

**CTN-0030 Protocol Amendment to Examine Long-term Outcomes
CTN Northern New England Node**

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STUDY OBJECTIVES: To examine long-term outcomes for individuals with opioid analgesic (OA) dependence who participated in CTN-0030. Specifically, we wish to describe the substance use trajectories of randomized participants and identify factors associated with long-term recovery from OA dependence for future research. This exploratory, naturalistic study is intended to help generate hypotheses and guidance for further treatment research on opioid analgesic dependence.

Specific research questions:

- Long-term recovery outcomes
 - What proportion of study participants, who have never used heroin before, later use heroin and how often?
 - What proportion of study participants who have previously used heroin but have not previously been dependent on goes on to later become dependent on heroin?
 - Among non-opioid injectors at study initiation, what proportion goes on to initiate opioid injection?
 - What proportion of study participants go on to receive other substance use treatment services including naltrexone, methadone maintenance, or buprenorphine maintenance?
- Identify factors associated with long-term recovery from OA dependence for future research
 - Are short-term treatment outcomes (i.e., Phase 1 success or Phase 2 substantial improvement) associated with long-term outcomes?
 - Are chronic pain, heroin use, major depressive disorder, PTSD, and smoking associated with long-term treatment outcomes?
 - To what extent is bodily pain associated with long-term treatment outcome?
 - For chronic pain patients, what happens to bodily pain over time?

STUDY DESIGN: Participants will be assessed via telephone at 1.5, 2.5, and 3.5 years post-Phase 1 randomization. This permits a consistent time interval for all participants. The assessment will require 45-60 minutes to complete. Participants will receive \$75 for each interview completed.

Data will be entered into the currently available DCRI INFORM data management system (DMS) by trained, certified research assistants.

Assessments

At each follow-up point, the following assessments will be administered: CIDI Section L for opioids (and heroin worksheet as appropriate), Brief Pain Inventory, ASI-Lite, and the Concomitant Treatment (Table 1 below). Data will be integrated with Main Trial data for analyses. Instructions for these assessments will be modified to guide interviewers in correct administration for the long-term follow-up study. As appropriate, interviewers will be trained and certified to administer these assessments.

For research questions involving long-term outcome, the primary outcome will be use of opioids on four or fewer days in the past 30 days [ASI-Lite FU]. Secondary outcomes will be perceived quality of health [SF36 item 1] and, for chronic pain participants, pain [SF36 item 8 and 9] will be examined.

Table 1. Assessments

| CRF/Instrument | Interval | Time (minutes) | Information Captured | Instruction Modifications |
|---|--|----------------|--|---------------------------|
| CIDI section L | past year | 5-20 | present DSM-IV dx-heroin and OA (3 or more symptoms in the past year) | yes |
| Pain and Opioid Analgesic Use History | past week | 5 | route of administration experiencing pain pain severity functional interference | yes |
| Concomitant Treatment & Medication | past year | 5-10 | treatment utilization | yes |
| ASI-Lite | past 30 days | 25 | substance use outcome substance-related problems | no |
| SF-36 (items 1, 2, 7, & 8) | item 1-no time frame item 2-past year items 8 & 9-past 30 days | 1 | global health bodily pain index | no |
| Fagerstrom | current | 2-3 | current nicotine behaviors | no |

Participant Enrollment in LTFU

Initial participant recontact will be managed by participating CTPs. Local sites will utilize pre-existing contact information to make CTN-0030 participants aware of the opportunity to participate in the LTFU. Training in procedures for recontacting participants will be conducted by Lead Node staff to ensure procedures are conducted in accordance with good research practice and human subjects protection guidelines. This training will also include specific training on strategies for tracking hard to reach potential participants utilizing contact information (e.g., call strategies). Monthly performance indicators will be established and monitored to ensure recontact activities are progressing.

LTFU Study Retention

Retention of consented participants will be managed by Lead Node staff with expertise and training in managing long-term follow-up studies. Retention strategies will include regular contact with participants by telephone and mail (with permission).

STUDY POPULATION: Participants will be all participants (648) randomized to Phase 1 who agree to participate in the long-term follow-up (LTFU) study.

Anticipated Sample Available for Analysis

As shown in Table 2 below, fewer potential participants are available for the 18 month follow-up period. If we assume that our first assessments can begin in January 2009, this results in 437 potential participants at 18mo follow-up, 642 at 30mo follow-up, and 648 at 42mo follow-up. To optimize participation in the LTFU study and ensure smooth transition of participants from CTPs to the Lead Node LTFU staff, we will develop standard procedures and train CTP staff on these procedures. For example, particular attention will be placed on minimizing the time between recontact, consent, and notification of the Lead Node.

Table 2. Participant flow (by month of randomization)

| Ph1 rand | rand | cum rand | 18mo | 30mo | 42mo |
|----------|------|----------|--------|--------|--------|
| Jun-06 | 3 | 3 | Nov-07 | Nov-08 | Nov-09 |

| | | | | | |
|---------|----|-----|--------|--------|--------|
| Jul-06 | 3 | 6 | Dec-07 | Dec-08 | Dec-09 |
| Aug-06 | 9 | 15 | Jan-08 | Jan-09 | Jan-10 |
| Sep-06 | 7 | 22 | Feb-08 | Feb-09 | Feb-10 |
| Oct-06 | 11 | 33 | Mar-08 | Mar-09 | Mar-10 |
| Nov-06 | 11 | 44 | Apr-08 | Apr-09 | Apr-10 |
| Dec-06 | 8 | 52 | May-08 | May-09 | May-10 |
| Jan-07 | 8 | 60 | Jun-08 | Jun-09 | Jun-10 |
| Feb-07 | 7 | 67 | Jul-08 | Jul-09 | Jul-10 |
| Mar-07 | 35 | 102 | Aug-08 | Aug-09 | Aug-10 |
| Apr-07 | 30 | 132 | Sep-08 | Sep-09 | Sep-10 |
| May-07 | 39 | 171 | Oct-08 | Oct-09 | Oct-10 |
| Jun-07 | 30 | 201 | Nov-08 | Nov-09 | Nov-10 |
| Jul-07 | 10 | 211 | Dec-08 | Dec-09 | Dec-10 |
| Aug-07 | 26 | 237 | Jan-09 | Jan-10 | Jan-11 |
| Sep-07 | 27 | 264 | Feb-09 | Feb-10 | Feb-11 |
| Oct-07 | 36 | 300 | Mar-09 | Mar-10 | Mar-11 |
| Nov-07 | 33 | 333 | Apr-09 | Apr-10 | Apr-11 |
| Dec-07 | 31 | 364 | May-09 | May-10 | May-11 |
| Jan-08 | 32 | 396 | Jun-09 | Jun-10 | Jun-11 |
| Feb-08 | 31 | 427 | Jul-09 | Jul-10 | Jul-11 |
| Mar-08 | 30 | 457 | Aug-09 | Aug-10 | Aug-11 |
| Apr-08 | 32 | 489 | Sep-09 | Sep-10 | Sep-11 |
| May-08 | 34 | 523 | Oct-09 | Oct-10 | Oct-11 |
| Jun-08 | 25 | 548 | Nov-09 | Nov-10 | Nov-11 |
| Jul-08 | 23 | 571 | Dec-09 | Dec-10 | Dec-11 |
| Aug-08 | 19 | 590 | Jan-10 | Jan-11 | Jan-12 |
| Sep-08* | 20 | 610 | Feb-10 | Feb-11 | Feb-12 |
| Oct-08* | 20 | 630 | Mar-10 | Mar-11 | Mar-12 |
| Nov-08* | 18 | 648 | Apr-10 | Apr-11 | Apr-12 |

**final three recruitment months are projected*

***assumes Jan 09 implementation & +/- 45 day window for each follow-up period*

STATISTICAL ANALYSIS: All analysis will be completed after completion of Main Trial primary outcome analyses and dissemination. DCRI will conduct analyses to address research questions identified above.

Sample size

We estimate conservatively that the sample available for analysis will be 224 at 18 month follow-up and 324 at 30 and 42 month follow-ups. The estimate assumes 35% participation from participants who participated only in Phase 1, and 65% participation from participants who participated in Phase 1 and Phase 2. This estimated sample size for each time period is based on experiences with long-term follow-up in the NIAAA COMBINE trial (in which McLean Hospital participated), rates in other long-term follow-up studies, and current Phase 1 and Phase 2 follow-up rates.

Table 3. Estimate Sample for Long-term Follow-up Study

| | 18mo | 30mo | 42mo |
|---------------------------|-------------|-------------|-------------|
| Potential Participants** | 437 | 642 | 648 |
| Estimated Sample for LTFU | 239 | 325 | 325 |

Statistical Analysis

The number of participants at each follow-up period will be summarized by CTP sites and overall. The description of categorical variables will be in terms of proportions; the description of continuous variables will be in terms of means and standard deviations, medians, quartiles, and minimum and maximum values. Analyses of substance use trajectories (e.g., probability of study participant going on to use heroin) will be based upon a logistic regression analysis that appropriately accounts for the correlation among the measures at months 18, 30, and 42. The logistic regression model, fitted using the generalized estimating equations (GEE) approach, will include the effect of time (18, 30, 42mo) considered as a purely categorical classification variable unless there is strong evidence that the pattern of change is approximately linear. Analyses involving long-term outcome [ASI-Lite FU] will also be based upon similar logistic regression models that include as additional covariates the effects of short-term treatment outcomes, chronic and ongoing pain. These longitudinal analyses will be supplemented by discrete time survival analyses that examine the effects of these factors on time to long-term recovery from OA dependence.

For all analyses, we will use statistical methods that incorporate partially observed data on subjects who drop out. For example, modern regression methods for longitudinal data (e.g., linear mixed effects models for quantitative outcomes and generalized linear mixed models for categorical outcomes) can incorporate all the available data on a subject, and these methods are relatively robust with respect to drop-out and missing data, unless the drop-out mechanism is informative. In our analyses and presentation of results, we plan to provide detailed descriptions of the patterns of missing data and assess the sensitivity of results to different assumptions about the mechanism by which data are missing, e.g., informative drop out mechanisms. For example, pattern-mixture models can be used to assess the sensitivity of results to informative drop out from this study (Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. New Jersey: Wiley, 2004.)

HUMAN SUBJECTS PROTECTION: After receiving appropriate IRB approvals from participating CTN-0030, local sites will contact their participants to describe the study and, if interested, consent participants for the long-term follow-up project. Consent will include sharing identifying information with Lead Node personnel. Once participants are consented, the Lead Node will conduct all study procedures. Human subjects protection will be ensured in accordance with the safeguards and procedures detailed in the CTN-0030 Main Trial protocol.

REGULATORY AND ADMINISTRATIVE CONSIDERATIONS: The study will be submitted as a protocol amendment and reviewed by the appropriate institutional IRBs. In consultation with the CCTN Clinical Coordinating Center, we will determine whether a separate Certificate of Confidentiality will be required.

STUDY TIMETABLE: As described above, the study will be completed by May 2012. Data lock would occur two months after that with the final report submitted to NIDA by September 2012.

Study Schema: CTN-0030 Long-term Follow-up Study

