a synopsis of the proposed study. The Director of the CCTN will provide a letter of support to the requesting investigator to use the CTN as a platform.

The externally funded protocol must fully cover all costs associated with the investigation, including expenses for the CTN staff. Investigators should acknowledge the role of the CTN in any papers prepared for publication.

Investigators must follow and comply with all applicable Human Subjects Protection and clinical research regulations (local, state and federal), funding entity policies and obtain IRB(s) approval, as appropriate, prior to implementing any study.