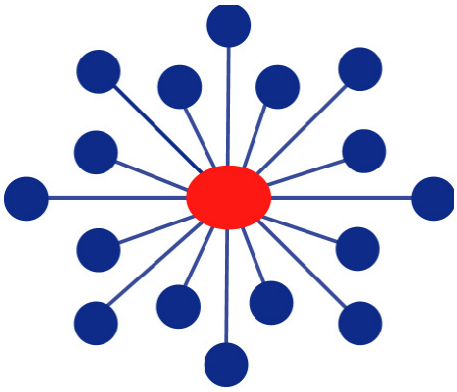

NIDA CTN Protocol 0051-A2

Treatment-as-Usual Opioid Use Outcomes Following Discharge from Detoxification and Short-Term Residential Programs Affiliated with NIDA CTN-0051

Lead Investigator: John Rotrosen, MD

August 5, 2016

Version 2.0

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CCC	Clinical Coordinating Center
CoC	Certificate of Confidentiality
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
DHHS	Department of Health and Human Services
EDC	Electronic data capture
ERC	Ethics Review Committee
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
LN	Lead Node
MDMA	Methylenedioxymethamphetamine (Ecstasy)
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OUD	Opioid use disorder
PI	Principal Investigator
SAE	Serious adverse event
TAU	Treatment-as-usual
TLFB	Timeline Follow-Back
UDS	Urine drug screen

2.0 STUDY SYNOPSIS

2.1 Study Objectives

CTN-0051-A2 (also referred to as “ancillary study”) is an observational study intended to describe opioid use amongst opioid use disorder patients following their discharge into the community from inpatient detoxification and/or short-term residential treatment programs affiliated with CTN-0051 (referred to as “parent study”).

2.2 Study Design and Outcomes

Participant recruitment will begin after recruitment for CTN-0051 has been completed. Opioid use disorder patients will be recruited prior to leaving detoxification and/or short-term residential programs. Screening and baseline data (focused on demographics, diagnosis and service utilization) will be collected prior to discharge, and follow-up data (focused on opioid use) will be collected at weeks 1, 4 and 8 following discharge to the community. All data measures are similar to those used in CTN-0051.

2.3 Sample Size and Study Population

Participants will be a convenience sample of approximately three hundred sixty (360) opioid dependent patients leaving detoxification or short-term residential units at sites participating in CTN-0051. Approximately 60 participants will be recruited at each of approximately six sites.

Since this study utilizes a convenience sample and the objectives are to simply describe opioid use post-discharge, only detectable effect sizes were calculated (i.e., no sample size calculations performed). These effect sizes considered the evaluation of the association between post-baseline opioid use and a binary covariate such as gender, and use of medication-assisted treatment. Results of the effect size calculations are shown in Section 13.2.

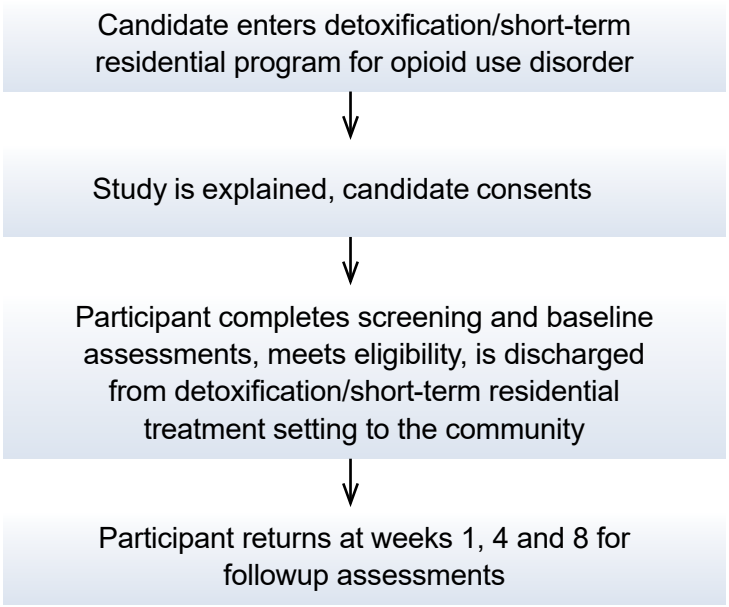
2.4 Assessments and Duration

Participants will be consented prior to their discharge from the detoxification and/or short-term residential unit, screening and baseline assessments will be conducted prior to discharge, and then patients will be followed at approximately week 1, week 4 and week 8 post-discharge to the community. Assessments include: DSM-5, detoxification service utilization, post-discharge treatment plans, Timeline Follow-Back (TLFB), and urine drug screen (UDS). See Study Assessments Table, Section 11.0. Participant-level data collected in the study will not be shared with the treatment programs.

2.5 Safety Reporting

Only overdoses, whether hospitalized or not, and all deaths will be collected for this study.

3.0 STUDY SCHEMA



4.0 INTRODUCTION

4.1 Background and Significance to the Field

For opioid use disorder patients in the U.S. and most of the rest of the world, detoxification or detoxification followed by short-term residential treatment, with the goal of achieving long-term abstinence from opioid misuse is a mainstay of treatment. Although it is widely believed that many patients treated in this way will rapidly relapse to opioid misuse – leading to a costly and ineffectual cycle of readmission for repeated detoxifications – there is scant data on opioid use outcomes following discharge from these programs. Searches of PubMed, NIH Reporter, and ClinicalTrials.gov for “clinical outcomes following opioid detoxification” and the like, mostly reveal

studies focused on detoxification methods, medication schedules, withdrawal symptomatology, tolerability and the proportion of patients completing detoxification.[1-6] Three studies,[7-9] two of them from Europe, focused on subsequent outcomes (e.g., use, misuse, relapse) after patients completed detoxification. Gossop et al[7] followed eighty patients discharged from 21-day methadone withdrawal programs at two United Kingdom hospitals between 1984 and 1986. Seventy-one percent used opioids within the first six weeks of discharge, and 81% used opioids at some point during the six-month follow-up, though at the six-month endpoint 51% were opioid-free. Broers et al[8] followed 73 patients discharged from a Geneva, Switzerland 15-day (average) methadone tapering program between 1994 and 1995. Sixty-five percent were using drugs again (half of them regularly) within the first four weeks. At the six-month endpoint half of the population was physically dependent again. Chutuape et al[9] followed 113 patients discharged from a 3-day medical (mostly clonidine) detoxification program in Baltimore, Maryland between May and November 1996. At the one-, three- and six-month post-discharge assessments, 25-36% reported almost daily use, 21-30% reported no use, and the remainder reported occasional use. Overall, the mean number of days of heroin use decreased from 28 days (in the month prior to admission) to 11-14 days. In addition, several studies, most of them randomized trials of buprenorphine detoxification, collected limited datasets on post-detoxification outcomes which were disappointing (only 3-47% self-reporting abstinence, and only 7-31% producing negative urine drug screens over one- to three-month follow up periods).[10-20]

The overarching goal of the CTN-0051 parent study is to foster adoption of new relapse- prevention pharmacotherapies in community-based treatment programs where these could have a substantial public health impact. CTN-0051 is an open-label randomized comparative effectiveness trial of extended-release injectable naltrexone (XR-NTX, Vivitrol®), an opioid antagonist recently approved and indicated for the prevention of relapse to opioid dependence, versus buprenorphine-naloxone (BUP-NX, Suboxone®), a high affinity partial agonist indicated for maintenance treatment of opioid dependence. Participants in the CTN-0051 parent study are recruited from detoxification and short-term residential units, randomized and inducted onto one or the other treatment, and are then discharged to the community and treated for 24 weeks and followed for an additional 3 months post-treatment. The primary outcome is the time to relapse.

A treatment-as-usual (TAU) arm was considered at the time CTN-0051 was developed, but was not pursued for reasons including added cost and that it would slow recruitment to the two arms addressing CTN-0051's primary goals. The goal of this ancillary study is to collect a minimal data set from a similar TAU group in order to describe naturalistic opioid use outcomes after discharge from these detoxification and/or short-term residential programs. This ancillary study will be carried out by existing CTN-0051 staff. Recruitment will begin once recruitment for CTN- 0051 has ended, and will continue during the treatment and follow-up phases of CTN-0051.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective is to follow a group of participants with opioid use disorder to estimate treatment-as-usual rates of opioid use clinical outcomes following discharge to the community from detoxification and/or short-term residential programs.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is an observational study of participants with opioid use disorder leaving the same detoxification and/or short-term residential units from which participants for CTN-0051 are recruited, but who are discharged to TAU in the community. We will collect similar drug use measures as are collected in CTN-0051 that will allow us to estimate (1) days to first use and days to regular use, (2) number of days of use during the first four and eight weeks post- discharge to the community, and (3) number of positive, negative and missing UDSs at weeks 1, 4 and 8 post-discharge to the community.

6.2 Duration of Study and Visit Schedule

Participants will be in the study for approximately 8 weeks following discharge to the community, with visits at baseline, week 1, week 4 and week 8.

7.0 STUDY POPULATION

Approximately three hundred sixty (360) participants will be enrolled. Participants will be patients that were admitted to detoxification or short-term residential programs associated with CTN-0051 for opioid use disorder and that were discharged to the community.

7.1 Participant Inclusion Criteria

1. 18 years of age and older;
2. Meet DSM-5 criteria for opioid-use disorder (heroin or prescription opioids);
3. Have used opioids other than as specifically prescribed within thirty days prior to consent;
4. Seeking treatment for opioid dependence;
5. Able to provide written informed consent; and
6. Able to speak English sufficiently to understand the study procedures.

7.2 Participant Exclusion Criteria

1. Serious medical, psychiatric or substance use disorder that, in the opinion of the Site Principal Investigator (PI), would make participation hazardous to the participant, compromise study findings or prevent the participant from completing the study;
2. Suicidal or homicidal ideation that requires immediate attention;
3. Maintenance on methadone at doses of 30mg or greater at the time of signing consent;
4. Presence of pain of sufficient severity as to require ongoing pain management with opioids;
5. Currently in jail, prison or any inpatient overnight facility as required by court of law or have a pending legal action which may prevent an individual from completing the study;
6. If female, currently pregnant or breastfeeding or planning on conception; or
7. Prior participation in parent study CTN-0051.

7.3 Participant Recruitment

Participants will be recruited from the same detoxification and/or short-term residential programs participating in CTN-0051. Candidates admitted for opioid use disorder will be approached by research staff and provided information about the study.

8.0 SITE SELECTION

8.1 Number of Sites

Approximately six of the CTN-0051 sites will participate.

9.0 OUTCOME MEASURES

9.1 Outcome Measures

Outcomes are (1) days to first use and days to regular use (from TLFB), (2) number of days of use during the first four and eight weeks post-discharge to the community (from TLFB), and (3) number of positive, negative and missing UDSs at weeks 1, 4 and 8 (from UDS). Overdoses and deaths will also be tracked (from safety event reporting).

10.0 STUDY PROCEDURES

10.1 Informed Consent

All candidates for the study will be given a current local Institutional Review Board (IRB)- approved copy of the Informed Consent Form (ICF) to read. Appropriately qualified and trained study personnel will explain all aspects of the study and answer all of the study candidate's questions. Study procedures and the potential risks and benefits of participating in the study will be explained. Permission to access and extract information from their medical record will be obtained. After signing the consent form, participants will be given a copy of the form to keep for their records.

10.2 Screening/Baseline Visit

The screening/baseline period may encompass the time from admission to the inpatient setting until discharge to the community. Most assessments can take place at any time during this period (following completion of informed consent) with several of these assessments needing to be completed or updated not more than 48 hours prior to discharge to the community. Screening/baseline assessments include: consent, medical release of information, demographics form, locator form, detox utilization, DSM-5 checklist, information on treatment plans, urine drug screen, and Timeline Follow-Back.

10.3 Randomization

There is no randomization in this study.

10.4 Treatment/Intervention

There is no treatment or intervention in this study.

10.5 Collection of Biospecimens

A urine sample will be collected at each in-person visit and will be tested for the presence of the following drugs using a UDS dip card: opioids, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, marijuana, methadone, buprenorphine and ecstasy (MDMA). Two additional single strip tests will be performed: one for buprenorphine (BUP10) and a more sensitive test for opiates (OPI300). Samples will not be stored. Participant-level data will not be shared with the treatment program.

10.6 Premature Withdrawal of Participants

All participants will be followed for the duration of the study (CTN-0051-A2) unless they withdraw consent, die, or the investigator (site PI or LI) or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or early termination of the study by the Data and Safety Monitoring Board (DSMB) for safety or other reasons.

10.7 Follow-up

Participants will be followed at weeks 1, 4, and 8 where the following assessments will occur:

Week 1: Timeline follow-back, UDS, update on treatment plans, update locator, protocol-defined safety event collection.

Week 4: Timeline follow-back, UDS, update on treatment plans, update locator, protocol- defined safety event collection.

Week 8: Timeline follow-back, UDS, update on treatment plans, protocol-defined safety event collection, study termination.

10.8 Blinding

This is not a blinded study.

10.9 Participant Reimbursement

Participants will receive compensation following contribution of a viable urine sample. Payments are as follows: Baseline: $20; Week 1: $20; Week 4: $20; Week 8: $50. Maximum possible compensation is $110.

10.10 Retention Plan

Participants will be tracked for follow-up using the same methods and rigor employed in the CTN-0051 parent study. Assessments may be collected by telephone as a last resort.

11.0 STUDY ASSESSMENTS

11.1 Table of Assessments

	Screening/ Baseline	Day 0	Week 1	Week 4	Week 8
Informed consent	X				
Medical release	X				
Inclusion/exclusion	X	X[1]			
Demographics	X				
DSM-5	X				
Locator form	X	X[1]	X	X	
TLFB	X		X	X	X
UDS		X	X	X	X
Treatment plans	X	X	X	X	X
Detox utilization	X				
Safety			X	X	X
Study termination					X

[1]Review/complete if last assessment done more than 48 hours prior to discharge to community and update if necessary.

11.2 General Measures

11.2.1 Inclusion/Exclusion

This form lists each inclusion and exclusion criteria to document eligibility.

11.2.2 Locator Form

A locator form is used to obtain information to assist in finding participants. This form collects the participant's current address, email address, and phone numbers. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends who may know how to reach the participant are collected, as well as information such as social security number, driver's license number and other information to aid in searches of public records. This information will be collected at screening, and will be updated at the Day 0, Week 1, and Week 4 visits. No information from this form is used in data analyses nor is this information captured in the electronic data capture system (AdvantageEDC).

11.2.3 Demographics Form

The demographics form collects information about demographic characteristics of the participant, including gender, date of birth, ethnicity, race, education, employment status, and marital status. This form is completed at screening.

11.2.4 Study Termination Form

This form tracks the participant's status in the study. It is completed at the final visit, once the Week 8 follow-up visit window lapses for participants who do not complete the final follow-up, or at any other time in the event that the participant terminates from the study (withdraws consent, dies, etc.). This form is used in data analyses to address the study completion variable. This form also provides a location for the Site PI attestation of review of all study data.

11.3 Measures of Primary and Secondary Outcomes

11.3.1 Timeline Follow-back (TLFB)

The Timeline Follow-back procedure[21] will be used to elicit the participant's self-reported use of substances at baseline and throughout study participation. At screening, this form will be used to assess substance use for the 30-day period prior to admission to the inpatient treatment program. At Week 1, the TLFB will assess the period from discharge to the community up to the date preceding the Week 1 visit (the time in detox and/or short-term residential is not captured on this assessment). At weeks 4 and 8, the TLFB will assess each day since the previous TLFB assessment.

11.3.2 Urine Drug Screen (UDS)

Urine is collected for a urine drug screen at each in-person study visit. All urine specimens are collected using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. The UDS tests for the presence of the following drugs: opioids, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, marijuana, methadone, and ecstasy (MDMA). Two additional single strip tests will be performed: one for buprenorphine (BUP10) and a more sensitive test for opiates (OPI300). In the event urine specimen tampering is suspected, either based on the observation or the adulterant tests, study staff should request a second urine sample and may observe the urine collection process according to clinic standard operating procedures.

11.3.3 Treatment Plans

The treatment plan form collects information about the participant's living situation and drug use at the screening visit. Assessment of the participant's intention for treatment after discharge to community (i.e., leaving the detox and/or short-term residential unit) will be assessed at the Day 0 visit. At weeks 1, 4 and 8, participants are asked whether they are continuing to receive treatment in the community as planned, have initiated other treatment, or discontinued treatment.

11.4 Clinical and Safety Assessments

11.4.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

For purposes of this study only overdoses, whether hospitalized or not, and all deaths will be collected. At weeks 1, 4 and 8, research staff will ask about any overdoses that have occurred since the last study contact. Reporting definitions and procedures are outlined in the Manual of Operations. Additionally, any deaths from any cause will be reported on the adverse event (AE) form. No other AEs or SAEs will be captured in the course of this observational study.

11.5 Additional Drug Use Measures

11.5.1 DSM-5 Criteria

Assessment of current opioid use disorder will be determined using DSM-5 criteria. This is completed at screening to determine eligibility.

11.5.2 Detoxification Utilization Form

Data on detoxification, including number of days on the unit and medications received will be collected from the medical record.

12.0 TRAINING REQUIREMENTS

The study will be carried out by CTN-0051 staff. A webinar will be held prior to study start to provide an overview, highlight differences between the parent and ancillary studies and review the separate AdvantageEDC system.

13.0 STATISTICAL DESIGN AND ANALYSES

13.1 General Design

This is an observational study of participants with opioid use disorder leaving the same detoxification and/or short-term residential units from which participants for CTN-0051 are recruited, but who are discharged to TAU.

13.1.1 Outcomes

We will collect the same drug use measures as are collected in CTN-0051. Outcomes are (1) days to first use and days to regular use (from TLFB), (2) number of days of use during the first eight weeks (or parts thereof, e.g., first week, first 4 weeks, etc.) post-discharge into the community (from TLFB), and (3) number of positive, negative and missing UDSs at weeks 1, 4 and 8. The days to first opioid use will also be assessed by self-report (TLFB) and calculated starting at the date of discharge to the community. The date of discharge to the community will be defined as Day 0. Overdoses and deaths will also be tracked (from safety reporting).

13.2 Rationale for Sample Size and Statistical Power

No formal statistical hypothesis tests will be calculated for this study; therefore, there is neither sample size nor statistical power calculations. The study population is a convenience sample and it is anticipated that each participating site should be able to enroll approximately 60 participants for a total of approximately 360 participants. While the main objectives of this study are descriptive in nature, such as estimating the opioid use rate eight weeks after discharge to the community, it may be of interest to evaluate whether these opioid use outcomes are associated with certain covariates. Potential independent predictors of opioid use include: age, gender, race, ethnicity, use of medication-assisted treatment, and type of treatment received prior to discharge to the community.

13.2.1 Projected Number of Sites

Approximately six sites with inpatient detoxification programs and/or short-term residential treatment programs associated with CTN-0051 will recruit participants.

13.2.2 Projected Number of Participants per Site

Approximately 60 participants will be recruited at each of the approximately six sites.

13.2.3 Detectable Effect Sizes

Table 1 summarizes detectable effect sizes for the two outcomes: (a) time to first opioid use, and (b) time to first regular opioid use. The detectable hazard ratios (HRs) are calculated for various values of the standard deviation of the outcome measure and the overall percent of participants who had (a) used opioids or (b) regularly used opioids during the eight week follow- up period. Total sample sizes of 280, 320 and 360 were considered. If the target sample size of 360 is reached, and 60-70% of participants use or regularly use opioids by the week 8 follow-up visit, then there will be at least 80% power to detect a HR of approximately 1.46 with a type I error rate of 5%. On the other hand if only 320 participants are enrolled, then the detectable HR is around 1.50 and for 280 participants, then the detectable HR is around 1.40-1.75.

Table 1. Detectable hazard ratios for the outcomes measures time to (a) first opioid use, and (b) first regular opioid use

Total Sample Size	Detectable Hazard Ratio	Power (%)	Proportion of Participants who Used Opioids/ Regularly Used (%)	Standard Deviation of the Number of Days to First Opioid Use/Regular Use
280	1.75	83%	60%	0.4
	1.40	82%	70%	0.5
320	1.50	81%	60%	0.5
	1.47	83%	70%	0.5
360	*1.47*	*82%*	*60%*	*0.5*
	1.45	*84%*	*70%*	*0.5*

Table 2 summarizes detectable effect sizes for the outcomes based on the number of days of opioid use during the eight weeks post-discharge to the community of the study. The detectable mean differences for the two-sample *t*-test are calculated for various values of the group- specific mean and standard deviations of the outcome measure. Total sample sizes of 280, 320 and 360 were considered. If participants in one group use opioids on average two weeks out of the month, then we can detect a difference of 1.5 use days with at least 80% power (assuming a type I error rate of 5%) if the target sample size of 360 is achieved. Similarly, if participants in one group use approximately three weeks out of a month, then we can detect a difference of 1.5 days. With 320 participants enrolled, a mean difference of 1.5 days can still be detected with at least 80% power, but the detectable difference increases to 2.8 days with a total sample size of 280.

Table 2. Detectable differences in means for the number of days of opioid use during the eight weeks of follow-up

Total Sample Size*	Detectable Difference** in Means (days)	Power (%)	Mean (SD) in Group 1	Mean (SD) in Group 2
280	2.8 days	84%	14.0 (5.0)	15.8 (6.0)
	1.5 days	88%	21.0 (4.0)	22.5 (4.0)
320	1.5 days	83%	14.0 (3.5)	15.5 (5.5)
	1.5 days	83%	21.0 (3.5)	22.5 (5.5)
360	*1.5 days*	*82%*	*14.0 (3.5)*	*15.5 (6.0)*
	1.5 days	*88%*	*21.0 (4.5)*	*22.5 (4.5)*

* Assumes equal distribution of participants across the two groups.
** The difference is defined as the mean in Group 2 – mean in Group 1.

Table 3 summarizes detectable effect sizes for the outcomes based on urine drug screen testing. The detectable odds ratios are calculated for various values of the proportion of participants in each subgroup and the event rate in Group 1. Total sample sizes of 280, 320 and 360 were considered. For various values of the percent of participants in each subgroup, an odds ratio of around 2 (1.85-2.40) can be detected assuming an event rate of 50% in Group 1 with at least 80% power and total sample sizes of 280 to 360.

Table 3. Detectable odds ratios for UDS-based outcomes

Total Sample Size	Detectable Odds Ratios	Power (%)	Proportion in Group 1 (%)	Event Rate in Group 1 (%)
280	2.40	81%	20%	50%
	2.15	81%	30%	50%
	2.05	82%	40%	50%
	1.98	80%	50%	50%
	2.00	80%	60%	50%
	2.10	80%	70%	50%
	2.40	82%	80%	50%
320	2.30	82%	20%	50%
	2.05	82%	30%	50%
	1.98	83%	40%	50%
	1.90	81%	50%	50%
	1.98	84%	60%	50%
	2.00	80%	70%	50%
	2.30	84%	80%	50%
360	*2.15*	*81%*	*20%*	*50%*
	1.95	*81%*	*30%*	*50%*
	1.85	*80%*	*40%*	*50%*
	1.85	*82%*	*50%*	*50%*
	1.85	*81%*	*60%*	*50%*
	1.95	*82%*	*70%*	*50%*
	2.15	*82%*	*80%*	*50%*

13.3 Statistical Methods for Primary and Secondary Outcomes

The primary objective of this study is to estimate opioid use rates, via various measures of use (Section 13.1.1), overall and separately for the sub-groups defined by use of medication- assisted treatment and type of treatment received at the enrolling site. Secondary exploratory analyses will involve modeling of opioid use as a function of certain independent predictors (see Section 13.2). For the primary objective all continuous variables (e.g., percent use days in the first week) will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the group-specific sample size) of observed levels will be reported for all categorical measures.

To evaluate secondary exploratory outcomes, two main sub-groups from the observational cohort are (1) participants who receive any medication-assisted treatment and (2) participants who do not receive medication-assisted treatment. All outcomes listed in Section 13.1.1 will be calculated separately for each of these subgroups of the observational cohort, as well as in the overall study sample. Program type, that is, short-term detoxification vs. short-term residential rehabilitation, will also define groups to be separately analyzed.

For modeling the days to first opioid use and days to regular opioid use outcomes measures, a Cox regression model will be used after an assessment of the proportional hazards assumption. Should the key proportional hazards assumption be violated for a particular outcome and covariate, alternative models will be considered. The second set of outcomes relate to the number of days of opioid use. It is anticipated that the number of days of use will be non-normal, however we elect to analyze the data via a *t*-test which is fairly robust to misspecification of the underlying outcome distribution. Quantile regression may be used if modeling with multiple covariates is appropriate. For UDS-based outcomes, the dependent variable is binary (i.e., indicator of use or indicator of missingness) so univariate comparisons will be made using Pearson's χ^2 and any multivariate modeling will be implemented using logistic regression.

13.4 Significance Testing

There are no hypotheses being evaluated in this observational study with solely descriptive primary objectives, thus no formal statistical testing will be conducted. Exploratory comparisons will be made via modeling as described in Section 13.3.

13.5 Missing Data and Dropouts

The number of missing as well as the number of positive and negative UDSs will be tabulated separately when calculating the UDS outcome at weeks 1, 4 and 8. Analyses of self-reported use will impute intermittent missing days as use, but will not impute missing days due to drop- out or loss-to-follow-up.

13.6 Demographic and Baseline Characteristics

Baseline demographic variables (gender, age, race, ethnicity, educational level, employment status, and marital status) will be summarized for participants enrolled in the ancillary study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

13.7 Safety Analysis

Since this is an observational study with no intervention, no formal safety analysis is planned.

14.0 REGULATORY COMPLIANCE AND SAFETY

14.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. A Manual of Operations will be provided as a reference guide and study quality assurance tool.

14.2 Statement of Compliance

This study will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local Institutional Review Board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local protocol defined safety event reports will be submitted to each IRB, according to its usual procedures.

14.3 Institutional Review Board Approval

Prior to initiating the study, site investigators will obtain written local IRB approval to conduct the study at their respective site. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials given to the participant. Annual reports and progress reports will be submitted to the IRBs annually or at a frequency requested by each IRB so that continuous study approval is maintained without lapse. The Lead Investigator is responsible for maintaining in his research files copies of all performance site(s) current IRB/ERC approval notice(s), and IRB-approved consent document(s), including approval for all protocol modifications. These materials must be received by the Lead Investigator prior to the initiation of research activities at a given site, and must be available at any time for audit.

14.4 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent form will include all of the required elements of informed consent. Each study site must have the study informed consent approved by their IRB(s). A copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) prior to the site initiation visit and with each subsequent consent revision. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

Prior to informed consent, research staff will explain the study to the potential participant and provide a copy of the consent to read. If the prospective participant is interested in participating in the study, a staff member will review each section of the informed consent form in detail and answer any questions the prospective participant

may pose. The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the Site PI to obtain informed consent must be listed on the Site Staff Delegation of Responsibilities and Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the study. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The prospective participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

14.5 Monitoring

Remote monitoring by the DSC and CCC team members will occur as well as on-site monitoring by NIDA contracted monitors.

The node personnel performing site management and local QA for the parent study will also provide oversight for this ancillary study. They will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately.

14.6 Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The Lead Investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating sites will be notified if revision to the CoC is necessary. Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

14.6.1 Health Information Portability Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

14.7 Investigator Assurances

Each community treatment program site must file (or have previously filed) a Federalwide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the Principal Investigator at each study site will sign a protocol signature page providing assurances that the study will be performed according to the standards stipulated therein.

14.7.1 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

14.8 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings.

14.9 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

14.10 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, and regulatory files) are to be maintained by the Site Principal Investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with local IRB, state, and federal requirements, whichever is longest. The Sponsor and Lead Investigator must be notified in writing and acknowledgement must be received by the site prior to the destruction or relocation of research records.

14.11 Reporting to Sponsor

The Site Principal Investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the study or increase risk to study participants. Safety events of concern in this study will be reported. At the completion of the study, the Lead Investigator will provide a final report to the Sponsor.

14.12 Audits

The Sponsor has an obligation to ensure that this study is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance.

The Lead Investigator and authorized staff from the Greater New York Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (DHHS), and the sites' Institutional Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

14.13 Study Documentation

Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

14.14 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor 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. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the site's IRB. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the study.

All protocol deviations will be recorded in the electronic data capture AdvantageEDC system via the Protocol Deviation eCRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is enrolled into the study.

Additionally, each site is responsible for reviewing their local IRB's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

14.15 Safety Monitoring

14.15.1 Data and Safety Monitoring Board (DSMB)

The existing CTN-0051 DSMB will review the protocol and ICF prior to study initiation and will serve as the DSMB for this ancillary study. As this is an observational study and there is no treatment or other intervention, ongoing DSMB activities will be limited to updates on study progress (regulatory status, enrollment, protocol deviations and protocol-defined reportable safety events) at its regular meetings and notification of any issues of concern identified by the Lead Investigator or the Sponsor (NIDA).

14.15.2 Adverse Events (AEs)

For purposes of this study only overdoses, whether hospitalized or not, and all deaths will be collected. At weeks 1, 4 and 8, research staff will ask about any overdoses that have occurred since the last study contact. Additionally, any deaths from any cause will be reported on the AE form. No other AEs or SAEs will be captured in the course of this observational study. Reporting definitions and procedures are outlined in the Manual of Operations.

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

14.15.3 Medical Monitor

The CCC Safety Monitor/Medical Monitor is responsible for overseeing safety and for evaluating all protocol-defined reportable safety events. The safety team will review/monitor protocol- defined reportable safety event information entered on the Adverse Event (AD1) eCRF on a weekly basis. No additional follow-up forms will be completed nor reviewed in the AdvantageEDC data system. Reporting definitions and procedures are further outlined in the Manual of Operations and research staff at each participating study site will be appropriately trained on safety event reporting for this protocol using only the AD1 eCRF in the AdvantageEDC data system.

The CCC Safety Monitor/Medical Monitor will report events to the Sponsor and regulatory authorities. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings.

15.0 DATA MANAGEMENT

15.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. AdvantageEDC^{SM}, a web- based distributed data entry system, will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

15.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in the AdvantageEDC^{SM} User's Guide.

15.3 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, and 5) rigorously monitor final study data cleaning.

15.4 Data Collection

The data collection process consists of direct data entry at the study sites into AdvantageEDC[SM]. In the event that AdvantageEDC[SM] is not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data entry into AdvantageEDC[SM] should be completed according to the instructions provided. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

15.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into the AdvantageEDC[SM] system in accordance with the AdvantageEDC[SM] User's Guide. Only authorized individuals shall have access to eCRFs.

15.6 Data Editing

Completed data will be entered into AdvantageEDC[SM]. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into AdvantageEDC[SM].

15.7 Data Transfer/Lock

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

15.8 Data Training

The study staff will be the same as the staff in CTN-0051. The training plan for CTP staff includes provisions for training on assessments, eCRF completion guidelines, and data management procedures.

15.9 Data Quality Assurance

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

15.10 Study Timeline

Study preparation will include obtaining IRB approval, applying for a Certificate of Confidentiality, receiving DSMB approval, developing the data collection system, developing the manual of operations, conducting all staff training, and endorsing sites. Recruitment is expected to take approximately 5-6 months, with follow-up continuing for approximately two months post completion of the recruitment phase. Two months will be allowed for data lock after the end of the follow-up period. Data lock is projected to occur concurrently with data lock for the parent protocol.

16.0 PUBLICATIONS AND OTHER RIGHTS

Per NIH Policy, the results of the proposed study are to be made available to the research community and the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

17.0 SIGNATURES

SPONSOR'S REPRESENTATIVE (CCTN DESIGNEE)

Printed Name	**Signature**	**Date**

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 2.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	**Signature**	**Date**

Site Name _____

Node Affiliation _____

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19.0 APPENDIX A: DATA AND SAFETY MONITORING PLAN

1.0 BRIEF STUDY OVERVIEW

CTN-0051-A2 will collect a minimal data set on post-discharge to community TAU clinical outcomes for a similar group of participants leaving detox or short-term residential programs from the same sites as CTN-0051.

2.0 DATA AND SAFETY MONITORING BOARD (DSMB)

The existing CTN-0051 DSMB will review the protocol and ICF prior to study initiation and will serve as the DSMB for this ancillary study. As this is an observational study and there is no treatment or other intervention, ongoing DSMB activities will be limited to updates on study progress (regulatory status, enrollment, protocol deviations and protocol-defined reportable safety events) at its regular meetings and notification of any issues of concern identified by the Lead Investigator or the Sponsor (NIDA).

3.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture system (AdvantageEDC^{SM}) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

The investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the Site Principal Investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

4.0 DATA LOCK AND TRANSFER

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will “lock” the study database from further modification. The final analysis dataset will be transferred to the Lead Investigator or designee. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated parties for posting on Datashare, as well as storage and archiving.

Reference: http://grants.nih.gov/grants/guide/notice-files/not98-084.html