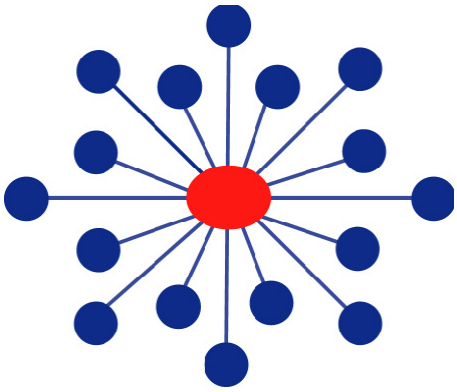

NIDA CTN Protocol 0055

Comparing Treatments for HIV-Infected Opioid and Alcohol Users in an Integrated Care Effectiveness Study (CHOICES)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Alcoholics Anonymous
AE	Adverse Event
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASI-Lite	Addiction Severity-Index-Lite
BHIVES	Buprenorphine and HIV Evaluation Study
BMI	Body Mass Index
BUP	Buprenorphine
BUP-NX	Buprenorphine+Naloxone (Suboxone®)
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CHRT	Concise Health Risk Tracking
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DSC	Data and Statistics Center
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

Abbreviation	Definition
IDU	Injection Drug User
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LI	Lead Investigator
mg	Milligrams
MMT	Methadone Maintenance Treatment
NDA	New Drug Application
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NTX	Naltrexone
NX	Naloxone
OHRP	Office for Human Research Protections
PI	Principal Investigator
PLG	Polylactide-co-glycolide
QA	Quality Assurance
RAB	Risk Assessment Battery
RRTC	Regional Research and Training Center
SAE	Serious Adverse Event
SL-BUP	Sublingual buprenorphine/naloxone
SOP	Standard Operating Procedures
TAU	Treatment as Usual
TLFB	Timeline Follow-Back
UDS	Urine Drug Screen
WHOQOL-BREF	World Health Organization Quality of Life BREF
XR-NTX	Extended-Release Naltrexone (Vivitrol®)

2.0 STUDY SYNOPSIS AND SCHEMA

Opioid and alcohol use disorders are common in HIV-infected individuals (Braithwaite, Conigliaro et al. 2007; Chander, Josephs et al. 2008; Korthuis, Josephs et al. 2008; Bertholet, Cheng et al. 2010; Korthuis, Fiellin et al. 2012). Untreated opioid and alcohol use disorders are associated with increased HIV risk behaviors (Stein, Hanna et al. 2000; Cook, McGinnis et al. 2006; Chaudhry, Botsko et al. 2011), decreased receipt of antiretroviral therapy (ART) (Andersen, Bozzette et al. 2000; Cook, Sereika et al. 2001; Miguez, Shor-Posner et al. 2003; Korthuis 2004), decreased ART adherence (Cook, Sereika et al. 2001; Wood, Montaner et al. 2003; Hicks, Mulvey et al. 2007; Azar, Springer et al. 2010; Kalichman, Grebler et al. 2012), decreased HIV viral suppression (Lucas, Cheever et al. 2001; Lucas, Gebo et al. 2002; Palepu, Tyndall et al. 2003; Wood, Montaner et al. 2003; Wu, Metzger et al. 2011), greater HIV-related symptoms (Mathews, McCutchan et al. 2000; Shacham, Agbebi et al. 2011), and higher hospitalization rates (Fleishman, Gebo et al. 2005; Palepu, Horton et al. 2005). Compared to other HIV risk groups, persons who inject drugs are less likely to engage in HIV care and achieve HIV viral suppression (Lucas, Cheever et al. 2001; Wood, Montaner et al. 2003; Fleishman, Yehia et al. 2012).

Treatment of substance use disorders can increase engagement in HIV care (Lucas, Chaudhry et al. 2010; Altice, Bruce et al. 2011; Korthuis, Fiellin et al. 2011). Opioid replacement therapy (ORT) with methadone (Metzger, Woody et al. 1993) and sublingual buprenorphine/naloxone (BUP/NX) (Sullivan, Moore et al. 2008) decrease HIV transmission risk behaviors and improve HIV outcomes, yet access to these medication-assisted therapies is limited and requires adherence to daily dosing. Use of medication-assisted treatment of alcohol use disorders is rare in HIV clinics but associated with decreased HIV RNA levels in alcohol-dependent, HIV-infected Veterans treated with oral naltrexone in addiction treatment settings (Tetrault, Tate et al. 2012).

HIV providers are well-positioned to integrate novel treatments for substance use disorders into HIV treatment settings, but thus far only BUP/NX has been adopted in HIV practice. In the Buprenorphine-HIV Evaluation and Support (BHIVES) Collaborative (a demonstration of integrated care for HIV and opioid dependence), HIV-infected individuals with opioid dependence who received office-based BUP/NX from an HIV clinic provider decreased opioid use (Fiellin, Weiss et al. 2011), increased ART use (Altice, Bruce et al. 2011), experienced higher quality of HIV care (Korthuis, Fiellin et al. 2011) and reported better quality of life (Korthuis, Tozzi et al. 2011). HIV treatment guidelines now recommend opioid agonist therapy as a key treatment strategy for engaging IDU in HIV treatment (Thompson, Aberg et al. 2012). Retention on agonist therapy remains limited, however, due to daily dosing requirements.

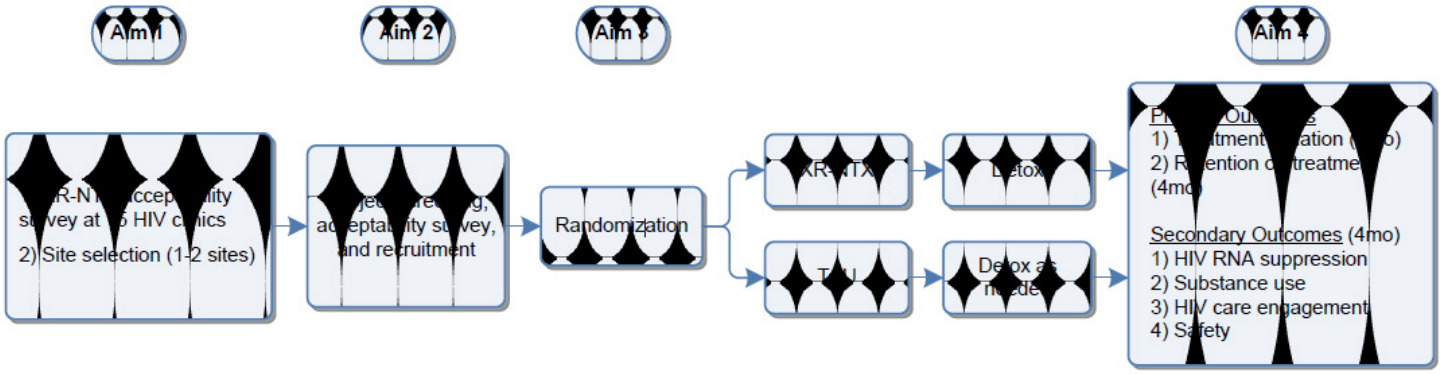
Long-acting antagonist treatment may provide an alternative to daily agonist therapy for patients with opioid and alcohol use disorders, though its acceptability to patients and providers is unknown. Extended-release naltrexone (XR-NTX), a deep muscle injection that lasts 28 days, eliminates the need for daily dosing. XR-NTX improves alcohol dependence treatment adherence and retention when integrated into primary care clinics (Lee, Grossman et al. 2010; Lee, Grossman et al. 2012), but has not been tested in HIV care settings. XR-NTX also may be preferred by some HIV-infected patients who prefer a non-narcotic treatment option or once a month dosing.

We propose an open-label, randomized, pilot trial of XR-NTX vs. treatment as usual (TAU) for treatment of opioid and alcohol use disorders in HIV-infected patients (Figure 2.0.1). The goal of this pilot study is to determine the acceptability and feasibility of XR-NTX in HIV practice and inform development of a multi-site comparative effectiveness trial of XR-NTX vs. TAU in HIV clinics. During the study start-up period, we will conduct a survey of HIV provider attitudes toward opioid antagonist therapy at 15 high-volume HIV clinics to assess willingness to prescribe antagonist therapy and inform the site selection process (Aim 1). During pilot study implementation,

we will survey HIV-infected patients regarding attitudes toward opioid antagonist therapy (Aim 2), track rate of participant recruitment (Aim 3), and randomize those who have untreated opioid and/or alcohol use disorders to receive XR-NTX vs. TAU (Aim 4). Participants will attend study visits every 4 weeks for 16 weeks. Treatment initiation will be assessed at 4 weeks and retention at 16 weeks (4 XR-NTX injections). Randomization will continue until a maximum of 50 participants or 12 months are reached. Pilot study duration will be a maximum of 17 months (maximum 12 months recruitment + 5 months study participation for those enrolled at the end of the recruitment period). We will assess feasibility of a multi-site trial of XR-NTX vs. TAU by addressing four pilot study specific aims.

2.1 Figure Study Schema

Study Start Up (4-6 month duration) **Pilot Study (Maximum 17 months duration)**



Aim 1: Assess HIV provider knowledge and attitudes toward opioid antagonist therapy in HIV clinics. We will survey HIV providers in 15 high-volume HIV clinics to assess knowledge and attitudes toward medication-assisted treatment for opioid and alcohol use disorders. Each HIV clinic director will also complete a) a survey of site characteristics (e.g. # patients with alcohol and opioid use disorders, # providers), and b) an anonymous survey of HIV clinic providers in these clinics. The results of both surveys will inform site selection.

Aim 1 Pilot Objective: Assess attitudes toward and willingness to use XR-NTX and estimate the proportion of HIV providers willing to prescribe XR- NTX for opioid and/or alcohol use disorders.

Aim 2: Assess patient acceptance of antagonist therapy in HIV clinics. During recruitment, potential subjects at the pilot RCT site(s) with alcohol and/or opioid use disorders will receive patient education materials about antagonist and agonist treatments, then complete a brief survey regarding knowledge and attitudes toward XR-NTX treatment of substance use disorders and willingness to be randomized to a trial of XR-NTX vs. TAU. Participants will be classified as accepting of XR-NTX for alcohol use disorders, opioid use disorders, or both.

Aim 2 Pilot Objective: Assess attitudes toward and willingness to use opioid antagonist therapy therapy and estimate the proportion of potential subjects approached willing to participate in a trial of XR-NTX vs. TAU.

Aim 3: Assess rate of participant recruitment. Recruitment from 2 sites will proceed until either

50 participants have been recruited or 12 months of recruitment have elapsed, whichever comes first. The recruitment time and number of participants recruited will be used to predict the length of enrollment required for a larger multi-site study.

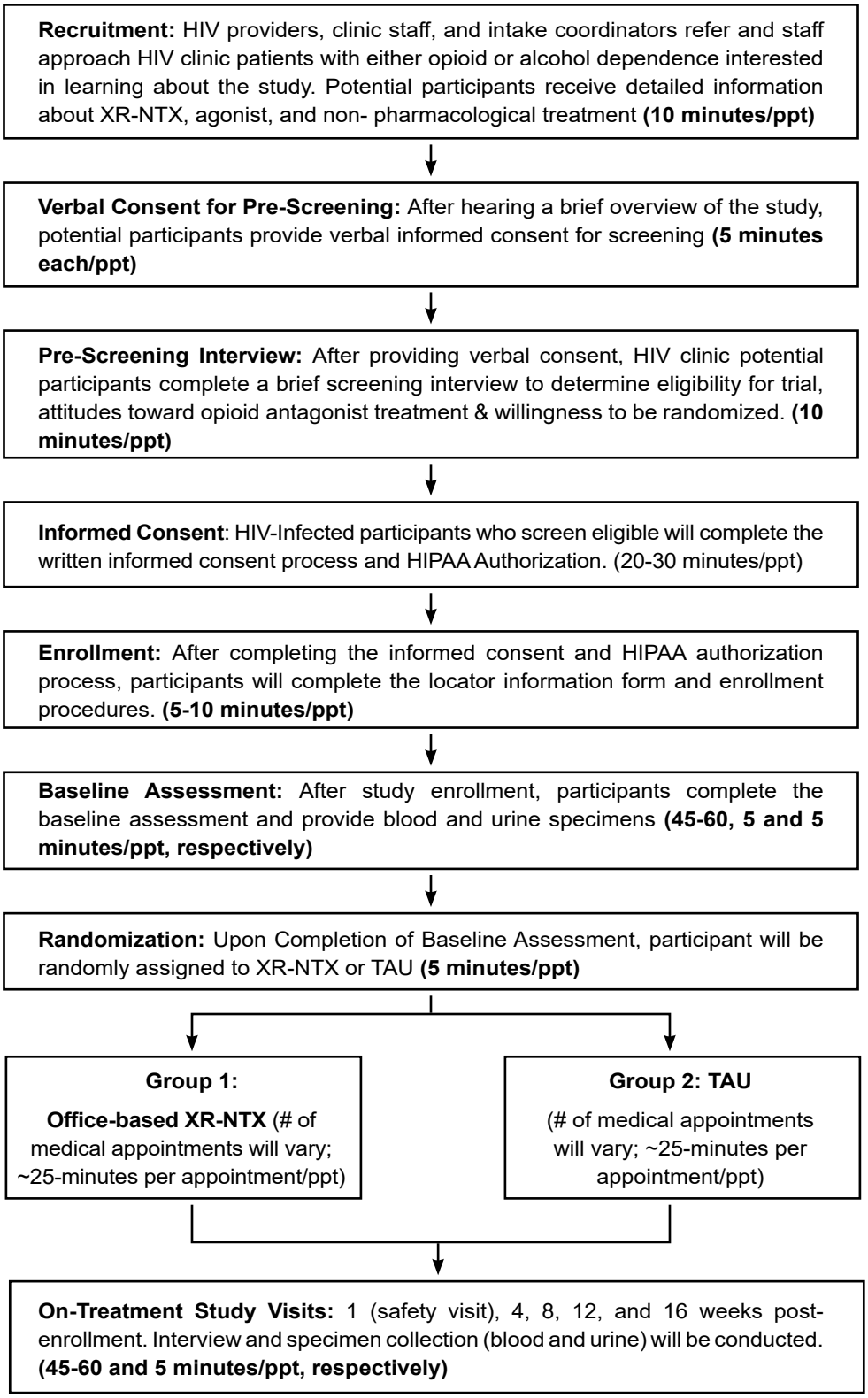
Aim 3 Pilot Objective: Assess the number of participants recruited per year.

Aim 4: Assess the feasibility of integrating XR-NTX for opioid and alcohol use disorders into HIV clinics. Data collection during study start-up will inform selection of 2 HIV clinics to implement XR-NTX treatment. HIV providers and staff will be trained in detoxification and XR- NTX induction and management. HIV-infected subjects with untreated opioid and/or alcohol use disorders will be randomized to XR-NTX or TAU, followed by detoxification (if needed) and treatment induction. The primary outcomes are 1) treatment initiation (successful treatment initiation of XR-NTX or TAU within 4 weeks of randomization), and 2) retention on treatment condition at 16 weeks. Secondary outcomes include change in 1) HIV-1 RNA viral suppression, 2) Illicit drug and alcohol use, 3) HIV care engagement (receipt of ART, HIV visit adherence, ART adherence), and safety (percent with precipitated withdrawal, hepatotoxicity, or overdose).

Aim 4 Pilot Objective A: Estimate effect size point estimates for rate of treatment initiation and 16 week retention among HIV-infected patients with alcohol or opioid use disorders randomized to XR-NTX vs. TAU.

Aim 4 Pilot Objective B: Estimate effect size point estimates for secondary outcomes of HIV-1 RNA viral suppression, illicit drug and alcohol use, HIV care engagement, and safety among HIV-infected patients with alcohol or opioid use disorders randomized to XR-NTX vs. TAU.

3.0 STUDY FLOW CHART



4.0 INTRODUCTION

4.1 Background and Rationale

Opioid Use Disorders in HIV-infected Persons. Opioid use disorders are common in HIV- infected individuals (Lum and Tulsky 2006; Korthuis, Josephs et al. 2008; Mathers, Degenhardt et al. 2008). When untreated, opioid dependence in HIV-infected persons is associated with increased HIV risk behaviors (Chaudhry, Botsko et al. 2011), decreased receipt of antiretroviral therapy (ART) (Andersen, Bozzette et al. 2000; Korthuis 2004), decreased ART adherence (Hicks, Mulvey et al. 2007), decreased HIV viral suppression (Lucas, Cheever et al. 2001; Lucas, Gebo et al. 2002; Palepu, Tyndall et al. 2003; Wood, Montaner et al. 2003), decreased health related quality of life (Korthuis, Tozzi et al. 2011), greater HIV-related symptoms, (Mathews, McCutchan et al. 2000), higher hospitalization rates (Fleishman, Gebo et al. 2005), and greater HIV disease progression and death (Lucas, Griswold et al. 2006). Only 21% of HIV- infected individuals referred are established and retained in ongoing HIV care (Fleishman, Yehia et al. 2012) and IDU are least likely to engage in HIV care and achieve HIV viral suppression compared to other HIV risk groups (Lucas, Cheever et al. 2001; Wood, Montaner et al. 2003; Fleishman, Yehia et al. 2012).

Opioid Use Disorder Treatment and HIV Outcomes. Treatment of opioid use disorders with methadone or buprenorphine can improve receipt of ART, ART adherence, and HIV viral suppression. Over four decades of evidence demonstrate that methadone maintenance therapy (MMT) is both efficacious in clinical trials and effective in the community in promoting and sustaining abstinence and reducing risks associated with opioid use disorders (Mattick, Kimber et al. 2008; Kreek, Borg et al. 2010). In a cohort of HIV-infected IDU in Vancouver, British Columbia, MMT was associated with greater ART adherence (AOR 1.52; 95% CI 1.16-2.00), HIV-1 RNA suppression (AOR 1.34; 95% CI 1.00-1.79), and CD4 cell count rise (AOR 1.58; 95% CI 1.26-1.99) over time (Palepu, Tyndall et al. 2006).

The approval of buprenorphine for office-based treatment of opioid dependence expanded patient treatment options and access to addiction care. In a pilot trial (n=93) of clinic-based buprenorphine vs. referral for methadone maintenance, HIV-infected participants randomized to clinic-based buprenorphine treatment were more likely to engage in treatment for opioid dependence vs. those referred for methadone (74% vs. 41%, p<.001) but ART receipt, HIV RNA and CD4 counts did not differ at 12 months (Lucas, Chaudhry et al. 2010). In the Buprenorphine-HIV Evaluation and Support initiative (BHIVES), HIV-infected individuals with opioid dependence who received clinic-based buprenorphine/naloxone (BUP/NX) from an HIV clinic provider decreased opioid use (Fiellin, Weiss et al. 2011), experienced higher quality of HIV care (Korthuis, Fiellin et al. 2011) and reported better quality of life (Korthuis, Tozzi et al. 2011). Sixty percent of BHIVES participants were already on ART at baseline. Participants initiating clinic- based BUP/NX (N = 295) were significantly more likely to initiate or remain on ART and improve CD4 counts over time compared with baseline. Retention on BUP/NX for three or more quarters was associated with increased likelihood of initiating ART (β = 1.34 [95% CI 1.18, 1.53]) and achieve viral suppression (β = 1.25 [95% CI 1.10, 1.42]) for the 64 of 119 (54%) participants not on ART at baseline compared with the 55 participants not retained on buprenorphine (Altice, Bruce et al. 2011).

Opioid agonist therapy with methadone (Metzger, Woody et al. 1993) or sublingual BUP/NX (Sullivan, Moore et al. 2008) is associated with decreases in HIV risk behaviors. A recent meta- analysis of 12 studies assessing the impact of opioid substitution treatment on HIV transmission showed a 54% reduction in HIV infection among IDU (MacArthur, Minozzi et al. 2012).

Alcohol Use Disorders in HIV-Infected Persons. Alcohol consumption is common in persons living with HIV (PLWH), with rates of heavy drinking twice that of the U.S. population (Galvan, Bing et al. 2002; Chander, Josephs et al. 2008). Untreated individuals with alcohol use disorders (AUDs) have lower utilization of HIV outpatient care (Cunningham, Sohler et al. 2006) and lower access and adherence to ART (Golin, Liu et al. 2002; Halkitis, Parsons et al. 2003; Samet, Horton et al. 2004; Chander, Himelhoch et al. 2006; Chander, Lau et al. 2006; Gordon, McGinnis et al. 2006; Braithwaite, Conigliaro et al. 2007; Azar, Springer et al. 2010). Among patients on ART who drink alcohol, 51% report skipping ART doses while drinking, which was associated with worse virologic and immunologic HIV control (Kalichman, Grebler et al. 2013). Heavy alcohol use has been associated with accelerated HIV disease progression measured by CD4 cell count and HIV RNA levels (Miguez, Shor-Posner et al. 2003; Samet, Cheng et al. 2007; Conen, Fehr et al. 2009; Azar, Springer et al. 2010; Baum, Rafie et al. 2010; Kalichman, Grebler et al. 2012) and with non-AIDS-related health conditions in PLWH, including liver disease (Salmon-Ceron, Lewden et al. 2005), certain cancers (McGinnis, Fultz et al. 2006) and neuropsychological impairment (Rothlind, Greenfield et al. 2005). In hepatitis C (HCV) co- infected patients, low CD4 count, alcohol consumption rate, and age at HCV infection are associated with liver fibrosis progression (Benhamou, Bochet et al. 1999). Among persons with untreated HIV, HIV infection may decrease the metabolism and clearance of alcohol, resulting in increased susceptibility to any given level of alcohol consumption (McCance-Katz, Lum et al. 2012). Finally, hazardous alcohol consumption (defined as 5 or more standard drinks on drinking days) is associated with decreased overall survival by more than 3 years in HIV- infected persons if consumption occurs once weekly or greater, and by 6.4 years with daily consumption (Braithwaite, Conigliaro et al. 2007).

Alcohol Use Disorder Treatment and HIV Outcomes. Few studies evaluate the effect of AUD treatment on HIV outcomes or transmission. Recent abstinence from alcohol was associated with improved ART adherence in a longitudinal study of HIV-infected patients with alcohol problems (Samet, Horton et al. 2004). In a prospective cohort study of HIV-infected patients with AUDs, receipt of alcohol treatment was associated with greater odds of receiving ART (adjusted OR 1.70, 95% CI 1.03, 2.83), but not ART adherence or HIV-1 RNA suppression (Palepu, Horton et al. 2004). In the same study, participants who received alcohol treatment reported less emergency department (ED) utilization (Palepu, Horton et al. 2003) and a non-statistically significant trend toward increased liver specialty care referrals (Palepu, Cheng et al. 2006), but reported no difference in hospital utilization (Palepu, Horton et al. 2005) or HIV risk behaviors (Palepu, Raj et al. 2005). A randomized trial of intensive adherence counseling in HIV-infected patients with AUDs had no effect on ART adherence, HIV viral load, CD4 count, or alcohol use (Samet, Horton et al. 2005). Previous trials of medication-assisted treatment for alcohol use disorders have not assessed HIV risk behaviors (Carroll, Nich et al. 1998; Kiritzé-Topor, Huas et al. 2004; Garbutt, Kranzler et al. 2005; Johnson, Rosenthal et al. 2007).

Need For Expanded Treatment Options in HIV Clinics. Despite the availability of MMT in most communities and recent adoption of office-based buprenorphine in some HIV practices, an expanded palette of treatment options for opioid and alcohol use disorders in HIV clinics is greatly needed. Only a minority of HIV-infected patients with opioid or alcohol use disorders receive addiction treatment (Burnam, Bing et al. 2001; Korthuis, Josephs et al. 2008). For those who receive pharmacologic treatment for opioid use disorders, treatment success is often limited by the need for daily dosing adherence for both methadone and buprenorphine.

MMT is tightly regulated and requires provider or self-referral to federally certified treatment centers for management. Some patients may prefer a once monthly treatment that can be administered in a primary care setting. Furthermore, HIV-infected participants receiving antiretroviral therapy with efavirenz or certain protease inhibitors can experience clinically significant reductions in methadone levels (McCance-Katz, Rainey et al. 2004;

Altice, Kamarulzaman et al. 2010; McCance-Katz, Sullivan et al. 2010) and increases in buprenorphine levels (Bruce and Altice 2006; McCance-Katz, Moody et al. 2007) that complicate methadone and buprenorphine dosing and ART choice. While medication-assisted treatment of alcohol use disorders with acamprosate, disulfiram, or naltrexone is uncommon in HIV clinics, HIV providers are well-positioned, to integrate novel treatments for substance use disorders such as XR-NTX into outpatient HIV practice. For example, BHIVES demonstrated that HIV providers and their patients readily adopted use of office-based buprenorphine for treatment of opioid dependence (Fiellin, Weiss et al. 2011).

Naltrexone Treatment of Opioid Use Disorders. Naltrexone (NTX), a full mu-opioid antagonist, has been FDA-approved for opioid pharmacotherapy since the 1980s. Though highly efficacious when taken as prescribed, oral daily dosing requirements limit its effectiveness due to lack of adherence. Consequently, it is rarely used as first-line treatment for opioid use disorders in the community (Mark, Kassed et al. 2009; Minozzi, Amato et al. 2011). Two recent studies of XR-NTX: 1) Comer et al. (Comer, Sullivan et al. 2006), testing Depotrex®, Biotech Inc., in New York City and Philadelphia; and 2) Krupitsky et al. (Krupitsky, Nunes et al. 2011), testing Vivitrol®, Alkermes Inc., in Russia, support efficacy of XR-NTX compared to placebo injections. In October 2010, largely on the basis of the Russian trial and an earlier U.S. safety study (Alkermes ALK21-006 and ALK21-006EXT), the FDA approved Vivitrol® for the prevention of relapse to opioid dependence. Patients and providers now have a remarkable opportunity to choose between two pharmacologically distinct treatment approaches, XR-NTX and BUP/NX, each with established efficacy and to expand options for medication-assisted recovery.

Yet little is known about XR-NTX implementation in U.S. office-based settings, and the FDA's decision has been criticized insofar as (1) the FDA "accepted a single trial of injectable naltrexone in Russia, unpublished at the time, as primary evidence of efficacy", and (2) "the study did not adequately assess risk of post-treatment overdose" (Wolfe, Carrieri et al. 2011). Because agonist therapy is prohibited in Russia, these authors question the use of these data to gain approval in the USA where methadone and buprenorphine are widely available. Regardless of the merit of these concerns, the data from the Russian placebo-controlled efficacy trial do not directly address the effectiveness, comparative effectiveness, safety, and costs of XR-NTX in U.S. HIV-infected populations.

Naltrexone for Treatment of Alcohol Use Disorders. Oral naltrexone received FDA approval in 1994 for treatment of alcohol use disorders and systematic reviews support its efficacy compared to placebo (Kranzler and Van Kirk 2001; Bouza, Angeles et al. 2004; Srisurapanont and Jarusuraisin 2005), but its success is limited by suboptimal adherence to daily dosing requirements (Hermos, Young et al. 2004; Kranzler, Stephenson et al. 2008). XR-NTX, which lasts 28 days, has improved response rates in alcohol-dependent patients. In a 6-month, multicenter trial of XR-NTX for alcohol dependence, those randomized to receive 380mg XR- NTX experienced a 25% greater decrease in heavy drinking day event rate compared to placebo (Garbutt, Kranzler et al. 2005), improved quality of life (Pettinati, Gastfriend et al. 2009), and decreased holiday drinking (Lapham, Forman et al. 2009). In a post-hoc analysis limited to those with higher severity alcohol dependence, XR-NTX reduced heavy drinking days by 37% and improved maintenance of abstinence compared with placebo (Pettinati, Silverman et al. 2011). Treatment responses were highest among participants with at least 4 days of voluntary alcohol abstinence prior to their first dose of XR-NTX (Garbutt, Kranzler et al. 2005; O'Malley, Garbutt et al. 2007), and were rapid in onset, with significant reductions in alcohol use observed after only 2 days (Ciraulo, Dong et al. 2008). XR-NTX did not significantly increase counseling or support group participation (Cisler, Silverman et al. 2010).

An open-label implementation study evaluating XR-NTX treatment of alcohol dependence in primary settings demonstrated that integrating XR-NTX was feasible and associated with marked reductions in drinking days, heavy drinking days, and improved abstinence (Lee, Grossman et al. 2010; Lee, Grossman et al. 2012). Partici-

pants completed a median 38 weeks (range 16-72) of treatment, with a median 8 monthly injections (range 4-15).

Naltrexone in HIV-infected populations. The CHOICES study is the first to assess XR-NTX in an HIV-infected clinic-based population. Daily oral naltrexone has been safely used to treat alcohol and opioid use disorders in HIV-infected persons. Tetrault, et al. assessed changes in liver enzymes and HIV biomarkers in 114 HIV-infected U.S. Veterans 365 days before, during, and 365 days after treatment with oral naltrexone (Tetrault, Tate et al. 2012). Thirty-two percent of participants had opioid dependence, 89% had a history of alcohol dependence, 53% were coinfected with hepatitis C, and 52% received antiretroviral therapy during naltrexone treatment. Participants were prescribed naltrexone for a median 49 days (interquartile range 30-83 days). Mean AST and ALT levels decreased during and after naltrexone treatment. Two of 114 participants (1.8%) experienced mild liver enzyme elevations during naltrexone treatment, less than 5-times the upper limit of normal, which resolved upon treatment discontinuation. Mean HIV RNA levels decreased after naltrexone treatment and mean CD4 count remained stable throughout. This study suggests the risk of hepatotoxicity is minimal in HIV-infected participants treated with naltrexone, and that there are no adverse immunologic or virologic effects of treatment.

Naltrexone and potential for ART Drug-Drug Interactions. Naltrexone is metabolized through both hepatic glucuronidation and minor extra-hepatic metabolism. When taken orally, it undergoes extensive first-pass metabolism, with reduction of naltrexone to the active metabolite 6-beta-naltrexol by dihydrodiol dehydrogenase. 6-beta-naltrexol levels are much lower with injectable extended-release naltrexone (Dunbar, Turncliff et al. 2006; Alkermes Inc. 2010; Saber-Tehrani, Bruce et al. 2011). Elimination of conjugated naltrexone and 6-beta-naltrexol is through renal excretion. Naltrexone has no effect on Cytochrome P450 metabolism. It is thus unlikely to have clinically significant drug-drug interactions with antiretroviral medications. There are theoretical interactions possible between naltrexone and antiretrovirals that undergo glucuronidation, such as raltegravir (a substrate of UDP-glucuronosyltransferase [UGT] 1A1) and zidovudine (a substrate of UGT 2B7). A pharmacokinetic study of oral zidovudine administered to 15 participants taking oral naltrexone revealed no change in Area Under the Curve (AUC) for zidovudine compared to controls (McCance-Katz, Rainey et al. 2001).

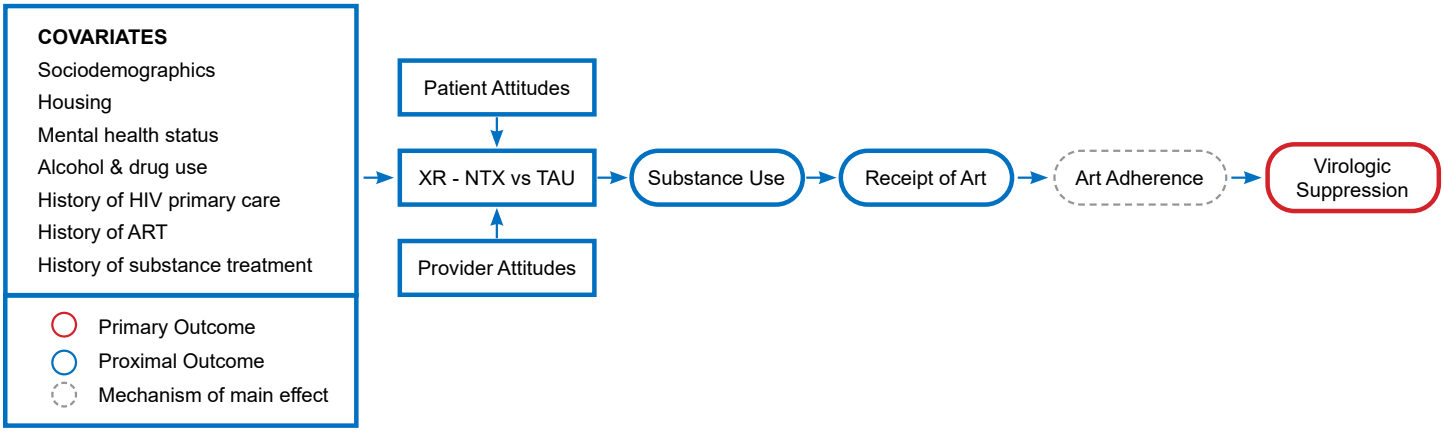
Potential Effect of Naltrexone on HIV Viral Suppression and Immune Function. In the observational study of HIV-infected Veterans receiving oral naltrexone for alcohol or opioid dependence, mean HIV RNA levels decreased after naltrexone treatment and mean CD4 count remained stable throughout (Tetrault, Tate et al. 2012). While the majority of decline in HIV viral load is likely due to increased receipt of or adherence to antiretroviral therapy, declines persisted even after adjusting for antiretroviral use in this study. This raises the possibility that naltrexone may have direct effects on HIV-1 viral activity. CD4+ lymphocytes express μ, κ, and delta opiate receptors that interact with opioid antagonists (Chuang, Chuang et al. 1995; Sharp, Roy et al. 1998). In vitro studies suggest that naltrexone inhibits alcohol-mediated HIV entry and replication in T-lymphocytes (Wang, Douglas et al. 2006). Gekker, et al. demonstrated naltrexone potentiates antiretroviral activity of zidovudine and indinavir in HIV-1 infected CD4 cell cultures (Gekker, Lokensgard et al. 2001) and hypothesized potential synergism between naltrexone and antiretrovirals for reducing viral load.

Furthermore, naltrexone has non-opioid receptor activity that may have beneficial effects for HIV-infected participants. Toll-like receptors (TLR), a recently discovered class of cell surface proteins that modulate innate immune responses, are expressed in many cells important to HIV pathogenesis and activated by opioid ligands.

For example, activation of TLR 4 and TLR 8 by morphine in microglial cell cultures promotes inflammatory cytokine production and release of neurotoxic substances that may contribute to HIV-associated neural deficits when exposed to a bacterial challenge (Dutta, Krishnan et al. 2012). Morphine and bacterial challenge in microglia cultures from TLR4/TLR8 knock-out mice showed no increase in inflammatory cytokines or neurotoxins. Blocking these receptors with opioid antagonists suggests they may be important modulators of pain perception (Lewis, Loram et al. 2012). Naloxone and naltrexone are TLR 4 receptor antagonists that alleviate rat models of acute and chronic neuropathic pain (Lewis, Loram et al. 2012) and reverse pain responses in microglial cell cultures (Hutchinson, Zhang et al. 2008). Little is known about the effect of opioid antagonism on immune function, but CD4 cells express several TLRs and TLR activation appears to suppress innate immune responses that promote chronic viral infection with HIV (Qin, Yao et al. 2011) and HSV-2 (Gill, Davies et al. 2008), *in vitro*. The *in vivo* effect of TLR blockade with opioid antagonists on immune function and HIV viral activity is unknown. The CTN-0055 CHOICES study provides an opportunity to investigate novel direct effects of chronic opioid blockade on immune function and HIV viral suppression in a clinical population of HIV- infected participants.

Conceptual Model. Substance use disorders impair patient engagement and retention in HIV care, contributing to gaps in the HIV care cascade (Gardner, McLees et al. 2011; Fleishman, Yehia et al. 2012). The CHOICES study seeks to compare office-based XR-NTX vs. TAU for treating opioid and/or alcohol use disorders in HIV-infected participants to improve engagement and retention in HIV treatment that leads to HIV viral suppression (Figure 4.1.1). Patient and provider attitudes, assessed in the pilot study, influence adoption of new treatment modalities (Rieckmann, Daley et al. 2007). The primary outcomes of the pilot study will be to assess critical implementation questions. The Consolidated Framework for Advancing Implementation Science suggests that patient, provider, and organizational attitudes are key inputs to adoption of new evidence-based technologies in healthcare settings (Damschroder, Aron et al. 2009). The proposed pilot study will assess HIV clinic provider and patient attitudes toward adoption of antagonist therapy as well as estimate treatment initiation and retention for participants randomized to XR-NTX vs. TAU. We will assess HIV virologic suppression and other key constructs in the causal pathway as secondary outcomes in the pilot study to obtain point estimates to inform development of a future multi-site clinical trial. Virologic suppression reduces HIV associated morbidity, prolongs survival, restores and preserves immunologic function and decreases HIV transmission (Department of Health and Human Services 2011). As shown in the conceptual model below, decreased use of opioids and alcohol and uptake of ART are proximal outcomes that will be assessed as secondary endpoints in the multi-site study. Most HIV-infected patients with alcohol and opioid use disorders who begin ART should be able to achieve virologic suppression if they continue in HIV care and adhere to ART (Cofrancesco et al., 2008; Hicks et al., 2007). In this model, successful treatment of alcohol and opioid use disorders is hypothesized as an important moderator of viral suppression. Previous research has shown that HIV-infected participants with a history of substance use treatment are more likely to use HIV primary care and receive ART (Bell et al., 2010; Knowlton et al., 2006; Loughlin et al., 2005; Strathdee et al., 1998). The model also includes other covariates that may be related to engagement in HIV primary care or substance use treatment.

4.1.1 Figure: Conceptual Model



4.2 Naltrexone (NTX) and Extended-Release Naltrexone (XR-NTX)

NTX is a potent opioid antagonist with high affinity for the mu-opioid receptor. In the U.S. it is approved for use in treating opioid dependence and alcohol dependence. It is highly efficacious in preventing relapse to opioid dependence provided that it is taken as prescribed, but adherence with oral naltrexone is problematic and leads to extremely high dropout rates, with the occasional exception of treatment in criminal justice and other settings where relapse may be linked to severe adverse consequences (Volpicelli, Rhines et al. 1997; O'Brien 2001; Rothenberg, Sullivan et al. 2002). This has led to intensive efforts - including NIDA- and NIAAA- funded grants to small businesses - to develop long-acting naltrexone preparations that can be administered as an injection or placed as an implant once per month or less frequently (NIDA 1976; Lobmaier, Kornor et al. 2008).

XR-NTX (Vivitrol®, NTX-containing polylactide-co-glycolide [PLG] biodegradable sterile microspheres suspended in a diluent) is delivered by monthly injection into the muscles of the upper outer quadrant of the buttock. Each vial of microspheres contains 380 mg NTX which are suspended by adding a diluent that comes with the product and shaking for about a minute prior to injection of the full (less dead-space) content of the vial. Plasma concentrations of NTX and 6-beta naltrexol (its main active metabolite) after a single XR-NTX injection are detectable for at least 30 days. Consistent with this, in human laboratory studies with Vivitrol® and Depotrex®, essentially complete blockade of opioid agonist effects is seen for 30 days (Comer, Collins et al. 2002; Bigelow, Preston et al. 2006). To maintain blockade beyond 30 days, XR-NTX must be re-administered. Long-term use of NTX and XR-NTX is not associated with tolerance, dependence, addiction or withdrawal on discontinuation. NTX and XR-NTX will, however, precipitate withdrawal in individuals physiologically dependent on opioids and decrease opioid tolerance.

As a consequence of its extended duration of action and assured treatment adherence, XR- NTX may dramatically and favorably alter the limited effectiveness profile associated with orally administered NTX. By ensuring 30-day medication adherence with a single injection, and thereby establishing a ~30 day mu-opioid antagonist blockade, the likelihood of an individual re- establishing opioid dependence during this period is very low. The two clinical trials cited above support efficacy for XR-NTX preparations compared to placebo injections (Comer, Sullivan et al. 2006; Krupitsky, Nunes et al. 2011).

The 2006 Comer et al. study (Comer, Sullivan et al. 2006) was a proof-of-concept, 2-month randomized, placebo-controlled trial with a subcutaneously administered product (Depotrex®, Biotek Inc.), and showed that long-acting injectable naltrexone in conjunction with outpatient counseling produced superior treatment retention

to placebo, providing evidence of the feasibility, efficacy, and tolerability of long-lasting antagonist treatments for opioid dependence.

The Krupitsky et al. study (Krupitsky, Nunes et al. 2011) was conducted in 2008 and 2009 in 13 sites in Russia, and was sponsored by the manufacturer, Alkermes Inc. Following inpatient detoxification, 250 opioid-dependent participants were randomized to XR-NTX or placebo, double-blind monthly injections, for 6-months, during which all participants received outpatient counseling. The percent of opioid abstinent weeks, by weekly urine toxicology, was the primary outcome. A response profile analysis compared the cumulative percent of participants at each level of the outcome (percent opioid-free weeks) between the active XR- NTX and placebo conditions. The difference between the response profiles was significant ($p < .0002$), with the median participant on XR-NTX having 90% abstinent weeks compared to 35% abstinent weeks for the median participant on placebo. Total abstinence (100% opioid-free weeks) was reported in 45 (35.7%) participants in the XR-NTX group versus 28 (22.6%) participants in placebo group ($p < .03$). Retention in treatment for the full 6 months was 53% on XR-NTX, compared to 38% on placebo ($p < .02$). The 6-month retention rate in the 50% range is similar to that observed in clinical trials of buprenorphine (Mattick, Kimber et al. 2008). Participants treated with XR-NTX showed an approximately 50% sustained reduction in craving compared to no change in craving in the placebo group ($p < .005$). XR-NTX was generally well tolerated. Data from this trial supported Alkermes' supplemental NDA for treatment of opioid dependence.

Prescribing and Safety: Details on XR-NTX prescribing, pharmacokinetics and pharmacodynamics, metabolism and elimination, safety and toxicity are in the XR-NTX package insert.

4.3 Treatment as Usual (TAU)

The current standard of care for treatment of opioid use disorders in HIV clinics is opioid agonist therapy. Recent HIV treatment guidelines recommend office-based BUP/NX or referral for methadone maintenance for HIV-infected patients with opioid use disorders (Thompson, Aberg et al. 2012; Thompson, Mugavero et al. 2012). Through the efforts of the Health Resources and Service Administration (HRSA)-funded Buprenorphine and HIV Evaluation Study (BHIVES) and Substance Abuse and Mental Health Services Administration (SAMHSA)-funded Physician Support Service for Buprenorphine, on-site treatment with office-based buprenorphine is increasingly being offered in HIV clinics. A recent HRSA HIV/AIDS Bureau monogram promotes adoption of office-based buprenorphine in HIV primary care (HIV/AIDS Bureau Special Projects of National Significance Program 2012), see Section 4.1 for evidence of effectiveness of methadone and buprenorphine. Office-based BUP/NX, together with referral for methadone maintenance therapy, is now the standard of care for treatment of opioid use disorders in many U.S. HIV clinics (Thompson, Mugavero et al. 2012).

HIV-infected patients with alcohol use disorders are typically referred for residential, outpatient, and self-help groups (Burnam, Bing et al. 2001; Kraemer, McGinnis et al. 2006). Medication- assisted treatment of alcohol use disorders in HIV clinics is rare.

Many HIV clinics in the U.S., including all those associated with NIDA CTN nodes, receive Ryan White Care Act funding to provide ancillary services for under-insured and uninsured PLWHA. These services typically include on-site case managers, social workers, and substance use counselors who provide critical treatment, referral, and support services for HIV-infected patients with substance use disorders. The site selection process will include a thorough survey of existing treatment services.

4.4 Significance to the Field

Expanding HIV providers' armamentarium for treating alcohol and opioid use disorders and improving viral suppression in HIV-infected patients advances all three major goals of the National HIV/AIDS Strategy, including 1) Reducing new HIV infections, 2) increasing access to care and improving health outcomes for people living with HIV, and 3) reducing HIV-related disparities and health inequalities (The White House Office of National AIDS Policy 2010). The primary driver of HIV transmission is HIV viral load. If XR-NTX is effective in increasing viral suppression, fewer new HIV infections will occur among the sexual and drug using partners of opioid and alcohol dependent individuals (Wood, Kerr et al. 2009; Montaner, Lima et al. 2010; Cohen, Chen et al. 2011). The CHOICES study increases access to care by engaging HIV- infected participants with suboptimal viral suppression to initiate and adhere to ART, and improves health outcomes by increasing viral suppression with resultant improvements in health outcomes and decreased mortality. The CHOICES study reduces HIV-related disparities and health inequalities by seeking to engage opioid- and alcohol-dependent participants in HIV treatment—a vulnerable population with persistently suboptimal access to high quality HIV care and outcomes, compared with other HIV risk behavior groups. The CHOICES study also advances the science of opioid and alcohol use disorders treatment by directly comparing antagonist therapy with TAU in a non-inferiority comparative effectiveness trial to assess the implementation of a novel therapy into HIV clinical practice.

5.0 OBJECTIVES

5.1 Primary Objectives

The overarching goal of the CHOICES pilot study is to determine the acceptability and feasibility of XR-NTX in HIV practice and inform development of a multi-site comparative effectiveness trial of XR-NTX vs. TAU in HIV clinics. We will achieve this goal by pursuing four primary pilot study objectives. Specific measures of study objectives outcomes are defined in Section 8.0.

Objective #1: Assess HIV provider acceptability of antagonist therapy by estimating the proportion of HIV providers willing to prescribe XR-NTX for opioid and/or alcohol use disorders.

Objective #2: Assess HIV-infected patient acceptability of antagonist therapy by estimating the proportion of potential subjects approached willing to take XR-NTX and be randomized to a trial of XR-NTX vs. TAU.

Objective #3: Estimate the rate of participant recruitment into a future comparative effectiveness trial based on this pilot study.

Objective #4A: Compare successful treatment initiation within 4 weeks of randomization in participants randomized to receive XR-NTX vs. TAU for opioid and alcohol use disorders in HIV clinics.

Objective #4B: Compare treatment retention at 16 weeks following treatment initiation in participants randomized to receive XR-NTX vs. TAU for opioid and alcohol use disorders in HIV clinics.

5.2 Secondary Objectives

Secondary objectives are to generate point estimates for comparing the effectiveness of XR- NTX vs. TAU in:

1) HIV outcomes, as measured by:

- **a)** HIV-1 RNA viral suppression (plasma HIV viral load of $\leq$ 200 copies/mL) at 16 weeks compared with screening.
- **b)** Change in CD4 count at the week 16 visit compared with screening.

2) Change in Substance Use:

- **a)** Change in 30 day opioid abstinence (by Addiction Severity Index (ASI)-lite self- report, Timeline Follow Back (TLFB) and urine drug screen (UDS) confirmation) in the final 30 days of the 16 week trial compared to screening.
- **b)** Change in past 30-day alcohol and other drug use by ASI-lite, TLFB, and UDS at week 16 week visit, compared to screening.

3) Engagement in HIV Care, as measured by:

- **a)** Change in the proportion of participants prescribed ART within 16 weeks following randomization compared to baseline.
- **b)** Proportion of participants taking 100% of prescribed ART doses in the past 3 days at 16 weeks for those prescribed ART at any point during the 16 week trial.
- **c)** Number of HIV primary care visits at 16 weeks. Adherence to HIV clinic visits in the year after ART initiation predicts HIV disease progression and death (Park, Choe et al. 2007).

4) Participant safety, as measured by:

- **a)** Change in liver enzymes between screening and week 16 visit.
- **b)** Any fatal and non-fatal opioid overdose between screening and week 16 visit
- **c)** Change in Concise Health Risk Tracking between screening and week 16 visit.
- **d)** Proportion of participants assigned to XR-NTX who develop precipitated opioid withdrawal.

6.0 STUDY DESIGN

6.1 Overview of Protocol Study Design

The CHOICES (CTN-0055) pilot study is designed to determine the acceptability and feasibility of XR-NTX in HIV clinical practice settings and to inform development of a multi-site comparative effectiveness trial of XR-NTX vs. TAU in HIV clinics. To maximize efficiency of research funding, we will begin data collection regarding feasibility during the study start-up period.

During the study start-up period (4-6 months duration), we will conduct a survey of HIV provider knowledge and attitudes about opioid antagonist therapy and other medication-assisted treatment at 15 high-volume HIV clinics as part of the study site selection process (Aim 1). Site selection will also survey clinic medical directors regarding clinic characteristics (number patients; providers; proportion of patients who are alcohol dependent only, opioid dependent only, or both, etc.), including an assessment of existing addiction treatment services (treatment as usual) for patients with alcohol and opioid use disorders in their clinic. HIV clinics will serve as community treatment programs (CTPs) for CTN-0055. Two clinics will be selected for the pilot study. Eligible study sites will: a) provide HIV primary care, b) have a sufficient population of potential participants to achieve study enrollment goals, c) have providers willing to be trained in use of XR-NTX for management of alcohol or opioid use disorders, d) have prior experience in participating in research/clinical studies, e) have the capacity to prescribe ART to participants, regardless of CD4 count, and f) offer on-site addiction counseling services as part of usual care.

The pilot study consists of a two-arm, 16-week, open-label, randomized, pilot trial of XR-NTX vs. TAU for treatment of opioid and alcohol use disorders in HIV-infected patients. Study participants are individuals with HIV infection and alcohol and/or opioid use disorders and who have received patient-centered information about both antagonist and agonist treatment options for alcohol and opioid use disorders. During screening, eligible participants will be surveyed regarding their attitudes about opioid antagonist therapy for opioid and alcohol use disorders (Aim 2). We will track the rate of participant recruitment (i.e., no more than 50 participants over no more than 12 months) to estimate duration of study recruitment required for a multisite study (Aim 3). Eligible patients are randomized in a 1:1 ratio to receive XR-NTX vs. TAU (Aim 4). Participants with both alcohol and opioid use disorders will be categorized by their self-reported substance of choice. XR-NTX (provided as Vivitrol®) will be administered by HIV clinic providers as a monthly intramuscular injection. Study visits will occur every 4 weeks for collection of blood and urine samples, safety, and other assessments. Primary outcomes of treatment initiation within 4 weeks of randomization, and retention at 16 weeks (maximum of 4 XR-NTX injections) and analyzed by intent-to-treat will be assessed. Secondary outcomes assessed at 16 weeks include change in 1) HIV-1 RNA viral suppression, 2) illicit drug and alcohol use, 3) HIV care engagement (receipt of ART, HIV visit adherence, ART adherence), and safety (percent with precipitated withdrawal, overdose, transaminitis).

6.2 Duration of Study and Visit Schedule

The CHOICES pilot study will target enrolling no more than 50 participants over no more than

12 months at 2 HIV clinic sites. Each participant will be engaged in the overall study for approximately 17-24 weeks (Figure 9.2) as follows:

- Up to 4 weeks: Consent, screening, randomization.
- Up to 4 weeks: Detoxification and induction.

- 16 weeks: Active treatment with monthly study visits.

6.3 Justification of 16 weeks active treatment and timing of ART initiation

The main purpose of this pilot study is to assess feasibility for a multisite trial. We have, therefore, opted to limit the length of treatment and follow up to 16 weeks. A multisite trial with a primary outcome of viral suppression would require a much longer duration of treatment (e.g., 36 weeks) in order to allow sufficient time for initiating ART and achieving viral suppression. Sixteen weeks, however, should provide sufficient time to assess the primary outcome of initial retention on study drug, since the majority of those lost to follow up in previous trials of XR-NTX for opioid or alcohol dependence occurred during the first 16 weeks (Garbutt, Kranzler et al. 2005; Krupitsky, Nunes et al. 2011).

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Participating individuals in the provider acceptability survey are HIV providers, defined as any physician, nurse practitioner, or physician assistant who serves as primary HIV provider for HIV- infected patients at least one half day per week.

Individuals participating in the pilot study must:

1) Meet DSM-5 criteria for moderate or severe opioid use disorder and/or alcohol use disorder.

2) Be willing to be randomized to antagonist-based therapy or TAU for treatment of opioid and/or alcohol use disorders.

3) Be HIV-infected as defined by history of positive HIV serology or HIV RNA pcr > 10,000 copies/mL).

4) Be willing to establish ongoing HIV care at CTP if not already receiving ongoing care.

5) Be willing to initiate ART if not already prescribed ART, regardless of CD4 count.

6) Be at least 18 years old.

7) Be able to provide written informed consent and HIPAA (if applicable) for medical record abstraction.

8) Be able to communicate in English.

9) If female, be willing to take measures to avoid becoming pregnant.

7.2 Exclusion Criteria

There are no exclusion criteria for the HIV provider survey. Individuals will be excluded from the pilot study participation if they:

Have a serious medical, psychiatric or substance use disorder that, in the opinion of the study physician, would make study participation hazardous to the participant, compromise study findings, or prevent the participant from completing the study.

Examples include:

1) Disabling or terminal medical illness (e.g., active opportunistic infection, uncompensated heart failure, cirrhosis or end-stage liver disease, acute hepatitis and moderate to severe renal impairment) as assessed by medical history, review of systems, physical exam and/or laboratory assessments;

- **a)** Severe, untreated or inadequately treated mental health disorder (e.g., active psychosis, uncontrolled manic-depressive illness) as assessed by history and/or clinical interview;
- **b)** Current severe benzodiazepine or other depressant or sedative hypnotic use requiring medical detoxification;
- **c)** Suicidal or homicidal ideation requiring immediate attention.

2) Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) liver enzymes greater than 5 times upper limit of normal on screening phlebotomy. Results from tests conducted within the past 30 days which are abstracted from medical record information are acceptable.

3) Have INR > 1.5 or platelet count <100k. Results from tests conducted within the past 30 days which are abstracted from medical record information are acceptable.

4) Have known allergy or sensitivity to naloxone, naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the Vivitrol® diluents.

5) Anticipate undergoing surgery during study participation.

6) Have chronic pain requiring ongoing pain management with opioid analgesics.

7) Pending legal action or other reasons that might prevent an individual from completing the study.

8) Currently pregnant or breastfeeding.

9) Body habitus that, in the judgment of the study physician, precludes safe intramuscular injection of XR-NTX, (e.g. excess fat tissue over the buttocks).

10) Received methadone or buprenorphine maintenance therapy for treatment of opioid dependence in the 4 weeks prior to screening.

11) Have taken an investigational drug in another study within 30 days of study consent.

12) Have ECG findings that, in the opinion of the study medical clinician would preclude safe participation in the study. Results from ECGs conducted within the past 30 days which are abstracted from medical record information are acceptable.

13) Have had treatment with XR-NTX for opioid or alcohol dependence in the 3 months prior to screening.

7.3 Recruitment

HIV Provider Survey Recruitment:

HIV providers are recruited from HIV practices to complete anonymous surveys regarding attitudes toward medication-assisted treatment for alcohol and opioid use disorders. Medical directors of 15- HIV clinics will provide email addresses of HIV providers at their clinic and encourage all clinic HIV providers to complete an anonymous web-based survey.

Pilot Study Recruitment:

Study participants are recruited from participating HIV outpatient clinics, which will serve as CTPs for CTN-0055. HIV clinics likely to participate in CTN-0055 typically serve as patient- centered medical homes for HIV-infected participants, offering a broad array of on-site case management, social work, and counseling support services to engage and retain patients in care. All members of the HIV clinic care team will be educated regarding the study and asked to refer potential participants who are interested in learning more about the study to clinic research staff for screening. The CTP PI will either be an attending HIV provider in the HIV clinic or have strong relationships with HIV providers, so we anticipate excellent cooperation in approaching potential participants. Because the study seeks to improve engagement in HIV care, the HIV clinic care team and research staff will interact with community-based outreach services to identify and engage potential participants who are new to HIV care. If a participant is interested in learning more about the study, a study staff member will meet with the participant to discuss the study. Potential participants will be briefly instructed regarding opioid agonist and antagonist therapy and complete a survey demonstrating understanding as part of the consent process prior to enrollment. Specific recruitment procedures (e.g., local educational activities, community outreach, print and web- based advertisements, etc.) will vary by site accordingly to local needs. Strict ethical guidelines regarding professional conduct

and confidentiality will be enforced for all study staff.

Enrolling participants in clinical settings poses many challenges to screening and interviewing potential participants (Berkman, Leipzig et al. 2001; Falcon, Bridge et al. 2011; Korthuis, Saha et al. 2011; Menezes, Eron et al. 2011), including the rapid pace of care, interruptions, clinic productivity requirements, space limitations, participants not feeling well enough, and the presence of multiple HIV care team staff members. To minimize the impact of these challenges, research staff will spend considerable time in participating HIV clinics interacting with staff, familiarizing themselves with clinic patient flow, and learning how to communicate and negotiate with clinic staff regarding the necessary space and time to conduct interviews. Site PIs, who are HIV clinic providers, will facilitate negotiation of space and time requirements and be a resource to research staff regarding participating HIV clinic procedures. Staff and sites with experience and expertise in conducting research studies in outpatient HIV clinic settings will be prioritized for site selection. A review of 13 clinical trials conducted in the University of North Carolina Infectious Disease Clinic suggested that integrating a dedicated research screener in clinic operations facilitates trial enrollment (Menezes, Eron et al. 2011). Our research team has experience successfully integrating clinical trial research teams with outpatient HIV clinic staff, enrolling 82% of HIV providers and 73% of their eligible participants in one recent trial (Korthuis, Saha et al. 2011).

The interviewer will negotiate the location of the interview as necessary to protect confidentiality and respect HIV clinic patient flow. If necessary, the potential participant will be given the option to participate in screening, consent and interview procedures in a nearby exam room or staff/patient lounge if it is unoccupied or to reschedule the interview at another time. If a participant feels ill during the interview, we will stop and reschedule the interview. In our prior experience conducting research interviews in outpatient HIV clinics, we found this level of flexibility achieved high levels of participation and did not impede the flow of usual HIV clinic activities (Korthuis, Saha et al. 2008; Altice, Bruce et al. 2011; Beach, Saha et al. 2011).

7.4 Special Populations to Consider

This study is likely to enroll persons involved in the criminal justice system who are receiving HIV care at participating CTPs. The study will not recruit persons incarcerated/detained in a correctional facility, but will not exclude parolees, probationers.

Those participants who become incarcerated during the course of their involvement with this study will continue to be followed to ensure safety and data integrity. All study interventions (XR- NTX or TAU) will be discontinued while the participant is incarcerated. If necessary for safety and with the permission of the participant, correctional facility officials will be informed of study participation. When possible, participants will be contacted to complete questionnaires and surveys, which would include safety checks. These visits can occur over the telephone or as in- person visit, whichever is more appropriate for the local research site and the correctional facilities' policies. The visits will only occur if confidentiality can be maintained. This generally assumes that in-person visits will be done in private rooms and that recording equipment (regardless of type of visit) can be turned off or destroyed. No biospecimens will be collected (blood or urine) during any visit that occurs with an incarcerated prisoner. Any document that is specifically for an incarcerated participant will be approved by the local IRBs, including contact letters. All local guidelines will be followed, including any required reporting to the IRB or other institution when a participant becomes incarcerated. Appropriate progress notes will be written to ensure complete documentation of any interaction with an incarcerated participant, specifically mentioning confidentiality procedures.

We will request a federal Certificate of Confidentiality. An OHRP Prisoner Research Certification Letter will be filed through the Lead Team's IRB and distributed to the sites for reference only. Sites are responsibile, through

their IRB, for obtaining their own OHRP Prisoner Research Certification Letter. The Lead Team's Letter will not cover participants at the local sites.

7.5 Number of CTP Sites

Two HIV outpatient clinics will serve as CTPs for this pilot study.

7.6 CTP Characteristics

HIV clinics will be selected on the basis of the following characteristics:

1) Provide HIV primary care.

2) Have a sufficient population of potential participants to achieve study enrollment goals.

3) Have providers willing to be trained in use of XR-NTX for management of opioid or alcohol use disorders.

4) Have prior experience participating in research/clinical studies.

5) Capable of prescribing ART to all participants, regardless of CD4 count.

6) Offer on-site addiction counseling services as part of usual care.

7.7 Rationale for CTP Selection

We will use the same site selection criteria for the pilot study as is planned for the multisite study. Sites will be selected for participation that have an adequate number of HIV-infected participants with untreated opioid use and/or untreated alcohol use disorders. In order to achieve target enrollment for this study, which is approximately 25 participants per site over 12 months of enrollment, we expect that participating HIV clinics will need to see ≥1,000 unduplicated HIV-infected potential participants per year. This number is based on estimates of the percent of HIV-infected patients in 17 HIV clinics that were informally queried regarding participant availability (Appendix C), and experience of CHOICES investigators in enrolling subjects in the BHIVES study (Altice, Bruce et al. 2011). We have also included site selection criteria that attempt to limit site variability in treatment effects (e.g., capacity for prescribing ART regardless of CD4 count, presence of on-site addiction counseling services).

7.8 Collaboration with CTSA for Site Recruitment

CTP recruitment will explore opportunities to partner with the NIH-funded Clinical and Translational Science Award (CTSA) consortium. CTSA institutions "work to transform local, regional, and national environment to increase the efficiency and speed of clinical and translational research" (CTSA Consortium 2012). Potential opportunities for collaboration between CTN-0055 and affiliated CTSAs include CTSA assistance with community based recruitment and/or some aspects of study implementation.

8.0 OUTCOME MEASURES

8.1 Primary Outcome Measures

Primary outcome variables for the CHOICES pilot study are:

1) HIV provider willingness to prescribe XR-NTX (Aim 1): HIV provider willingness to prescribe opioid antagonist treatment will be assessed with survey measures adapted from the Medical Opinion Survey (MOS) during the study start-up period (mean; survey data).

2) Patient acceptance of opioid antagonist therapy (Aim 2): HIV-infected patient acceptance of opioid antagonist treatment will be assessed with measures adapted from the Medical Opinion Survey (MOS), administered during participant recruitment. Patients will be asked whether they are willing to participate in a trial of XR-NTX vs. TAU (binary; survey data).

3) Rate of participant recruitment into trial (Aim 3): This will be used to estimate the speed at which a multisite trial could enroll participants. The number of participants randomized will be assessed on a monthly basis until either 50 participants have enrolled, or 12 months of recruitment have elapsed, whichever comes first (rate; randomization data).

4) Treatment initiation (Aim 4A): Treatment initiation is defined as receipt of at least one dose of study medication for those randomized to XR-NTX within 4 weeks of randomization. For those randomized to TAU, treatment initiation will be defined as receiving at least one dose of medication-assisted therapy other than XR-NTX (e.g., buprenorphine for opioid use disorder, disulfiram for alcohol use disorder), or attendance on at least 1 day of non- medication-assisted therapies (e.g., 12-step groups, outpatient rehab referral, etc.) within 4 weeks of randomization. For the TAU group, treatment initiation will be assessed with weekly phone calls from research staff until treatment is initiated or 4 weeks from date of randomization have elapsed, as which point a participant will be considered to have failed treatment initiation (binary; chart review and self-report).

5) Retention on treatment (Aim 4B): Retention on treatment is defined as the percent of assigned treatment received over 16 weeks after treatment initiation. Only participants who initiate treatment (as defined in Aim 4A) will be assessed for retention on treatment. Retention will be assessed by the study clinician at 4, 8, 12, and 16 weeks following treatment initiation. For those randomized to XR-NTX, retention on treatment is defined as the mean percent of expected XR-NTX doses received (25%, 50%, 75%, or 100% of 4 possible doses). For those randomized to TAU, study clinicians will estimate the percent of recommended treatment a participant received in the past 4 weeks at weeks 4, 8, 12, and 16. Retention on treatment for TAU is defined as the mean percent of recommended TAU treatment received (1-100% possible range), as estimated by the study clinician (percent; chart review and self-report).

8.2 Secondary Outcome Measures

1) HIV outcomes:

a) HIV-1 RNA viral suppression (plasma HIV-1 RNA pcr < 200 copies/mL) at 16 weeks compared with screening (binary, laboratory assay).

b) Change in CD4 count at 16 weeks following treatment intiation compared with screening (count; laboratory measurement).

2) Substance Use:

a) Change in 30 day opioid abstinence (by Addiction Severity Index (ASI)-lite self- report, Time-Line Follow-Back (TLFB) and urine drug screen (UDS) confirmation) in the final 30 days of the 16 week trial compared to screening (binary; laboratory data and self-report).

b) Change in past 30-day alcohol and other drug use by ASI-lite, TLFB and UDS at week 16 visit, compared to screening (binary; laboratory data and self-report).

3) Engagement in HIV Care:

a) Change in the proportion of participants prescribed ART within 16 weeks following randomization, compared to baseline (binary; medical record abstraction).

b) Proportion of participants taking 100% of prescribed ART doses in the past 3 days at 16 weeks for those prescribed ART at any point during the 16 week trial (proportion; self-reported ACTG adherence measure).

c) Number of HIV primary care visits at 16 weeks (count, chart abstraction).

4) Participant safety:

a) Change in liver enzymes between screening and week 16 visit (laboratory assay).

b) Any fatal and non-fatal opioid overdose between screening and week 16 (binary; medical record abstraction and self-report).

c) Change in Concise Health Risk Tracking score between screening and week 16 visit (continuous; self-report).

d) Proportion of participants assigned to XR-NTX who develop precipitated opioid withdrawal.

9.0 STUDY PROCEDURES

9.1 Provider Survey Study Procedures

During the study start-up period, clinic medical directors at 10-20 candidate sites will be asked to provide the study team with the number of HIV providers in their clinic and associated email addresses. The lead team will email all HIV providers a brief description of the survey and a website link that will redirect the provider computer to the Provider Survey Study. Once the link is activitated, HIV providers will provide brief consent and complete a brief (10 minute) anonymous survey regarding their knowledge, attitudes and willingness to prescribe medication- assisted therapy for patients with opioid use disorders (methadone, buprenorphine, XR-NTX) or alcohol use disorders (disulfiram, acamprosate, XR- NTX), demographic, and practice characteristics. In collaboration with the DSC, the study team will track response rates and encourage medical directors to help in maximizing provider participation. Providers will be given a maximum of 4 weeks to complete the survey.

9.2 Pilot Study Procedures

Activity:	Screening/Enrollment	Detox/Induction	Active treatment
Duration:	1-4 weeks	0-4 weeks	16 weeks
		Total Duration:	17-24 weeks

9.2.1 Pre-screening

Individuals will be approached by study staff in HIV clinic settings or referred to study staff by HIV clinical care and outreach teams. Study staff will present a brief recruitment script to the individual and provide written information regarding XR-NTX. Individuals will provide verbal consent (determined by local IRB guidelines, and HIPAA authorization/Waiver as necessary) for pre- screening and will be asked to complete the Pre-Screening Interview. The Pre-Screening Interview will elicit information about the potential participant's demographics, use of antiretroviral therapy, drug use, and attitudes toward medication-assisted treatment of opioid and alcohol use disorders. The screening informed consent, HIPAA authorization (if necessary), and screening interview will take approximately 5, 5, and 10 minutes to complete, respectively.

9.2.2 Screening and Enrollment Procedures (1-4 weeks duration)

Once a person has completed the Pre-Screening Interview process and meets basic eligibility, they will either be asked to stay for the Screening Visit or scheduled to come back (based on staff and candidate's availablity).

9.2.3 Informed Consent Process

Study procedures and the potential risks and benefits of participating in the trial will be explained by research staff. Staff will be available to answer questions about the consent form while participants are reviewing it. After signing the consent form, participants will be offered a copy of the form to keep for their records. The process will take approximately 20-30 minutes.

9.2.4 Locator Form

Participants will complete a locator information form which will be used to contact them to remind them of follow-up visits and to locate participants who cannot be found. When completing this form, participants provide their names, addresses, and telephone numbers as well as contact information for at least two other persons. Permission will also be requested to obtain locating information from additional agencies and publicly accessible databases or search engines including, but not limited to, Medicare/Medicaid and Social Security offices, department of motor vehicles, local jail logs, white pages, Facebook, etc. Locator information will be updated as needed during the study. The locator information form will take approximately 5-10 minutes to complete.

9.2.5 Medical Record Release Form

Participants will complete these forms throughout the study (as applicable) to grant permission to study staff to review inpatient, outpatient, mental health, and substance use treatment clinic records as needed. The purpose of medical record review at the end of study participation is to document information needed to evaluate secondary outcomes. Specifically, study staff will abstract medical record information to corroborate participants' self-report of information including, but not limited to the following: HIV viral load and CD4 count, liver enzymes, hepatitis B and C serologies, CBC, metabolic panel, INR, utilization of HIV primary care, utilization of HIV and addiction treatment services, and overdose events. Records review/abstraction will occur throughout the study (as needed) and up to 24 weeks post- randomization.

9.2.6 Collection of Biological Specimens

Study staff will collect blood and urine specimens at screening and baseline to confirm study eligibility and 0, 1, 4, 8, 12, and 16 weeks following treatment initiation to assess participant safety, and assess the pilot study secondary aim of change in HIV-1 RNA pcr and drug use. Baseline hepatitis B and C serologies drawn in the 90 days prior to consent may be abstracted from participant medical records, when available. Other baseline studies may be abstracted from medical records if drawn in the 30 days prior to consent. Some participating sites may require that copies of some or all lab results collected for study purposes be filed in participants' medical records.

9.2.7 Baseline Assessment

After the enrollment process is complete, study staff will prepare a new data record for the participant and the baseline assessments will be administered through a computer assisted data collection instrument. Each assessment question is displayed on a computer monitor, allowing the interviewer to read the questions and then enter the participants' responses directly into the computer. The baseline assessments are detailed in Section 10.0 and capture participant medical, psychiatric, and drug use history, HIV status and care, quality of life and current health status. The baseline assessment will take approximately 45 - 60 minutes to complete.

9.2.8 Randomization

We anticipate that the timing of randomization will be variable, but follow shortly after baseline assessments and final confirmation of eligibility. Participants will have up to 4 weeks follwing randomition to initiate his or her assigned treatment. Success in initiating assigned treatment will be tracked.

Participants will be randomized in a 1:1 fashion to either office-based XR-NTX or TAU using a permuted block design with randomly-sized blocks. Predominance of alcohol vs. opioid use disorder for a given participant will

likely be strongly correlated with primary and secondary outcomes, and this variable will be recorded upon randomization. The severity of opioid and alcohol use disorder will also likely be an important independent predictor of treatment retention and substance use (Sullivan, Rothenberg et al. 2006; Carpenter, Jiang et al. 2009; Brooks, Comer et al. 2010). Participants need not be abstinent from opioids or alcohol at the time of randomization.

The randomization procedure will be conducted in a centralized process through the Data and Statistical Center (DSC). Specifically, randomization schedules will be created by the study statistician for each site. The randomization schedules will be of a randomized-block nature to ensure relative equality of assignment across condition across the recruitment period and to prevent the potential for study staff guessing the next assignment which is heightened when a fixed block-size is used. After the baseline assessment is successfully completed, a designated study staff member will perform the randomization. Randomization for each participant is done over the Internet using the Enrollment Module in AdvantageEDC.

The DSC statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new participant due to the intent-to-treat nature of the study.

9.3 Treatment Conditions

9.3.1 HIV Usual Care (Both Arms)

All participants receive comprehensive HIV primary care, case management, addiction counseling, and social support services from HIV clinics as they would regardless of study participation. As part of protocol training, HIV clinic providers will be encouraged to offer ART within 4 weeks of randomization for participants not already prescribed ART. Current guidelines recommend offering ART to all HIV-infected participants, regardless of CD4 count (Thompson, Aberg et al. 2012). The schedule of medical care provided will be as deemed appropriate by the treating provider. HIV-infected participants are typically seen at least twice within the first month of initiating ART, and at least every 3 months thereafter for monitoring. Medical visits will not be considered study visits, though they may coincide with study visits. HIV clinic treatment will also include usual addiction counseling services, which are offered as a part of usual care in most large U.S. HIV clinics. As part of protocol training, HIV clinic providers will be asked to refer study participants to existing addiction counseling services in their clinic, as they would do regardless of study participation. Throughout the course of the trial, HIV clinics will be monitored for any potential changes that might occur in standard practice around medical management of HIV infection or addiction treatment services. HIV clinic medical and counseling visits will be tracked through medical record abstraction throughout study participation (See Section 10 Assessments).

9.3.2 Medical Management (When applicable)

Study clinicians will be trained in medical management (MM). MM is a brief counseling intervention delivered by non-addiction medical providers to improve response to medication- assisted addiction treatments delivered in medical settings (Pettinati and National Institute on Alcohol Abuse and Alcoholism (U.S.) 2004). It has augmented care for medication- assisted treatment of alcohol dependence with accamprosate and oral naltrexone in the COMBINE study (Anton, O'Malley et al. 2006), integration of XR-NTX treatment of alcohol dependence in primary care settings (Lee, Grossman et al. 2010), and integration of BUP/NX for treatment of opioid dependence in primary care (Fiellin, Pantalon et al. 2006). Since MM is meant to facilitate medication-assisted addiction treatment, it will be performed only for participants offered medication assisted treatment in the HIV clinic (e.g. participants with opioid use disorders randomized to XR-NTX and TAU participants receiving clinic-based

buprenorphine/naloxone or methadone for opioid use disorder and those prescribed disulfiram, accamprosate, etc. for alcohol use disorder). TAU participants referred for off-site methadone maintenance or buprenorphine/ naloxone will not receive MM since medical oversight is the responsibility of the treating provider. TAU participants who receive non-medication-assisted treatments such as 12- step groups or psychosocial counseling will not receive MM. During brief MM sessions, study clinicians will review recent drug and alcohol use, recommend abstinence, review medication side effects, and encourage adherence to medication-assisted treatment and participation in clinic and/or community support groups.

9.3.3 Clinic-based Extended-Release Naltrexone (XR-NTX)

9.3.3.1 XR-NTX Detoxification and Induction (0 - 4 weeks duration)

Following randomization, participants assigned to office-based XR-NTX will undergo detoxification and naltrexone induction in accordance with published guidelines (Asplund, Aaronson et al. 2004; Mayo-Smith, Beecher et al. 2004; Center for Substance Abuse Treatment 2006; Sigmon, Bisaga et al. 2012). Participating HIV providers will be trained to assess potential participants for the anticipated severity of opioid and alcohol withdrawal symptoms and manage outpatient detoxification procedures for participants with mild to moderate anticipated opioid or alcohol withdrawal severity. Participants with anticipated severe withdrawal symptoms (e.g., > 6 bags per day of heroin; >100 mg/day morphine equivalents prescription opioid use) will be referred to local detox facilities for medication-assisted inpatient detoxification that may involve opioid medications. Participants with anticipated severe alcohol withdrawal (increased risk of delirium tremens, seizures) should be admitted for inpatient detoxification. Guidelines for detoxification and induction onto XR-NTX are provided in study SOPs.

Prior to the naloxone challenge, participants randomized to XR-NTX must complete/have completed opioid detoxification, be at least 24 hours removed from the last dose of opioid agonist (heroin, prescription opioids, methadone or buprenorphine) and have a UDS negative for the extended opioid spectrum. If initial UDS is positive, UDS is repeated daily until negative. Only then will the naloxone/ challenge take place.

9.3.3.2 Naloxone Challenge

The naloxone challenge is performed to confirm the absence of opioids. Only those with recent opioid use are required to complete a naloxone challenge. The naloxone challenge consists of the delivery of 0.8 mg naloxone IV, with an observation period of 10-20 minutes. Heart rate and blood pressure measurements are completed prior to injection and 10-20 minutes post-injection, along with clinical assessment of opioid withdrawal symptoms. Significant changes in vital signs (blood pressure and heart rate) or signs of opioid withdrawal should be taken as a positive result of the challenge. If the challenge is positive, the participant should be encouraged to remain opioid abstinent and repeat the UDS and the naloxone challenge over the next several days. Participants may be re-challenged in this manner for up to one week. If participants do not have adequate peripheral venous access for IV naloxone administration, SC, intranasal, or IM administration is acceptable with the caveat that a 30-40 minute observation period be used, to account for longer absorption times. If no reaction to a naloxone challenge, the study clinician may proceed to XR- NTX injection.

9.3.3.3 Active Treatment with XR-NTX (Treatment Week 0 through Week 16)

Following a negative naloxone challenge, XR-NTX monthly injections will begin. XR-NTX (4cc, ~380mg of naltrexone base) will be administered approximately every four weeks (weeks 0, 4, 8, 12) for a maximum of 4 doses in the form of Vivitrol®, which will be obtained by NIDA or the NIDA contractor for distribution to the sites. XR-NTX will be administered by intramuscular injection to the buttocks (alternating sides monthly) according to the injection preparation and administration procedures specified in the Vivitrol® product package insert. These procedures are designed to minimize the risk of injection site reactions.

9.3.3.4 Handling of Missed XR-NTX Doses, Lapses, and Relapses

Use of illicit opioids presents different concerns in the management of participants receiving XR- NTX maintenance, compared to those receiving agonist therapy. A participant receiving XR- NTX may miss a scheduled injection, and resume opioid use. However, because of the long duration of action of XR-NTX (full blockade out to 5 weeks after the last injection (Comer, Collins et al. 2002)) a grace period of at least 7 days can be expected during which repeat XR- NTX injection can be rescheduled without risk of relapse. If the participant misses a scheduled injection and uses opioids during at least two of the seven days following the date of the scheduled injection, relapse will be suspected and the provider will perform a repeat naloxone challenge as described above. If the challenge is negative, XR-NTX administration will be resumed. If positive, then XR-NTX administration would risk precipitating withdrawal. However, because naltrexone blood levels remain and there is partial blockade beyond week 5, vulnerability to relapse may be more gradual, and the possibility of mild or equivocal reactions to naloxone challenge more common. In this instance, a second challenge within 72 hours will be attempted, and if tolerated, the next injection can be given. Missing a scheduled XR-NTX injection is the most important threat to the success of naltrexone maintenance. In the event of missing a scheduled injection, clinic study staff will contact the participant for follow up. The goal of these contacts is to re-establish commitment to the XR-NTX treatment and schedule a next injection as soon as possible. Participants who miss a scheduled XR-NTX dose but remain abstinent (i.e., return to clinic reporting no opioid use, urine negative for all opioids, and passing naloxone challenge), may be restarted on XR-NTX up to 3 weeks after the scheduled dose.

9.3.3.5 Dispensing of XR-NTX

Study medication (XR-NTX) will be provided by the study at no cost to the participant. XR-NTX will be administered in clinic at induction (week 0) and at treatment weeks 4, 8, and 12.

9.3.4 Treatment as Usual (TAU)

Participants assigned to the TAU group will receive the standard treatment for alcohol and opioid use disorders provided at each HIV clinic. The standard of care in U.S. and Canadian HIV clinics is currently to link with opioid agonist treatment services. Opioid substitution therapy is recommended for HIV-infected participants with opioid dependence (Thompson, Aberg et al. 2012; Thompson, Mugavero et al. 2012), and many HIV practices are being encouraged to adopt clinic-based BUP/NX (HIV/AIDS Bureau Special Projects of National Significance Program 2012). The standard of care for treatment of alcohol use disorders in HIV clinics is referral to detoxification, if needed, as well as outpatient or inpatient rehabilitation programs and 12-step groups, and/or on-site substance abuse counseling services. Medication-assisted treatment of alcohol use disorders with naltrexone, disulfiram, or acamprosate is rare in HIV clinics.

Many HIV clinics receive funding from the Ryan White Care Act for case management and addiction/mental health counseling services to facilitate engagement of HIV-infected patients with substance use disorders in treatment. In a 6-month randomized trial of methadone maintenance referral strategies, passive referral of heroin users resulted in 8% methadone maintenance enrollment at 6 months vs. 29% enrollment among those randomized to case- management assisted referrals ($p = .006$) (Coviello, Zanis et al. 2006).

Methadone maintenance referrals in HIV clinics may more closely approximate case-managed referral enrollment due to the presence of Ryan White Care Act-funded case managers and counselors.

During the formal site selection process, a thorough assessment will be conducted of each site's standard practice for linkage to addiction treatment services. Throughout the course of the trial, HIV clinics will be monitored for any potential changes that might occur in standard practice around linking HIV-infected clinic patients to substance use treatment.

9.4 Ancillary Treatments

Participants who experience withdrawal symptoms or nausea associated with detoxification and induction may be treated with ancillary medications (see guidelines in study SOPs). Depression is also common in opioid-dependent participants and, though not causally related to XR-NTX use, may adversely affect prognosis of naltrexone treatment (Sullivan, Rothenberg et al. 2006). Participants who show depressive symptoms may be treated by their HIV clinic providers with antidepressants and/or referred for mental health evaluation and treatment.

9.5 Provisions for Access to Investigational Treatment after Study

Prior to the conclusion of the 16 week active treatment phase, the research team will make an effort to arrange for continued treatment with XR-NTX as locally appropriate. In most cases, the study physician will continue to prescribe this FDA-approved study medication as the participant's HIV primary care provider. Where this is not possible (due to insurance or availability of treatment resources, etc.), alternative treatment referrals (e.g., methadone maintenance, intensive outpatient psychosocial aftercare), special access programs, and manufacturer medication assistance plans will be made as appropriate.

9.6 Drug Packaging/ XR-NTX

Drug Packaging/ XR-NTX will be supplied in single use kits. Each kit will contain one 380 mg vial of Vivitrol® microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of Vivitrol®, one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1.5-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices. Lot number and medication expiration date will be included on the kit labels as supplied by the manufacturer.

9.7 Participant Discontinuation

All participants will be followed for the duration of the study (17-24 weeks, depending on length of time required for completion of screening, detoxification, and induction procedures) unless they withdraw consent, or the investigator 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 DSMB early termination of the study for safety or effectiveness reasons.

9.8 Blinding

CTN-0055 is an unblinded study.

9.9 Participant Compensation

Participants will be compensated for their time and effort for baseline and follow-up visits. Participants may receive a maximum amount of up to approximately $410.00 US Dollars for completing the following activities: screening interview, baseline assessment, and visits at 1, 4, 8, 12, and 16 weeks.. The specific amounts and format (e.g., cash, debit card, voucher, etc.), and distribution schedule will be determined by the participating site with the approval of the lead investigator or co-lead investigators and the corresponding IRB(s) of record.

10.0 STUDY ASSESSMENTS AND INSTRUMENTS

The selected assessments attempt to balance the value of comprehensive data against the costs of data collection in terms of staff time, feasibility of completing assessments in an outpatient HIV clinic setting, financial cost, and response burden. Therefore, assessments have been limited to those that contribute directly to the study objectives or that are necessary for reasons of safety or regulatory compliance. When choosing between comparable instruments, we have chosen instruments for which CRFs have already been built for other recent CTN trials to minimize the cost of new CRF construction.

10.1List of all CRF's and Table of Assessments

Assessment/Activity	Associated CRF	Pre-Screening	Screening	Baseline	Randomization	Week 0 (induction)	Week 1	Week 4	Week 8	Week 12	Week 16	End of Treatment (≠Week 16)	As Needed Only
Inclusion/Exclusion checklist	ENR-B				X								
Informed Consent/HIPAA	ENR-A		X										
Inventory Form	INV												X
Locator Form			X	X	X	X	X	X	X	X	X	X	
Master Enrollment Log			X	X									
Medical Release			X										X
Missed Visit Form	MVF												X
Pre-Screening Interview	PSI	X											
Progress Note Checklist			X	X	X	X	X	X	X	X	X	X	
Protocol Deviation	PDV												X
Screening Log		X											
Study Termination	STT										X	X	
Visit Compensation Log			X	X	X	X	X	X	X	X	X	X	
General Measures													
Demographics	DEM		X										
Quality of Life, from PhenX	QLP			X							X	X	
Tobacco Use History, from PhenX	TUH			X							X	X	
Safety & Medical Measures													
Adverse Events	AD1-3												X
ARV Medication Log	ARV			X							X	X	
CBC	LAB		X										
CD4 Count	LAB				X			X		X	X	X	
Confirmed Pregnancy and Outcome	PRG,PO1- 4												X
Detoxification	DTX					X							

Assessment/Activity	Associated CRF	Pre-Screening	Screening	Baseline	Randomization	Week 0 (induction)	Week 1	Week 4	Week 8	Week 12	Week 16	End of Treatment (≠Week 16)	As Needed Only
ECG Results	ECG		X										
Ethyl Glucuronide	UDS		X				X	X	X	X	X	X	
Fatal Overdose	FOD										X	X	
Vital Signs (blood pressure, pulse, temperature, height, and weight)	VIS		X								X	X	
Hepatitis B surface antigen (HBs AG)	LAB				X								
Hepatitis C virus antibody (HCV ab)	LAB				X								
Hepatitis C pcr confirmation, when HCV ab +	LAB												X
HIV-1 RNA PCR	LAB				X			X	X	X	X	X	
Injection Site Abnormality	INA												X
Injection Site Examination	INX						X	X	X	X	X	X	
LFT (AST, ALT) and INR	LAB		X				X	X	X	X	X	X	
Medical and Psychiatric History	MHX		X										
Medication Adherence	MAD			X				X	X	X	X	X	
Pain Assessment	PEG			X				X	X	X	X	X	
Naloxone Challenge	NXC					X*							
Non-Fatal Overdose	NFO			X							X	X	
PBMC	LAB				X			X					
Physical Examination	PEX		X										
Pregnancy and Birth Control Assessment	PBC		X			X	X	X	X	X	X	X	
UDS	UDS		X			X	X	X	X	X	X	X	
XR-NTX administration log	INJ					X		X	X	X			
XR-NTX Injection						X		X	X	X			
Drug Use, HIV & Psychological Measures													
ASI Lite Drug/Alcohol Use	ASD			X							X	X	
Concise Health Risk Tracking	CHRT			X		X	X	X	X	X	X	X	

Assessment/Activity	Associated CRF	Pre-Screening	Screening	Baseline	Randomization	Week 0 (induction)	Week 1	Week 4	Week 8	Week 12	Week 16	End of Treatment (≠Week 16)	As Needed Only
DSM-5 Substance Use Disorders	DSM		X										
HIV Care Utilization	HCU			X							X	X	
Medication Assisted Treatment	MAT			X				X	X	X	X	X	
Readiness for Substance Drug Treatment	RST			X							X	X	
Risk Assessment Battery	RAB			X				X	X	X	X	X	
Timeline Follow Back	T55			X		X	X	X	X	X	X	X	
Treatment Plan	TXP				X	X		X	X	X	X	X	
Treatment Satisfaction	TTS										X	X	
Treatment Services Review	TSR			X		X		X	X	X	X	X	
Visual Analog Scale	VAS			X				X	X	X	X	X	

* Only for participants randomized to the XR-NTX arm

11.0 GENERAL MEASURES

11.1 Implementation Assessment

The Western States Node has led the analysis of Site Influences on Treatment Effects (SITE) for prior CTN trials. To assess provider and site characteristics, the SITE instruments and procedures will be modified to fit the CTN-0055 design. During pre-implementation visits to potential study sites, the SITE survey will be completed with study interventionists (physicians, nurses and counselors) and site variables will be assessed through an interview with the clinical director. The Interventionist Survey assesses training, demographics, and attitudes toward the use of buprenorphine, extended-release naltrexone, and methadone for treatment of opioid use disorders among HIV infected individuals who use opioids.

11.2 Inclusion/Exclusion

This form will include each inclusion and exclusion criterion to document eligibility. Eligibility will be assessed continually as appropriate. Only participants who continue to meet study eligibility criteria will be allowed to continue with the screening process and randomization.

11.3 Locator Form

A locator form will be used to obtain information to assist in finding participants during treatment and at follow-up. This form will collect participants' current address, email address, and phone numbers. In order to facilitate locating participants if direct contact efforts are unsuccessful, we will collect addresses and phone numbers of 2-3 family/friends, who may know how to reach the participant, as well as information such as Social Security number, driver's license number, social media, and other information to aid in searches of public records. This information will be collected at screening, and will be updated at each visit. No information from this form will be used in data analyses.

11.4 PhenX Core Tier 1 Form

The Substance Abuse and Addiction Collection of the PhenX Toolkit (www.phenxtoolkit.org) includes highly recommended measures that are being adopted across NIDA-funded research (National Institute on Drug Abuse 2012). The Core Tier 1 collection includes measures for demographics (age, ethnicity, gender, race, educational attainment, employment status and marital status), BMI, quality of life, and HIV Risk & Status; substance use measures include age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco and other substances. We will delete Core Tier 1 Items regarding HIV testing, since only HIV-infected participants are eligible for the current study. Where possible, answers to Core Tier 1 questions will be populated from the answers to questions from other assessments. Core Tier 1 assessments will be completed at Baseline only, with selected items repeated at week 16 (or the end-of-medication/end-of-treatment visit if medication or TAU intervention is stopped early).

11.5 Demographics Form

The demographics form will collect information about demographic characteristics of the participant, including gender, date of birth, ethnicity, race, education, employment pattern, and marital status. The PhenX Core Tier 1 form will be completed during the screening process to collect demographic data.

11.6 Treatment Satisfaction Survey

Satisfaction with treatment will be recorded on the Treatment Satisfaction Survey completed at the end-of-medication visit (if medication is stopped early), the end-of-treatment visit (if TAU intervention stopped early), or the week 16 visit (for participants who complete study participation).

11.7 End of Medication/End of Treatment Form

This form tracks the participant's status with regard to the study intervention/medication. It will be completed at the end-of-medication visit (if XR-NTX is stopped early, the end- of-treatment visit (if TAU intervention is stopped early), or at the week 16 visit (for participants who complete study participation).

11.8 Study Termination Form

This form tracks the participant's status in the study. It will be completed at the week 16 visit or once the week 16 visit window elapses for participants who do not complete this final visit. This form will be used in data analyses to address variables such as treatment retention and completion.

12.0 SAFETY AND MEDICAL MEASURES

The study clinician must review and approve all safety and eligibility assessments in order to confirm participant eligibility prior to randomization.

12.1 Medical and Psychiatric History

The study clinician will obtain a medical and psychiatric history from the participant covering past and present health conditions to help determine eligibility and to provide baseline information. This form will be collected during screening. Information from this form may be used in data analyses.

12.2 Physical Exam

The study clinician will complete a physical examination at screening, to ensure that there are no medical concerns regarding participation and to gather baseline information regarding the participant's physical health. During the screening physical exam, a description of the participant's body habitus will be documented and the study medical clinician will examine the planned injection sites to ensure adequacy for XR-NTX gluteal intramuscular injection of naltrexone with the supplied needle.

12.3 Vital Signs

Study personnel will complete vital signs (blood pressure, pulse, temperature, height, and weight) to inform overall medical fitness for participation, along with the physical exam.

12.4 Electrocardiogram (ECG)

A 12-lead ECG will be administered by appropriately qualified and trained medical personnel at screening, and assessed by a study clinician. The results of ECG tests conducted within 30 days prior to randomization will be acceptable.The screening ECG will assist in determining participant eligibility.

12.5 DSM-5 Checklist

The DSM-5 Checklist is a semi-structured, interviewer administered instrument that provides current diagnoses for substance use disorders based on DSM-5 diagnostic criteria. The DSM-5 Checklist will be completed at screening to determine eligibility. Participants will also indicate their preference substance if they use both opioids and alcohol.

12.6 Clinical Laboratory Tests

Trained staff will be responsible for collecting and processing biologic specimens. Local laboratories at participating pilot sites will be used to conduct laboratory tests. Laboratories must be accredited by the College of American Pathologists (CAP) or equivalent, and participate in the Clinical Laboratory Improvement Act of 1998 (CLIA) or equivalent evidence of laboratory certification. Laboratories will provide reference ranges and proof of laboratory certification.

HIV-1 RNA PCR: will be drawn following randomization, and at 4, 8, 12, and 16 week follow-up visits (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early) for outcomes assessment.

CD4 Count (T-helper cells): will be drawn following randomization and at 4, 8, 12, and 16 week visits (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early) for secondary outcomes assessment.

Peripheral Blood Mononuclear Cells (PBMCs): For all participants, we will collect 4 CPT tubes for PBMC analysis following randomization and at the Week 4 visit or the first blood draw following study drug initiation. PBMC analysis will be conducted in a related NIH application to assess the effects of opioid blockade on TLR mediated immune responses. Samples must be drawn during CTN-0055 study implementation, but may be analyzed at a later time.

Safety labs: AST, ALT, CBC, INR, and urine pregnancy test (for females) will be performed to help determine eligibility at screening. Receipt and review of laboratory test results is necessary before confirming eligibility, conducting randomization and starting study medication. Results of laboratory tests conducted within 30 days prior to randomization (e.g., collected as part of routine detoxification admission) will be acceptable.

Liver profile: (AST, ALT, INR) will be repeated 1 week after study treatment initiation and at 4, 8, 12, and 16 week visits (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early).

Hepatitis: Following randomization, blood will be collected for hepatitis B surface antigen (HBsAG) and Hepatitis C virus antibody (HCVab). These tests do not determine eligibility and will only be conducted on samples from subjects who are randomized. Results of laboratory tests conducted within 90 days prior to randomization (e.g., collected as part of routine detoxification admission) will be acceptable. If needed Hepatitis C pcr confirmation will be performed, when HCVab is positive.

12.7 Pregnancy and Birth Control Assessment

This form will document the administration of pregnancy tests, test results, and female participants' self-reports of an acceptable method of birth control. The pregnancy and birth control assessment form, including on-site urine pregnancy tests will be collected at screening. Birth control assessment and a urine pregnancy test will be repeated prior to study drug induction (Week 0), and 1, 4, 8, 12, and 16 week visits (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early). This will correspond to medical visits for repeat study drug dosing (week 0, 4, 8, 12) and week 16 (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early).

12.8 Injection Site Examination

The study clinician will examine the injection site on the next visit following each XR-NTX administration. Participants will be asked to immediately report any injection site reactions to study staff for evaluation, monitoring, and possible referral, as needed. Injection site reactions will be documented on the Injection Site Abnormality Log.

12.9 Pain Assessment

Pain assessment will occur at baseline, 4, 8, 12, and 16 weeks. Participants will be assessed for experiences of pain during the past 4 weeks using the 3-item PEG (Krebs, Lorenz et al. 2009). The PEG asks respondents to estimate on a scale of 0 to 10 their average pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G). Participants will also be asked how pain was managed.

13.0 DRUG USE AND PSYCHOLOGICAL MEASURES

13.1 Urine Drug Screen

Urine drug screens will be collected at screening, study drug induction, week 1 safety visit, and 4, 8, 12, and 16 weeks (or the end-of-medication/end-of-treatment visit if medication or TAU intervention stopped early) for assessment of secondary outcomes. All urine specimens will be collected using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. The UDS will test for the presence of the following drugs: opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamines, marijuana, methadone, buprenorphine and ecstasy (MDMA). The UDS will be performed using three separate testing strips (10Panel, OPI300, and BUP10). In the event urine specimen tampering is suspected, either based on observation or the adulterant tests, study staff should request a second urine sample, directly observed.

13.2 Urine Ethyl Glucuronide

Urine will be collected for ethyl glucuronide testing at screening, 1 week after induction (Safety Visit), and 4, 8, 12, and 16 weeks (or end-of-medication/end-of-treatment visit if medication or TAU intervention is stopped early) for assessment of secondary outcomes. Ethyl glucuronide is a biomarker of alcohol consumption in the previous 22 to 31 hours and will be used to confirm self-reported alcohol abstinence (Dahl, Stephanson et al. 2002; Wurst and Metzger 2002).

13.3 Addiction Severity Index-lite (ASI-Lite)

The ASI-Lite is derived from the Fifth Edition of the ASI (McLellan, Kushner et al. 1992), a structured clinical interview that yields scores for seven areas of functioning typically impacted by addiction, including medical status, employment status, drug use, alcohol use, family status, legal status, and psychiatric status. Only the drug use and alcohol use sections of the ASI-Lite will be used. Opioid and alcohol use questions, including the main type of opioid used by the participant, whether a prescription opioid or heroin, the onset of the use, the participant's perception of the substance that is most problematic, and their present treatment goal will also be assessed at baseline as part of the ASI-Lite assessment. The ASI-Lite drug and alcohol sections will be completed at baseline and 16 weeks (or end of medication/end-of-treatment visit if medication or TAU intervention is stopped early) for assessment of secondary outcomes.

13.4 Timeline Follow Back (TLFB)

Timeline Follow Back (TLFB) assesses self-reported drug and alcohol use over the past 30 days, with high test-retest reliability and validity (Sobell and Sobell 1992; Sobell and Sobell 2000). Participants will be asked to report daily drug and alcohol use since the last visit at baseline, induction onto study medication, 1 week after induction (Safety Visit), and at 4, 8, 12, and 16 weeks (or the end-of- medication/end-of-treatment visit if medication or TAU intervention is stopped early) for assessment of secondary outcomes.

13.5 Visual Analog Craving Scale (VAS)

Participants' craving for opioids, and alcohol will be documented on a visual analog scale (VAS) that ranges from 0 (no craving) to 100 (most intense craving possible). Participants will be instructed specifically to indicate the overall intensity of craving experienced This scale will be completed at baseline and at 4, 8, 12, and 16 weeks (or the end-of- medication/end-of-treatment visit if medication or TAU intervention is stopped early) for assessment of secondary outcomes.

13.6 Treatment Services Review (TSR), Version 6 (28 days)

Select items from the Treatment Services Review, Version 6 (TSR-6) addiction treatment modules will be used to collect data on the number of counseling sessions attended in the past

28 days, as well as detoxification, outpatient, inpatient, and medication-assisted addiction treatment services (Cacciola, Alterman et al. 2008). Participants will complete TSR-6 at baseline, treatment initiation, and 4, 8, 12, and 16 weeks (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early) for assessment of TAU and counseling exposure in both TAU and XR-NTX arms.

13.7 Medication-Assisted Treatment

In order to assess study drug and other medication-assisted treatment exposure, TSR-6 responses will be augmented regarding use of medications for treatment of addiction with additional items asking specifically about use of XR-NTX, methadone, buprenorphine, disulfiram, and acamprosate during the past 28 days for participants randomized to both TAU and XR-NTX arms. Participants will be asked to report the number of days in the past 28 days that each medication was taken at least once per day. This information will be collected from participants at baseline, Week 0, 4, 8, 12, and 16 (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early). Additional information gleaned from medical record review, to assess the dose and number of days of treatment prescribed for each medication will further augment this assessment.

13.8 Concise Health Risk Tracking - Self Report (CHRT-SR) Suicidal Behavior Evaluation

The CHRT-SR (Trivedi, Wisniewski et al. 2011) is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner et al, 2007). The CHRT-SR will be assessed at baseline, Week 0, and 1, 4, 8, 12, and 16 week visits (or end-of-medication/end-of-treatment if medication or TAU intervention stopped early). The CHRT-SR will assess high risk suicide ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of, thoughts of how and/or a specific plan to commit suicide) and prompt a clinician assessment for suicide risk before leaving the clinic.

13.9 Concise Health Risk Tracking - Clinician Rated

Clinician Rated (CHRT-CR (Trivedi, Wisniewski et al. 2011). This assessment will be performed by the medical clinician only if a participant answers any of questions 14-16 on the CHRT-SR as agree or strongly agree as described above.

13.10 Readiness for Drug Treatment

Participants' attitudes toward and readiness for drug treatment will be measured by a 4 item readiness scale (Longshore and Teruya 2006) and a 4 item-negative attitudes scale (Conner, Longshore et al. 2009) both of which have good reliability in prior studies and relationships with treatment retention. Readiness for drug treatment is hypothesized to be a potential predictor of response to study drug treatment. It will be assessed at baseline and 16 week (or end-of- medication/end-of-treatment if medication or TAU intervention stopped early).

14.0 HIV RELATED MEASURES

14.1 Antiretroviral Medication Prescription and Adherence

Since HIV viral suppression is most strongly influenced by optimal use of ART, evaluation of adherence to one's ART regimen is essential. Self-reported antiretroviral use and adherence will be assessed with the AIDS Clinical Trials Group (ACTG) Adherence Questionnaire for measuring antiretroviral adherence (Reynolds, Sun et al. 2007) at baseline, Week 0, and 4, 8, 12, and 16 weeks or the end-of-medication visit (if medication is stopped early) for assessment of secondary outcome if participant is prescribed ART at the time of follow up visits. The ACTG questionnaire asks the participant to list each prescribed antiretroviral medication and then asks about adherence to each medication yesterday, 2, 3, and 4 days ago, adherence to schedule, instructions, during the last weekend and when any medication was last skipped. The questionnaire's responses are weighted to calculate an adherence level from 0 - 100 (Chesney, Ickovics et al. 2000; Reynolds, Sun et al. 2007). We will assess the proportion of participants taking 100% of prescribed ART doses in the past 3 days at 16 weeks for those prescribed ART at any point during the 16 week trial (proportion; self-reported ACTG adherence measure).

Because self-reported use of specific antiretrovirals has limited reliability when compared with medical record review (Korthuis, Asch et al. 2002; Brouwer, Napravnik et al. 2011), we will confirm ART use with medical record review at baseline and 16 weeks to assess the secondary outcome of ART prescription. Specifically, we will assess change in the proportion of participants prescribed ART within 16 weeks following randomization, compared to baseline (binary; medical record abstraction).

14.2 HIV Care Utilization

Will assess the number of HIV primary care visits at baseline and 16 weeks (count, chart abstraction).

14.3 HIV Risk Assessment Battery

The Risk Assessment Battery (RAB) (Navaline, Snider et al. 1994) is a self-administered assessment of engagement in activities that increase the likelihood of HIV transmission only sexual and drug-related HIV risk behavior items will be included, in an effort to limit instrument redundancy and participant response burden. Several scores that measure drug risk, sex risk, and total risk will be computed. It will be assessed at baseline, and 4, 8, 12, and 16 weeks (or the end-of-medication visit if medication is stopped early).

15.0 SAFETY ASSESSMENTS

15.1 Adverse Events, including Serious Adverse Events, and Protocol Deviations

Adverse Events, Serious Adverse Events, and Protocol Deviations will be assessed and documented.

Study staff members will assess for any medical or psychiatric side effects, by asking: “How have you been feeling since your last visit?” AEs will be solicited at each study visit, but will be recorded at any visit after consent when reported by the participant according to the adverse event reporting definitions and procedures outlined in the protocol.

If a reported AE suggests medical or psychological deterioration, it will be brought to the attention of the study medical clinician for further evaluation. SAEs will be medically managed, reported, and followed in accordance with applicable regulatory requirements. Safety assessments will be performed at all visits.

15.2 Non-Fatal Overdose

Non-fatal overdoses in the past 4 weeks will be assessed using a self-reported instrument used in previous studies at baseline and 16 weeks or the end-of-medication visit (if medication is stopped early) (Coffin, Tracy et al. 2007). Overdose events are sentinel events that are less likely to be prone to recall bias than other events. If non-fatal overdose resulted in adverse event, it should also be captured on the AE/SAE CRF.

15.3 Fatal Overdose

We will collect data on fatal overdoses using medical chart record review at 16 weeks for participants who are lost to follow-up. We will supplement this with information from contacts with persons listed on the participant’s locator form when participants are lost to follow-up throughout the study. If a fatal overdose occurred, the event also should be captured on the AE/SAE CRF.

15.4 Precipitated Withdrawal

For participants assigned to XR-NTX, the study clinician will record the presence or absence of precipitated opioid withdrawal following each XR-NTX injection.

16.0 STUDY CONDITIONS

The two study conditions are: 1) office-based XR-NTX, and 2) TAU. Study conditions are discussed in detail in section 4.2, 4.3, and 9.0.

16.1 Clinic-Based XR-NTX

The office-based XR-NTX study condition is discussed in detail in Sections 4.2 and 9.0.

16.2 TAU

The TAU study condition is discussed in detail in Sections 4.3 and 9.0.

16.3 Training

Training in study-specific assessments will be provided as specified in a comprehensive training plan that will be developed by EMMES, the Lead Team, and other participating nodes. The trainings will include modules targeting all research team members conducted via web, telephone and in-person training sessions. Training will cover standard NIDA training for all CTN Trials (e.g., Good Clinical Practices), as well as protocol specific training as needed (e.g., assessments, study intervention, fidelity to the protocol, safety procedures, data management and collection, research procedures). Attention will be given to provide the study clinic staff providers training in management of opioid and alcohol withdrawal, XR-NTX induction and maintenance, and to familiarize study personnel with study procedures. Support mechanisms are identified (e.g., who to contact for aid, questions, resources) as well as re-training procedures. All study staff will be required to complete any local training requirements per study site and IRBs. Further details are presented in the study Training Plan located in the Operations Manual.

16.4 Concomitant Medications

Participants will be instructed to contact the study medical clinician if they plan on taking any concomitant medications (including prescription, over-the-counter, and herbal supplements) during the course of the study.

As described in the eligibility criteria, participants will be excluded if there is a need for ongoing opioid analgesic treatment. The study medical clinician may also exclude any participant taking medications that could interact adversely with study drugs at his/her clinical discretion.

Study screening and treatment induction procedures (requirement for negative UDS for opioids on day of induction) are anticipated to greatly decrease the risk of precipitating opioid withdrawal. In the event a participant experiences opioid withdrawal following XR-NTX injection, the study clinician may dispense symptomatic treatments (e.g. oral clonidine, prochlorperazine, ibuprofen, etc.) to alleviate symptoms of opioid withdrawal, according to local SOPs. XR-NTX can also be associated with transient nausea unrelated to opioid withdrawal, typically lasting 2-8 hours. Should participants develop nausea or vomiting during naltrexone induction, this will be treated with oral anti-emetics such (e.g. prochlorperazine) as needed.

17.0 STATISTICAL ANALYSIS

Primary Objective of the Analysis:

The Primary Objective of the CHOICES pilot study is to determine the acceptability and feasibility of XR-NTX in HIV practice and inform development of a multi-site comparative effectiveness trial of XR-NTX vs. TAU in HIV clinics.

17.1 Primary Outcome Measures

Primary outcome variables for the CHOICES pilot study are:

1) HIV provider willingness to prescribe XR-NTX (Aim 1): HIV provider willingness to prescribe opioid antagonist treatment will be assessed with measures adapted from the Medical Opinion Survey (MOS) in the provider survey (mean; survey data).

2) Patient acceptance of opioid antagonist therapy (Aim 2): HIV-infected patient acceptance of opioid antagonist treatment will be assessed with measures adapted from the Medical Opinion Survey (MOS), administered during participant recruitment. Patients will be asked whether they are willing to participate in a trial of XR-NTX vs. TAU (binary; survey data).

3) Rate of participant recruitment into trial (Aim 3): Number of participants randomized in pilot study per 12 months. This will be used to estimate the speed at which a multisite trial could enroll participants. The number of participants randomized will be assessed on a monthly basis until either 50 participants have enrolled, or 12 months of recruitment have elapsed, whichever comes first (rate; randomization data).

4) Treatment initiation (Aim 4A): Treatment initiation is defined as receipt of at least one dose of study medication for those randomized to XR-NTX within 4 weeks of randomization. For those randomized to TAU, treatment initiation will be defined as receiving at least one dose of medication-assisted therapy other than XR-NTX (e.g., buprenorphine for opioid use disorder, disulfiram for alcohol use disorder), or attendance on at least 1 day of non-medication-assisted therapies (e.g., 12-step groups, outpatient rehab referral, etc.) within 4 weeks of randomization . Treatment initiation will be assessed with weekly phone calls from research staff until treatment is initiated or 4 weeks from date of randomization have elapsed, as which point a participant will be considered to have failed treatment initiation. (binary; chart review and self- report).

5) Retention on treatment (Aim 4B): Retention on treatment is defined as the percent of assigned treatment received over 16 weeks after randomization. Only participants who initiate treatment (as defined in Aim 4A) will be assessed for retention on treatment. Retention will be assessed by the study clinician at 4, 8, 12, and 16 weeks following treatment initiation. For those randomized to XR-NTX, retention on treatment is defined as the mean percent of expected XR-NTX doses received (25%, 50%, 75%, or 100% of 4 possible doses). For those randomized to TAU, study clinicians will estimate the percent of recommended treatment a participant received in the past 4 weeks at weeks 4, 8, 12, and 16. Retention on treatment for TAU is defined as the mean percent of recommended TAU treatment received (1-100% possible range), as estimated by the study clinician. (percent; chart review and self-report).

17.2 Secondary Outcome Measures

1) HIV outcomes:

a) HIV-1 RNA viral suppression (plasma HIV-1 RNA pcr ≤ 200 copies/mL) at 16 weeks compared with screening (binary, laboratory assay).

b) Change in CD4 count at the week 16 visit compared with screening (count; laboratory measurement).

2) Substance Use:

a) Change in 30 day opioid abstinence (by Addiction Severity Index (ASI)-lite self- report, TLBF (self-report) and urine drug screen (UDS) confirmation) in the final 30 days of the 16 week trial compared to screening (binary; laboratory data and self-report).

b) Change in past 30-day alcohol and other drug use by ASI-lite and UDS at week 16 visit compared to screening (binary; laboratory data and self-report).

3) Engagement in HIV Care:

a) Change in the proportion of participants prescribed ART within 16 weeks following randomization, compared to baseline (binary; medical record abstraction).

b) Proportion of participants taking 100% of prescribed ART doses in the past 3 days at 16 weeks for those prescribed ART at any point during the 16 week trial (proportion; self-reported ACTG adherence measure).

c) Number of HIV primary care visits at 16 weeks (count, chart abstraction).

4) Participant safety:

a) Change in liver enzymes between screening and week 16 visit (laboratory assay).

b) Any fatal and non-fatal opioid overdose between screening and week16 visit (binary; medical record abstraction and self-report).

c) Change in Concise Health Risk Tracking score between screening and week 16 visit (continuous; self-report).

d) Proportion of participants assigned to XR-NTX who develop precipitated opioid withdrawal.

Sample Size and Duration of Randomized Pilot Study Recruitment Phase

The randomized pilot study will recruit until either 50 participants have been enrolled or 12 months of recruitment have elapsed, whichever comes first. Justification for this decision follows:

The proposal for a phase III randomized trial assumes enrollment of 400 participants from 8 sites in 18 months, implying a recruitment rate of about 2.28 participants per site-month. **Table 17.2.1** explores by simulation the consequences for the precision of various pilot-study-derived estimates of having a pilot study in which per site-month recruitment rate = (1.14, 2.28), number of sites = (1,2), and time period = (12 months, 18 months). **Table 17.2.1** investigates limiting the pilot sample size to 50 participants (n-limited), or limiting the enrollment time to 12 or 18 months (t-limited), or limiting both sample size and recruitment time simultaneously (n- and t-limited). The columns of **Table 17.2.1** headed – “Parameters” depict all the parameter combinations investigated.

5) The notation used in **Table 17.2.1** follows:

- n = pilot study sample size
- t = pilot study recruitment time (months)
- s = number of sites in the pilot study
- rate = recruitment rate (participants per site-month) assumed for both the pilot study and the subsequent phase III randomized trial
- N = randomized trial sample size (assumed to be 400)
- T = randomized trial recruitment time (months). This assumes that the sites in the randomized trial will exhibit the same performance that they did in the pilot study.
- S = number of sites in the randomized trial (this is not actually shown in **Table 17.2.1**, but is assumed to be 8)
- $\hat{T} = \frac{s/n}{S/N} t$, the estimator, derived from the pilot study, of the recruitment time for the subsequent phase III randomized trial
- p(init) = the probability of treatment initiation, which is the chance that a participant who is randomized to one of the two arms within the pilot study will obtain the 1st dose of the treatment. There is one p(init) calculated for each of the two arms.
- p(ret) = the probability of retention, which is the chance that a pilot-study participant who has obtained the 1st dose will still be on treatment at 4 months. There is one p(ret) calculated for each of the two arms.

6) The columns of **Table 17.2.1** headed “Outcomes (Percentiles)” show the consequences for various outcomes, given the parameters controlling the pilot study. Their meanings follow:

- 20% n = the 20th percentile of the sample size of the pilot study. The pilot study will very likely recruit at least this many participants
- 80% t = the 80th percentile of the recruitment time for the pilot study (months). The pilot study will very likely not take longer than this time to recruit.
- 80% p(init) = the 80th percentile of the 95% confidence interval half width for the pilot- study-derived estimate of the probability of treatment initiation. If this value is x, it means that the 95% confidence interval for the estimate of the probability of treatment initiation will very likely not be wider than ±x.
- 80% p(ret) = = the 80th percentile of the 95% confidence interval half width for the pilot- study-derived estimate of the probability of treatment retention. If this value is x, it means that the 95% confidence interval for the estimate of the probability of treatment retention will very likely not be wider than ±x. This confidence interval is slightly wider than for p(init) because **Table 17.2.1** assumes 10% attrition between the time of recruitment and initiation.
- 80% T = the 80th percentile of the time to recruit in the subsequent phase III randomized trial.
- 80% $|\hat{T} - T|$= the 80th percentile of the absolute value of the predictive bias of $\hat{T}$ for T

16.1.1 Table 17.2.1

Consequences for Outcomes and Their Precision of Having a Randomized Pilot Study with Specified Parameters.

States of Nature	Parameters				Outcomes (Percentiles)				
	Limits			20%	80%				
rate	**80%T**	**n**	**t**	**s**	**n**	**t**	**p(init)**	**p(ret)**	**$\lvert\hat{T} - T\rvert$**
							(95% CI Half width)		
n-limited									
1.14	46	50	.	1	50	49	0.2	0.21	5
1.14	46	50	.	2	50	25	0.2	0.21	5
2.28	23	50	.	1	50	25	0.2	0.21	3
2.28	23	50	.	2	50	12	0.2	0.21	3
t-limited									
1.14	46	.	12	1	9	12	0.45	0.47	12
1.14	46	.	12	2	22	12	0.3	0.32	8
2.28	23	.	12	1	22	12	0.3	0.32	4
2.28	23	.	12	2	48	12	0.21	0.22	3
1.14	46	.	18	1	16	18	0.37	0.38	9
1.14	46	.	18	2	35	18	0.24	0.25	6
2.28	23	.	18	1	34	18	0.24	0.26	3
2.28	23	.	18	2	73	18	0.17	0.17	2
both n- and t-limited									
1.14	46	50	12	1	10	12	0.47	0.5	12
1.14	46	50	12	2	22	12	0.3	0.32	8
2.28	23	50	12	1	22	12	0.3	0.32	4
2.28	23	50	12	2	48	12	0.21	0.22	3
1.14	46	50	18	1	16	18	0.35	0.37	9
1.14	46	50	18	2	35	18	0.24	0.25	6
2.28	23	50	18	1	34	18	0.24	0.25	3
2.28	23	50	18	2	50	12	0.2	0.21	3

To use **Table 17.2.1**, observe that the columns are broken into three groups:

States of Nature: These are design quantities that are fixed by nature. That is, you have to assume them, but you cannot manipulate them to get a better pilot study. These include the recruitment rate and its implication for the 80th percentile of the time it will take to recruit in the phase III randomized trial.

Parameters: These are design quantities that you can choose to optimize the pilot study. They include the limits on pilot-study sample size (n) and time to recruit (t), and the number of sites (s) in the pilot study.

Outcomes: These are the results of the States of Nature assumed and the Parameters chosen. They include the 20^{th} percentile of the pilot study sample size and the 80_{th} percentiles of t, p(init), p(ret) and $|\hat{T} - T|$.

For example, the highlighted row in the last – "paragraph" of **Table 17.2.1** shows that, if you assume that the pilot study recruitment rate is 2.28 participants per site-month (implying that the phase III randomized trial will likely require no more than 23 months to recruit), and if you choose to stop the pilot study after either 50 participants or 12 months of enrollment time (whichever comes first), and you choose to have two sites in the pilot study, then it is likely that the pilot study will recruit at least 48 participants and stop recruitment at 12 months. In this case, the 95% confidence intervals for p(init) and p(ret) will very likely be no wider than ±.22 and the prediction derived from the pilot study of the recruitment time for the subsequent randomized study will probably be off by no more than ±3 months. This degree of imprecision appears acceptable for the pilot study.

17.3 Analysis of Randomized Pilot Study Primary Outcomes

The probability of treatment initiation (Aim 4A) and the probability of retention on treatment (Aim 4B), which are calculated separately for the two arms, are both based on ordinary (conditional) binomial samples, and will be estimated using maximum likelihood techniques, with exact binomial confidence intervals. We do not contemplate a multiplicity adjustment.

The rate of participant recruitment into the trial (Aim 3) can be estimated simply using maximum likelihood assuming an underlying Poisson process, but we feel it is more meaningful and useful for planning to predict the time required for recruitment in a subsequent randomized trial with 400 participants coming from 8 sites. We will do this via a bootstrap simulation. In each iteration of the simulation, the steps will be as follows:

- Draw a bootstrap sample of 8 sites from the 2 pilot-study sites.
- For each site, draw a bootstrap sample of, say, 1000 inter-arrival times from the inter- arrival times for that site to get 1000 simulated enrollment times (starting from time 0) for the site. Note that we consider that the time between the last enrollment at that site and the 12 month time point is also an inter-arrival time for that site. We will use this inter- arrival time in the simulation, but will not associate it with a simulated enrollment[1].
- Treating the 8 bootstrapped sites as simultaneously enrolling, determine T, the time of enrollment of the 400th patient in the simulated trial.

Repeating this iteration 10,000 times will generate 10,000 T-values that will constitute a predictive distribution for the enrollment times in the subsequent randomized trial. It is necessary to assume that the sites in the pilot study are a representative sample of the sites that will participate in the subsequent randomized trial.

17.4 Analysis of other primary outcomes

The other primary outcomes, namely HIV provider willingness to prescribe XR-NTX (Aim 1) and Patient acceptance of XR-NTX. (Aim 2) are both results from pre-randomization surveys based on convenience samples. We will present descriptive statistics for all such survey results.

[1] The rationale for this fine point follows: Consider a pilot-study site that recruited its only patient one day after the trial starts. If, in our subsequent bootstrap simulation, we ignored this site's 364-day waiting period after the only enrollment, it would look like the site inter- arrival time for all recruitments was only 1 day -- clearly a misrepresentation of that site's behavior. This means we cannot ignore the final waiting time. Now consider another site that waits 364 days before its only recruitment. If we consider the final (1-day) waiting time to trial's end to terminate in an enrollment, it will look in the bootstrap simulation like this site is recruiting much faster than it really did. So we can't ignore the final waiting time, but we can't assume it terminates in an enrollment, either. The solution of not ignoring the final waiting time, but also not allowing an enrollment at the end of it, better represents the behavior of both these types of sites in the subsequent bootstrap simulation.

17.5 Analysis of secondary outcomes

The pilot study is small and thus probably under-powered for hypothesis tests. Any conclusions arising from secondary analysis must be regarded as hypothesis-generating only, and need to be validated by independent data. We contemplate no adjustment for multiplicity.

Secondary outcomes will be analyzed as indicated in the italicized text describing each secondary endpoint.

HIV outcomes:

a) Sustained HIV RNA viral suppression (plasma HIV viral load of < 200 copies/mL) at 16 weeks *(binary, laboratory assay). Chi-squared test of independence of sustained viral suppression on treatment assignment.*

b) Change in CD4 count at 16 weeks following randomization compared with baseline *(count; laboratory measurement)*. T-test.

1) Engagement in HIV Care:

a) Change in the proportion of study participants prescribed ART within 16 weeks following randomization, compared to baseline *(binary; medical record abstraction). Each individual can be scored either 0 (not prescribed ART) or 1 (prescribed ART) at both baseline and follow-up, after which his or her outcome score will be the follow- up score minus the baseline score. Outcome scores will be analyzed via rank-based methods such as Wilcoxon rank-sum tests. Covariates can be considered via the cumulative logit model.*

b) Proportion of participants taking 100% of prescribed ART doses in the past 3 days at 16 weeks for those prescribed ART at any point during the 16 week trial *(proportion; self-reported ACTG adherence measure). Chi-squared test comparing proportion to treatment assignment, for those prescribed ART*).

c) Number of HIV primary care visits at 16 weeks (count, chart abstraction) *outcome scores will be analyzed via rank-based methods such as Wilcoxon rank-sum tests.*

2) Substance Use:

a) Change in 30 day opioid abstinence (by ASI-lite self- report, TLFB and urine drug screen (UDS) confirmation) in the final 30 days of the 16 week trial compared to baseline *(binary; laboratory data and self-report). Analysis using rank-based methods as in outcome 2a*.

b) Change in past 30day alcohol and other drug use by ASI-lite, TLFB, and UDS at 16 weeks, compared with baseline *(binary; laboratory data and self-report). Analysis using rank-based methods as in outcome 2a.*

3) Participant safety, as measured by:

a) Change in liver enzymes between baseline and 16 weeks or last lab measurement *(continuous; laboratory assay). Analysis via paired t-test, or analysis of change via ordinary least squares.*

b) Any fatal and non-fatal opioid overdose at 16 weeks *(binary; medical record abstraction and self-report). Chi-squared test or logistic regression.*

c) Change in Concise Health Risk Tracking score at 16 weeks compared to baseline *(continuous; self-report). Analysis via paired t-test, or analysis of change via ordinary least squares.*

d) Proportion of participants assigned to XR-NTX who develop precipitated opioid withdrawal.

17.6 ITT and Per-Protocol Analyses, Missing Data and Dropouts

Analysis will be ITT in the sense that patients will be analyzed as being members of the arm to which they were originally randomized. We plan no special adjustments for missing data.

17.7 Interim Analysis

No interim analysis is contemplated.

17.8 Safety Analysis

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, body system, and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available. Treatment arm differences will be monitored by the DSMB.

18.0 REGULATORY COMPLIANCE AND SAFETY

18.1 Regulatory Compliance

Prior to local study initiation, site investigators will obtain written IRB approval to conduct the study at their respective sites. When changes to the study protocol become necessary, amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, local 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 yearly or at a frequency requested by each IRB. Each site investigator is responsible for maintaining research files that include copies of IRB-approved consent documents and all IRB/IEC (Institutional Ethics Committee) approval memos for Initial and Continuing/Annual Reviews, protocol modifications, and any other modification made in the course of the study. All initial approval documents (approval memos and informed consents) must be provided to the lead team investigator prior to the initiation of research activities at a given site and all regulatory documents must be available at any time for an audit.

18.2 Statement of Compliance

This trial will be conducted in compliance with the current version of the 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, informed 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 Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

18.3 Confidentiality

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 that 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 CTP sites will be notified if CoC revision is necessary.

Participant records will be kept confidential by the use of study codes for identifying participants on CRFs, secure and separate storage of any documents that have participant identifiers, and secure computer procedures for entering and transferring electronic data.

18.4 Health Insurance 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.

18.5 Investigator Assurances

Each CTP (community treatment program) and their respective IRB that will be reviewing the study must have on record a Federal Wide Assurance (FWA) with the DHHS Office of Human Research Protection. This sets forth the commitment of the organization (CTP or IRB) to establish appropriate policies and procedures for the protection of human research subjects, with documentation to be sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA's 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 and sub-investigators at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

18.6 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. It is the responsibility of the investigator and the entire local research team to maintain appropriate disclosure to their individual institution according to their requirements.

18.7 DEA Registration

XR-NTX is not a controlled substance. No DEA registration is required for facilities to receive, prescribeor dispense study drug.

18.8 Drug Accountability

Upon receipt, the investigator, pharmacist, or authorized designee at each site is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent must be accounted for.

18.9 Inclusion of Women and Minorities

Unless specified in the eligibility criteria, the study enrollment is open to any gender, race, or ethnicity. A diverse group of study sites will be involved so that the study can enroll a diverse study population. If difficulties are encountered in recruiting an adequate number of women and/or minorities, these will be discussed in national conference calls and face-to-face meetings, encouraging such strategies as linkages with medical sites and/or treatment programs that serve a large number of women or minorities or advertising in newspapers or radio stations with a high female or minority audience.

18.10 IND Requirements

Medications to be used in this study will be used in accordance with their approved labeling and therefore there is no plan to submit an IND application.

18.11 Regulatory Files

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

18.12 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 investigator in a secure location for a minimum of 3 years after the study is complete and closed. These records are also to be maintained in compliance with local IRB, state, and federal requirements, whichever is longest. In the case of HIPAA-protected records, this time length is six years. The sponsor and lead investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

18.13 Audits

The sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform periodic quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the National Lead Study Team; 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), the Office for Human Research Protection (OHRP) 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.

18.14 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 trial or increase risk to study participants. Adverse Event and Serious Adverse Event reporting will occur as described in Appendix A - Adverse Event Reporting Definitions and Procedures. At the completion of the trial, the national Lead Investigator will provide a final report to the Sponsor.

18.15 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. All potential candidates for the study will be given a current local IRB-approved copy of the Informed Consent Form to read. Appropriately qualified and trained study personnel will explain all aspects of the study in lay language and answer all of the study candidate's questions. Participants who remain interested after receiving an explanation of the study will be given an informed consent quiz to test his/her understanding of the trial, the purpose and procedures involved, and the voluntary nature of his/her participation. Those who cannot successfullyanswer the quiz questions will have the study re-explained by research staff with a focus on those aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participant and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the Informed Consent Form. Participants will not be administered any assessments or study procedures prior to signing the informed consent.

For this study, there will be two consents, one for pre-screening and one for trial consent. Both consents are to be treated equally in terms of regulatory and protocol requirements (e.g., approved by Lead Team and local IRB before site initiation, signed and dated by participant, etc.).

Each study site must have the pre-screening and trial consents approved by their local IRBs. A copy of the IRB-approved consents, along with the IRB study approval, must be sent to the Clinical Coordinating Center

(CCC) and the Lead Node prior to the site initiation visit and with each subsequent consent revision. 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 a study participant's participation in the trial. The site must maintain the original and signed Informed Consent Form for each participant in a locked and secure location that is in compliance with their local IRB and institutional policies. The consent forms must also be accessible for quality assurance review and regulatory compliance. Every study participant should be given a copy of the signed document to keep for their reference. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

18.16 Clinical Monitoring

Monitoring of the study site will be conducted on a regular basis using a combination of NIDA- contracted monitors and Node Quality Assurance (QA) staff. Investigators will host periodic visits by both the NIDA-contracted monitors and local site managers; the purpose of which is to encourage and assess compliance with GCP requirements and to document the integrity of the trial progress. The national and local monitors will audit the following items, but not exclusively: regulatory documents, case report forms, Informed Consent Forms, and any corresponding source documents for every participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant Informed Consent Forms, protocol adherence, reported safety events and corresponding assessments, study drug accountability, and principal investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA CCTN.

Qualified node personnel will provide site management and monitoring for each site during the trial. This will take place as specified by the local protocol team, node PI, or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node (QA) staff will audit source documentation, including all Informed Consent and HIPAA forms (if applicable). Node QA staff will verify that study procedures are being properly followed and that site staff is trained and able to conduct the protocol appropriately. If the node QA staff's review of study documentation indicates that additional training of study personnel is needed node QA staff will undertake or arrange for that training. Details of the contract, Node QA, and data monitoring are found in the study monitoring plan.

18.17 Study Documentation

Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence and approved current and previous consent forms 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. The original recording of an observation should be retained as the source document. If the original recording of an observation is the electronic record, that will be considered the source.

19.0 SAFETY MONITORING

19.1 Data and Safety Monitoring Board (DSMB)

This study will utilize the CTN DSMB to oversee ongoing trial progress to assure protection of participants' safety while maintaining that the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, evidence that study procedures should be changed, or if the trial should be halted (for safety, efficacy, or recruitment or performance reasons). This process is intended to assure the IRBs, sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in CTN research trials.

Monitoring will begin with the initial review of the protocol during the study development process and continue throughout the study with meetings at least annually. Recommendations and reports from these reviews will be distributed to the site lead investigator for submission to their IRB.

19.2 Protocol Deviations Reporting and Management

Any departure from procedures or requirements outlined in the protocol will be classified as protocol deviations. A protocol deviation is an action (or inaction) that alone may or may not affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. In some cases, a protocol deviation may compromise participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and is cause for corrective action to resolve the departure and to prevent re-occurrence. 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 trial. The decision about whether a deviation from the protocol will be designated as minor or major will be made by the Clinical Coordinating Center (CCC) in conjunction with the protocol's Lead Investigator(s). The consequences will be specified and participating sites will be informed.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized 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.

19.3 Adverse Events (AEs)

The Lead Investigator may appoint a Study Clinician (MD, DO, NP or PA) for this study, who will review or provide consultation for each serious event as needed. These reviews will include an assessment of the severity and causality of the event to the study intervention (drug or therapy) or other 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 centralized Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary for submission to IRBs for regulatory compliance. The medical monitor will determine which safety events require expedited reporting to NIDA, the DSMB, pharmaceutical/distributors, and regulatory authorities. This will include events that are serious, related, and unexpected. The study staff will be trained to monitor for and report Adverse Events and Serious Adverse Events.

19.3.1 Adverse Events

For the purposes of this study, all Adverse Events will require reporting in the data system.

19.3.2 Serious Adverse Events:

For the purpose of this study, the following events will not be reported as an SAE, but will be recorded on study specific forms in the data system. They would be reported to local IRBs per local IRB guidelines:

1) Detox admissions (documented instead on the DTX form).

2) Admission for labor and delivery.

3) Admission for elective or pre-planned surgery.

19.4 Known Potential Toxicities of Study Drug/Intervention

Refer to the package insert for XR-NTX.

19.5 Known Potential Adverse Events Related to the Underlying Clinical Condition and/or Study Populations

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

As this population will have significant ongoing health and substance use issues, events related to complications of HIV, substance use treatment or admission for substance detoxification, hospitalizations for medical and psychological reasons and deaths will be captured on study specific forms and not duplicate reported as an adverse or serious adverse event. These data will still be included in the reports to the DSMB at the regular meetings.

20.0 DATA SAFETY MANAGEMENT AND PROCEDURES

20.1 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, 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.

20.2 Site Responsibilities

The data management responsibilities of each individual CTP will be specified by the DSC and outlined in the AdvantageEDC User's Guide.

20.3 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 CTPs, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

20.4 Data Collection

Data will be collected at the study sites either on source documents, which will be entered at the site into eCRFs, or through direct electronic data capture. The eCRFs will be supplied by the DSC. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. Paper CRFs and eCRFs should be completed according to the CRF instruction manual and relevant instructions in the study operations manual. 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.

20.5 Data Acquisition and Entry

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

20.6 Data Editing

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

20.7 Data Lock and Transfer

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.

20.8 Data Training

The training plan for CTP staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of AdvantageEDC.

20.9 Data QA

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.

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22.0 APPENDIX A

ADVERSE EVENT REPORTING DEFINITIONS AND PROCEDURES

Each participating site's principal investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

22.1 Definition of Adverse Events and Serious Adverse Events:

An **Adverse Event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status or any findings from ECGs, lab results, x-rays, physical examinations, etc., that are considered clinically significant by the study medical clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered **"serious"** (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study medical clinician or sponsor, it:

1) Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study drug/intervention, must be reported.

2) Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.

3) Requires inpatient hospitalization or prolongation of existing hospitalization.

4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Is a congenital abnormality or birth defect.

5) Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

22.1.1 Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the investigator brochure or the package insert or is not listed at the specificity or severity that has been observed. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

22.2 Pregnancy

Any pregnancies that occur while a participant is enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Women who become pregnant during the active treatment period will be discontinued from further medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

22.3 Medical and Psychiatric History

A thorough medical and psychiatric history during the screening phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

22.4 Site's Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained study staff will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Study staff will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to their IRB, per their IRB's guidelines.

Site staff is required to enter reportable AEs and SAEs in the AdvantageEDC system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate serious adverse events and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

22.5 Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained medical personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review reportable AEs for seriousness, severity, and causality at least on a weekly basis.

22.6 Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event.

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/ therapy required, hospitalization not necessary (non- prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.

22.6.1 Guidelines for Determining Causality

The study medical clinician will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the study drug/intervention caused the event?

22.6.2 Site's Role in Monitoring Adverse Events

Local quality assurance monitors (Node QA staff) will visit study sites and review respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

22.6.3 Sponsor's Role in Safety Management Procedures of AEs/SAEs

A NIDA-assigned Medical Monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Medical Monitor, Lead Investigator, and designees. All SAEs will be reviewed by the Medical Monitor in AdvantageEDC and, if needed, additional information will be requested. The medical monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA assigned Medical Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the medical monitor in writing for review by the sponsor and DSMB. Subsequent review by the Medical Monitor, DSMB, FDA and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor, DSMB and FDA retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

22.7 Regulatory Reporting for an IND study

Not applicable as this study is not being conducted under an IND application.

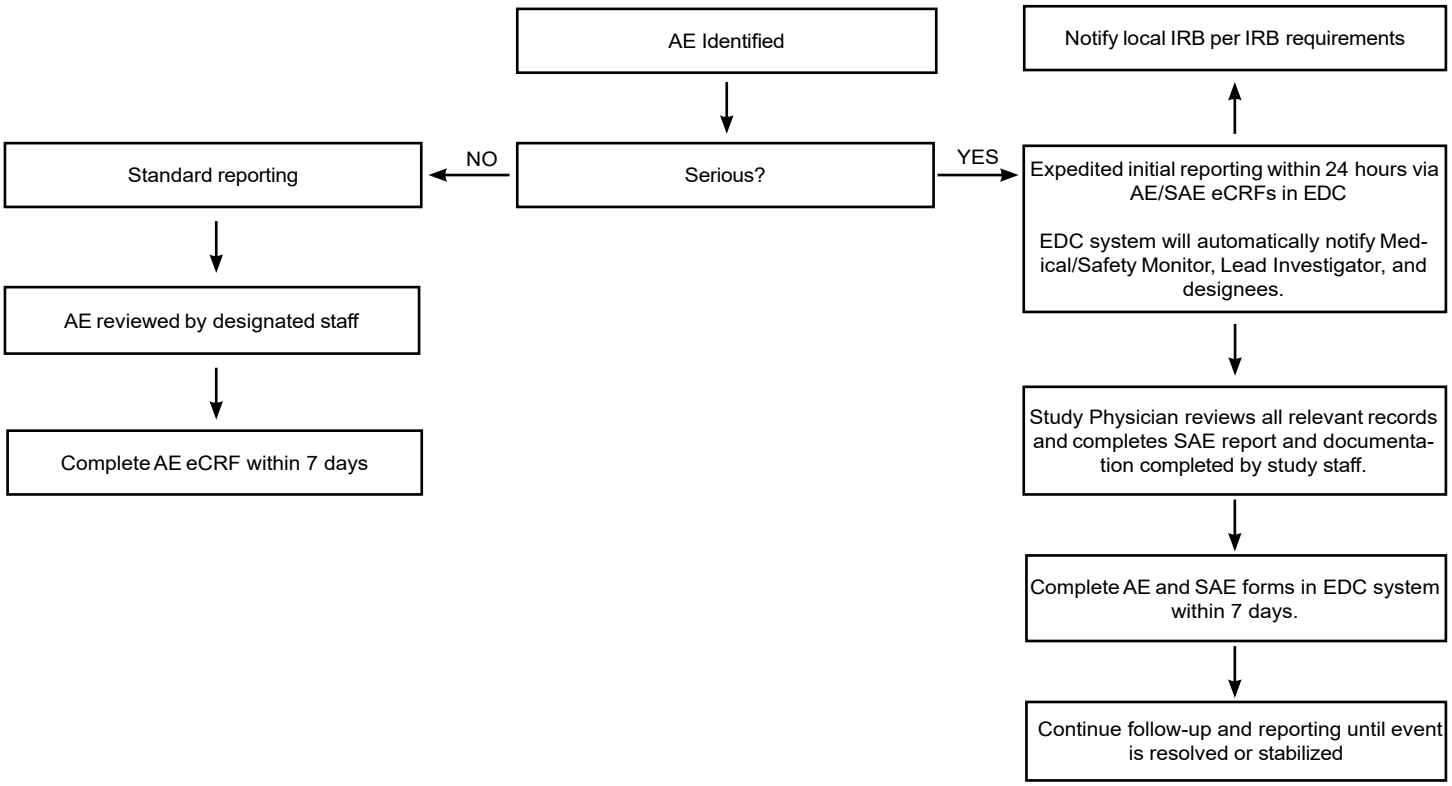
22.8 Reporting to the Data and Safety Monitoring Board

The DSMB will receive a listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

22.9 Participant Withdrawal

The study medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant is withdrawn from further study medication administration. Extended-release naltrexone will be discontinued in participants with evidence of clinically significant deterioration in hepatic function and/or acute hepatitis, as assessed by the study clinician. The study medical clinician should consult with the site principal investigator, the lead investigator and/or Medical Monitor as needed. If necessary, a study medical clinician may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end-of-medication visit to assure safety and to document end-of-medication outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.

22.10 Adverse Event Reporting Chart



23.0 APPENDIX B

DATA SAFETY AND MONITORING PLAN (DSMP)

Brief Study Overview

The primary goal of the CTN-0055 study is to compare HIV viral suppression (HIV-1 RNA < 200 copies / ml at 6 months) among study participants randomized to XR-NTX vs those randomized to office-based BUP/NX. Secondary aims are to compare the effectiveness of XR-NTX vs BUP/NX in 1) HIV outcomes 2) engagement in HIV care 3) change in substance use, 4) change in HIV risk behaviors, 5) change in health related quality of life, and 6) participant safety. Details for the definitions and reporting of safety events are found in the protocol (Appendix A).

23.1 Oversight of Clinical Responsibilities

23.1.1 Site Principal Investigator

Each participating site's PI is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Regarding safety and in accordance with FDA reporting requirements, all Adverse Events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol. The assessment of Adverse Events (medical and/or psychiatric) will commence at the time of participant consent and will continue through 30 days post last active treatment visit.

The occurrence of AEs and Serious Adverse Events (SAEs) will be assessed at each clinic visit during the study. Serious adverse events will be followed until resolved or considered stable, with reporting to the CCC Safety Monitor/Medical Monitor through the follow-up period.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events).

23.1.2 Medical Monitor/Safety Monitor

The NIDA Clinical Coordinating Center (CCC) Safety Monitor/Medical Monitor is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed at the time they are reported in the EDC. The Medical Monitor will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed the Safety monitor/Medical monitor will discuss the event with the site. Reviews of SAEs will be conducted in AdvantageEDC data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

The CCC Safety Monitor/Medical Monitor will in turn report events to the sponsor and regulatory authorities if the event meets the definition of an expedited event. All SAEs that meet expedited reporting based on federal regulations will be reported to the FDA in writing within 15 calendar days of notification of the CCC. If the SAE meets the criteria for death or immediately life- threatening, the CCC will notify the FDA electronically, by phone or by fax as soon as possible but no later than 7 calendar days of notification of the CCC, with a follow-up written report within 15 calendar days of notification of the CCC. The CCC will prepare an expedited report (MedWatch Form 3500A or similar) for the FDA and copies will be distributed to all site investigators. Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings.

23.1.3 Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. The DSMB will make recommendations to the NIDA as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication detailing study safety information will be submitted to participating IRBs.

23.1.4 Quality Assurance (QA) Monitoring

The monitoring of the study site will be conducted on a regular basis using a combination of NIDACCC contract monitors and the local RRTC site managers. Investigators will host periodic visits for the NIDA CCC contract monitors and RRTC site managers. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. Areas of particular concern will be the review of Inclusion/ Exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and Principal Investigator supervision and involvement in the trial. The Monitors will interact with the sites to identify issues and re-train the site as needed to enhance research quality.

QA Site Visit Reports will be prepared by the NIDA CCC contract monitors following each site visit. These reports will be and forwarded to the site Principal Investigator, the study Lead Investigator and NIDA.

23.1.5 Management of Risks to Participants

23.1.5.1 Confidentiality

Confidentiality of participant records will be secured 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. No identifying information will be disclosed in reports, publications or presentations.

23.1.5.2 Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required to be reported and the fact that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

23.1.5.3 Human Subject Protection

The study medical clinician will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. Adverse events (AEs) and concomitant medications will be assessed and documented at each clinic visit. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end-of medication visit to assure safety and to document end-of-medication outcomes.

23.1.5.4 Pregnancy

Pregnancy is an exclusion criterion for study participation. A positive pregnancy test post- randomization will result in the cessation of study medication. Participants who discontinue medications will be expected to continue with study visits. Pregnancy test results and related outcome information will be collected on a Pregnancy and Outcome CRF. The site staff will follow the participant until an outcome of the pregnancy is known.

23.1.5.5 Study Specific Risks

XR-NTX blocks the effects of exogenous opioids after administration. After treatment, participants are likely to have reduced tolerance to opioids. Following Vivitrol® treatment, opioid use at the end of a dosing interval or after missing a dose could result in potentially life- threatening opioid intoxication (involving respiratory compromise or arrest, circulatory collapse, etc.) Attempting to overcome the blockade effects of Vivitrol® by administering large amounts of exogenous opioids is associated with potential risk of overdose. Participants in this study will receive an information card that will notify clinicians that they are receiving XR-NTX as part of a research study.

23.2 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) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

23.3 Data and Statistics Center Responsibilities

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (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) prepare instructions for the use of AdvantageEDC and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, 6) perform data cleaning activities prior to any interim analyses and prior to the final study database lock.

23.4 Data Collection and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in AdvantageEDC, or will be collected via direct entry into the eCRF. In the event that AdvantageEDC is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into AdvantageEDC in accordance with the instructions provided during project-specific training and guidelines established by the DSC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

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

23.5 Data Monitoring, Cleaning and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in AdvantageEDC. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in AdvantageEDC on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into AdvantageEDC.As described above, the CCC will conduct regular visits to sites, during which, audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding RRTC (node), the Lead Investigator, the coordinating centers, and NIDA, to monitor the sites' progress on the study.

23.6 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 returned to NIDA, as requested, for storage and archive.

24.0 APPENDIX C

INFORMAL QUERY OF HIV CLINICS REGARDING PARTICIPANT AVAILABILITY FOR CTN-0055

To help inform protocol development, we conducted an informal query of HIV clinics affiliated with CTN nodes to inform CTN-0055 protocol development. This was not a site selection survey. HIV clinics not included in the informal query will still be considered for CTN 0055 participation. HIV clinic medical directors at these sites were e-mailed and asked to estimate: 1) the number of unduplicated HIV-infected potential participants per year at their site, 2) the number of opioid-dependent HIV-infected potential participants at their site, and 3) the number of HIV-infected potential participants with alcohol and opioid use disorders who had detectable HIV viral load. Thirteen of 17 HIV clinics responded.

Results in **Table 24.1** support the availability of more than 1,000 participants in 13 geographically diverse clinics. Eight of the responding HIV clinics are located in the "12 Cities Project", cities that account for 44% of the U.S. AIDS cases and are targeted for expanded National HIV/AIDS Strategy HIV prevention and treatment activities by the U.S. Department of Health and Human Services (U.S. Department of Health and Human Services 2011). Three of the 13 respondents had fewer than 50 potential participants, though estimates for these sites were particularly conservative.

24.1 Table Preliminary Site Feasibility Query

HIV Clinic Site	# Unique participants/Year	# Opioid-Dependent	# Lacking viral suppression
CORE Clinic Chicago	5,250	410	205
Moore Clinic, Baltimore	1,981	297	149
Montefiore CHCC, NYC	400	160	80
OHSU, Portland	586	47	15
Parkland, Dallas	5,072	200	100
U. Minn, Minneapolis	1,700	50	20
UAB, Birmingham	2,000	200	50
St. Luke's Roosevelt, NYC	4,571	675	270
UCSF, San Francisco General Hospital	2,543	206	41
Jackson Memorial, Miami	2,750	82	73
UCSD Owen Clinic, San Diego	3,062	92	50
Wayne State, Detroit	1,800	90	54
BMC, Boston, MA	1,400	69	52