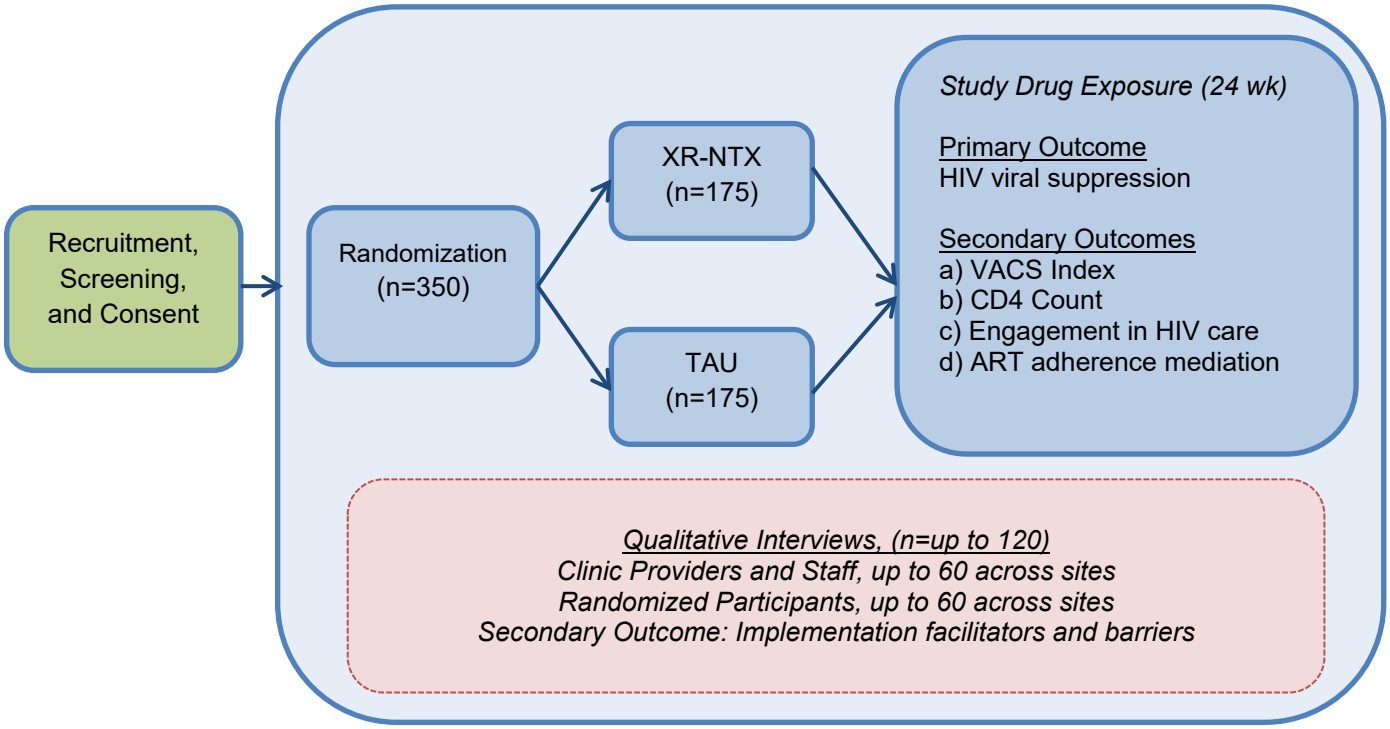
Abbreviation	Definition
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HCV	Hepatitis C Virus
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
IEC	Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LFTs	Liver Function Tests
LI	Lead Investigator
MAT	Medication-Assisted Treatment
MAR	Missing at Random
Mg	Milligrams
MM	Medical Management
MMT	Methadone Maintenance Treatment
MNAR	Missing not at Random
MOP	Manual of Operating Procedures
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
OHSU	Oregon Health and Science University
ORT	Opioid Replacement Therapy

2.1 Figure 1. Study Schema



Specific Aim: The *specific aim* is to compare the effect of office-based extended-release naltrexone (XR-NTX) versus treatment as usual (TAU) on HIV viral suppression at 24 weeks from randomization for HIV-infected participants with untreated opioid use disorder and HIV RNA PCR > 200 copies/ml at baseline.

Secondary Specific Aims: Secondary aims compare the effectiveness of XR-NTX versus TAU in 1) other HIV outcomes (VACS Index, CD4 count), 2) engagement in HIV care (receipt of ART, ART adherence, retention in HIV care, HIV risk behaviors), 3) ART adherence as mediated by number of opioid use days at 24 weeks, and 4) qualitiative interviews with participants, providers, and staff to document the HIV primary care treatment environment and describe XR-NTX formative implementation strategies, challenges, and best practices.

4.0 INTRODUCTION

4.1 Background and Rationale

Opioid Use Disorders in People Living with HIV. Opioid use disorders are common in HIV-infected individuals [3, 38, 39]. Patients with opioid use disorder experience wide gaps in the HIV care cascade. Only 21% of HIV-infected individuals referred are established and retained in ongoing HIV care [25] and PWID are least likely to engage in HIV care and achieve HIV viral suppression compared to other HIV risk groups [13, 17, 25].

When untreated, opioid use disorder in people living with HIV is associated with decreased receipt of antiretroviral therapy (ART) [9, 40], decreased ART adherence [14], and decreased HIV viral suppression [13, 17-19]. Other adverse outcomes include decreased health-related quality of life [34], greater HIV-related symptoms, [21], higher hospitalization rates [23], and greater HIV disease progression and death [41]. Opioid use disorder is also associated with increased HIV risk behaviors [8].

Opioid Use Disorder Treatment and HIV Outcomes. Treatment of opioid use disorders with methadone or buprenorphine can improve engagement and retention in care, receipt of ART, ART adherence, and HIV viral suppression. The International Association of Providers of AIDS Care guidelines recommend scale-up of evidence-based medication-assisted treatments for substance use disorders for optimizing the HIV care continuum [42]. 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 [39, 43]. In a cohort of HIV-infected PWID 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 [44].

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 compared to those referred for methadone (74% vs. 41%, p<.001); however, ART receipt, HIV RNA and CD4 counts did not differ at 12 months [28]. In the Buprenorphine HIV Evaluation and Support Collaborative (BHIVES), HIV-infected individuals with opioid dependence who received clinic-based buprenorphine/naloxone (BUP/NX) from an HIV clinic provider decreased opioid use [32], experienced higher quality of HIV care [33] and reported better quality of life [34]. A majority (60%) 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 achieving viral suppression (β = 1.25 [95% CI 1.10, 1.42]) among the 64 of 119 (54%) participants not on ART at baseline compared with the 55 participants not retained on buprenorphine [29].

Opioid agonist therapy with methadone [30] or sublingual BUP/NX [31] is associated with decreases in HIV risk behaviors. A meta-analysis of 12 studies assessing the impact of opioid substitution treatment on HIV transmission showed a 54% reduction in HIV infection among PWID [45].

Need for Expanded Opioid Treatment Options in HIV Clinics. Despite the availability of MMT in most communities and recent adoption of office-based buprenorphine in some HIV practices,

6.0 STUDY DESIGN

6.1 Overview of Protocol Study Design

The CHOICES scale-up (CTN-0067) study is designed to compare the effectiveness of HIV clinic-based XR-NTX versus TAU in engaging HIV-infected persons with opioid use disorder in care to improve HIV viral suppression. The CTN-0067 CHOICES scale-up study builds on lessons learned from the pilot and uses the Consolidated Framework for Implementation Research [90] to advance understanding of XR-NTX adoption.

HIV clinics will serve as primary care clinic settings for CTN-0067. Eligible study sites must 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 opioid use disorder, d) have the capacity to prescribe ART to participants, regardless of CD4 count, e) offer on-site addiction counseling services as part of usual care, and f) offer access to opioid agonist treatment, either on-site or by referral.

The CTN-0067 CHOICES scale-up study will utilize no more than 8 HIV primary care clinics to conduct the trial. The study is an open-label, randomized, comparative effectiveness implementation trial of office-based XR-NTX for 24 weeks (approximately 6 monthly injections) (n = 175) versus TAU (n = 175) in HIV-infected participants with untreated opioid use disorder (**Figure 1**).

In the pilot, 60 (85%) of 71 pre-screened individuals who reported using opioids in the past year said they were interested in stopping opioid use. Of these, 59 (98%) were willing to enroll in a clinical trial of XR-NTX for treatment of OUD, and 24 (41%) of those willing to try XR-NTX were randomized. Thus, 24 (34%) of 71 pre-screened individuals with past year illicit opioid use were ultimately randomized. Nine (38%) of these had an unsuppressed HIV viral load at baseline. Assuming the same proportion of pre-screened as randomized opioid users will be unsuppressed at prescreening, enrolling 350 participants in the scale-up may require pre-screening of about 2,709 [350/(0.34*0.38)] patients with past year opioid use.

The trial will be powered as a non-inferiority trial since the overall goal of the research is to add to rather than to supplant currently available effective opioid agonist treatment options. The *primary outcome* is the proportion of participants who achieve HIV viral suppression (HIV-1 RNA ≤ 200 copies/ml), measured at 24 weeks. *Secondary outcomes* include 1) other HIV outcomes (VACS Index, CD4 count), 2) engagement in HIV care (receipt of ART, ART adherence, retention in HIV care, HIV risk behaviors), and 3) ART adherence as mediated by number of opioid use days at 24 weeks. A fourth secondary objective documents facilitators and barriers of implementing XR-NTX to improve retention in HIV primary care (**Figure 1**).

6.2 Study Duration and Visit Schedule

The CTN-0067 CHOICES scale-up study will target enrolling 350 participants over approximately 22 months at no more than 8 HIV clinic sites. Each participant will be engaged in the overall study for an expected duration of 25-28 weeks (**Figure 3**) as follows:

- Weeks 1-4: consent, screening, randomization.
- 24 weeks: Active treatment with study visits every 4 weeks.
- Week 24: A single follow-up visit at the end of active treatment.

6.3 Justification of 24 weeks active treatment and timing of ART initiation

Assessment of the primary outcome of HIV viral suppression requires a minimum of 6 months, given the high potency of currently available ART regimens. While longer follow-up periods are required to assess sustained viral suppression, nearly all people initiating ART can now achieve an HIV viral RNA ≤ 200 copies/mL within 6 months of ART initiation. Participants not already taking ART at study enrollment will be encouraged to begin ART as soon as possible following enrollment. The timing of XR-NTX initiation or ART initiation is up to the discretion of the HIV provider on the basis of the patient's clinical priorities. Finally, previous efficacy trials of XR-NTX for opioid use disorder [55] and alcohol use disorder [64] provided 24 weeks of XR-NTX.

6.4 Justifcation of Implementation Study Procedures

Overview. The HIV primary care treatment environment is likely to change during the course of the study, reflecting broader healthcare policy changes in society. Documenting the HIV primary care treatment environment and describing XR-NTX formative implementation strategies, challenges, and best practices is crucial both for interpreting study findings and advancing understanding of generalizability and sustainability in other settings. A mixed-methods implementation analysis of HIV providers, staff, administrators, and study participants enrolled in CTN-0067 assesses barriers and facilitators to the use of XR-NTX in participating HIV clinics. Results inform policy-making for dissemination of clinic-based XR-NTX to other settings.

Qualitative Interview Justification. Qualitative interviews provide critical detail for enhanced understanding of the findings from the comparative effectiveness trial (Secondary Aim). Using the Taxonomy of Mixed Method Designs [115-117], our design has a QUAN + qual structure with simultaneous data collection and emphasis/weight placed on the quantitative (comparative effectiveness trial) efforts. Recurrent themes extracted from key informant interviews document provider, organizational, and participant experiences over time to examine these findings in parallel with staff surveys and study participant outcomes data (i.e., HIV viral suppression). This approach is consistent with Type I hybrid implementation study designs recommended for comparative effectiveness trials [118]. HIV clinic characteristics and provider attitudes (inner setting), as well as detail about the use of XR-NTX (intervention characteristics), and community awareness, linkage across service settings, and policy support (outer setting) help identify the full range of complex variables associated with implementation of clinic-based XR-NTX. This approach represents an innovative strategy to integrate available quantitative study results (Secondary Aim) to examine the provider, patient, organizational, and policy-level changes that influence the uptake of XR-NTX in HIV clinics. Corresponding with the CFIR, we identify individual, organizational and contextual characteristics that influence uptake of XR-NTX. We will particularly explore barriers to XR-NTX adoption identified in substance abuse treatment center setting using a CFIR framework, such as cost, complexity of prescribing, health plan policies, and reluctance to change [91]. Mixed-methods including QUAN + qual data are well suited for studying implementation of clinic-based XR-NTX and assessing the influence of individual and organizational characteristics on utilization.

Data Collection and Management. Lead Node investigators will conduct audio-recorded key informant interviews with HIV clinic providers, staff and administrators (up to 60 total across sites) over the study period. A convenience sample of CTN-0067 study participants assigned to XR-NTX (up to 60 total across sites) will be approached by site research staff and consented for participation in qualitative interviews. Interview guides use the CFIR framework to probe participant perceptions of the characteristics of XR-NTX and TAU (e.g., intervention quality, advantage, adaptability), outer setting (e.g., resources, social support, social interactions, external policies and incentives), inner setting (e.g., clinic organization, networks and

9.0 STUDY PROCEDURES

9.1 Duration of Participant Study Procedures

9.1.1 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 provide a brief verbal overview of the study to the individual and provide written information regarding XR-NTX. Individuals will provide verbal consent and HIPAA Authorization/Waiver as necessary for pre-screening and will be asked to complete the Pre-Screening Interview. This verbal consent and HIPAA Authorization/Waiver will only apply for the Pre-Screening visit. The Pre-Screening Interview will elicit information about the potential participant's demographics and drug use. The Pre-screening informed consent, HIPAA Authorization/Waiver (if necessary), and pre-screening interview will take approximately 5, 5, and 10 minutes to complete, respectively. Individuals who undergo pre-screening will be captured on the Pre-Screening Log.

9.1.2 Figure 3. Study Duration

Activity:	Screening & Enrollment	Active Treatment	Total Participant Time in Study
Duration:	1-4 weeks	24 weeks	25-28 weeks

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

Once a person has completed the Pre-Screening Interview process and meets basic eligibility criteria, they will either be asked to stay for the Screening Visit or scheduled to come back for the visit (based on staff and candidate's availability). It is expected that the screening and enrollment phase will take approximately 1-4 weeks; however, participants will have 60 days from the date of consent to complete screening and be randomized before being considered a screen failure.

9.1.4 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 and consent quiz while participants are reviewing them. After signing the consent form, participants will be given a copy of the form to keep for their records. The process will take approximately 20-30 minutes.

9.1.5 Locator Form

Participants will complete a locator information form which will be used to contact them to remind them of follow-up visits, as well as to locate participants who may not have attended appointments. 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, and Facebook. Locator information will be reviewed at each visit and updated as needed during the study. The locator

10.1 List of all CRFs and Table of Assessments

Assessment/Activity	Pre-Screening	Screening	Baseline	Random-ization^^	Treatment Initiation	Safety Visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	End of Study (≠Week 24)	As Needed
Enrollment														
Pre-Screening Verbal Consent and HIPAA Authorization/Waiver	X													
Pre-Screening Interview	X													
Demographics (from PhenX)		X												
Master Enrollment Log++		X	X											
Informed Consent/HIPAA		X												
Inclusion/Exclusion Checklist				X										
Locator Form++		X	X	X	X	X	X	X	X	X	X	X	X	
Medical Release++		X												X
Study Administration														
Inventory Form														X
Pre-screening Log++	X													
Secure Document Upload		X												X
Missed Visit Form														X
Progress Note Checklist++		X	X	X	X	X	X	X	X	X	X	X	X	
Protocol Deviation														X
Visit Compensation Log++		X	X	X	X	X	X	X	X	X	X	X	X	
End of Treatment												X		X
Study Completion												X		X
Safety and Medical Measures														
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X
ARV Medication Log			X									X	X	
Concomitant Medications		X												
CBC		X										X	X	
CD4 Count				X					X			X	X	
Serum Creatinine		X										X	X	
Confirmed Pregnancy and Outcome														X
Detoxification					X									
Fatal Opioid Overdose														X

Assessment/Activity	Pre-Screening	Screening	Baseline	Random-ization^^	Treatment Initiation	Safety Visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	End of Study (≠Week 24)	As Needed
Vital Signs (blood pressure, pulse, temperature, height and weight)		X										X±	X±	
Hepatitis B surface antigen (HBs AG)				X										
Hepatitis C virus antibody (HCV ab)				X								X**		
Hepatitis C PCR confirmation, when HCV ab +				X**								X**		
HIV-1 RNA PCR		X							X			X	X	
LFT (AST, ALT) and INR		X							X			X	X	
Medical and Psychiatric History		X												
Medication Adherence			X		X		X	X	X	X	X	X	X	
Pain Assessment			X				X	X	X	X	X	X	X	
Non-Fatal Opioid Overdose			X									X	X	
PBMC				X					X			X	X	
Physical Examination		X												
Pregnancy and Birth Control Assessment (including urine pregnancy test)		X			X*,^	X*,^	X	X	X	X	X	X	X	
Naloxone Challenge*														X
XR-NTX Administration Log* ++					X		X	X	X	X	X			
XR-NTX Injection*					X		X	X	X	X	X			
Injection Site Abnormality*														X
Injection Site Examination*						X	X	X	X	X	X	X	X	
ASI Lite Drug/Alcohol Use			X									X	X	
Concise Health Risk Tracking – Self Report		X			X	X	X	X	X	X	X	X	X	
Concise Health Risk Tracking – Clinician Rated														X
DSM-5 Substance Use Disorders		X												
Urine Drug Screen		X			X*	X*	X	X	X	X	X	X	X	
HIV Care Utilization			X									X	X	
Buprenorphine and Methadone Chart Abstraction							X	X	X	X	X	X	X	
Quality of Life, from PhenX			X											
Quality of Life, from EQ-5D			X									X	X	

11.5 Table 1: Point Values Used to Calculate VACS Index

Component		VACS Index
Age	<50	0
	50-64	12
	≥65	27
CD4	≥500	0
	350 to 499	6
	200 to 349	6
	100 to 199	10
	50 to 99	28
	<50	29
HIV-1 RNA	<500	0
	500-1x10^5	7
	>1x10^5	14
Hemoglobin	≥14	0
	12 to 13.9	10
	10 to 11.9	22
	<10	38
FIB-4	<1.45	0
	1.45 to 3.25	6
	>3.25	25
eGFR	≥60	0
	45 to 59.9	6
	30 to 44.9	8
	<30	26
Hepatitis C		5

Definitions:

- FIB-4 = (years of age x AST in U/L) ÷ (platelets in 10^9/L x square root of ALT in U/L)
  - Measure of liver fibrosis
- eGFR = 186.3 x (serum creatinine$^{-1.154}$) x (age$^{-0.203}$) x (0.742 for women) x (1.21 if black)
  - Estimated glomerular filtration rate; Measure of renal function

12.7 Medication Adherence

This form will track the participant's adherence to recommended addiction pharmacotherapy (i.e., methadone, buprenorphine, or XR-NTX) as described in the Treatment Plan.

12.8 End of Treatment Form

This form tracks the participant's status with regards to the study intervention/medication or treatment(s) received as part of TAU. It will be completed if the participant permanently stops treatment early or at the week 24 visit (for participants who complete study participation) or at the end of study visit (for participants who permanently stop the study trial early).

12.9 Study Completion Form

This form tracks the participant's status in the study. It will be completed at the week 24 visit, once the week 24 visit window elapses for participants who do not complete this final visit or after the week 24 visit is completed for participants who complete the final visit, or once the site confirms that a participant is permanently done with the study (i.e., participant died or withdrew consent). This form will be used in data analyses to address variables such as treatment retention and completion.

12.10 Treatment Initiation and XR-NTX Non-Initiation

The Treatment Initiation form will track participants randomized to the TAU arm only and will track initiation of TAU. This form will be completed once the participant reports that they have intitated TAU treatment. If treatment is not initiated, the form must be completed by end of study.

The XR-NTX Non-Initiation form will track non-initiation of XR-NTX injections for participants randomized to the XR-NTX treatment arm. This form will be completed as needed if a participant does not receive any XR-NTX injections. If the participant receives *at least* one injection, this form will not be completed.

12, and 24 (or end of study visit if not week 24). Blood draws may coincide with other research blood draws. PBMC analysis will be conducted in a related NIH application to assess the effects of opioid blockade on TLR mediated immune responses at a later time. PBMC samples will be shipped to a lab at Oregon Health & Science University and kept indefinitely. PBMC samples will be used for immunologic testing. It is also possible that banked PBMC specimens will be shared with other investigators for performance of genetic testing in the future.

Safety labs: AST, ALT, CBC, INR, serum creatinine, and urine pregnancy test (for all 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 (not including urine pregnancy) conducted within 30 days prior to date of informed consent (e.g., collected as part of routine detoxification admission) will be acceptable. Urine pregnancy test will be repeated at the Treatment Initiation Visit (required for XR-NTX arm only), the safety visit (required for XR-NTX arm only), and weeks 4, 8, 12, 16, 20, and 24 (or the end of study visit, if not week 24). AST, ALT, CBC, INR and serum creatinine will be repeated at week 24 or the end of study visit, if not week 24.

Liver profile: AST, ALT, and INR will be repeated at the Week 12 and Week 24 visits (or the end of study visit, if not Week 24). This is consistent with recent studies supporting the lack of hepatotoxicity in patients receiving XR-NTX that led to dropping of the previous FDA black box warning regarding hepatoxicity.

Hepatitis: Blood will be collected at randomization for Hepatitis B surface antigen (HBsAG) and Hepatitis C virus antibody (HCVab) with reflex hepatitis C RNA PCR testing if antibody positive. These tests do not determine eligibility. Results of laboratory tests conducted within 90 days prior to date of informed consent (e.g., collected as part of routine detoxification admission) will be acceptable.

13.6 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 at the Treatment Initiation Visit prior to study drug induction (urine pregnancy test required for XR-NTX arm only), the safety visit (urine pregnancy test required for XR-NTX arm only) and the 4, 8, 12, 16, 20, and 24 week visits or the end of study visit, if not week 24. This will correspond to medical visits for repeat study drug dosing and a final assessment at week 24 or the end of study visit, if not week 24.

13.7 Injection Site Examination

The study clinician will examine the injection site on the next visit following each XR-NTX administration and document this on the Injection Site Examination form. The study clinician will also examine the injection site per standard of care before administering a new injection. 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.

13.8 Pain Assessment

Pain assessment will occur at baseline, 4, 8, 12, 16, 20, and 24 weeks (or the end of study visit, if not week 24). Participants will be assessed for experiences of pain during the past 4 weeks

15.6 Concise Health Risk Tracking - Clinician Rated

The Clinician Rated (CHRT-CR) [161] assessment will be performed by the study clinician only if a participant answers any of questions 14-16 on the CHRT-SR as “Agree” or “Strongly Agree” as described in Section 15.5.

15.7 Patient Health Questionnaire (PHQ-9) Depression Symptoms

We measure depression symptoms using the self-reported PHQ-9, a 9-item scale validated for screening, diagnosing, and assessing the severity of depression symptoms in diverse populations [163]. The PHQ-9 will be administered at baseline, 12, and 24 weeks (or the end of study visit, if not week 24). Endorsements of suicidality on the PHQ-9 will be addressed locally at each site.

15.8 Suicidal Risk

This assessment will be performed by research staff if the participant endorses suicidality on the PHQ-9 by answering Q9 (“Thoughts that you would be better off dead, or of hurting yourself in some way”) as “Several days”, “More than half the days” or “Nearly every day.”

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 the Lead Team, which includes the Lead Node, CCTN, CCC and DSC staff. The training sessions will include modules targeting all research team members conducted via web, telephone and/or in-person training sessions. Training will cover standard NIDA training for all CTN Trials (e.g., Human Subjects Protection and 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.

16.4 Concomitant Medications

Participants will be instructed to contact the study clinician at their research site if they plan on taking any concomitant medications (including prescription, over-the-counter, and herbal supplements) during the course of the study. Concomitant medications will also be assessed at screening.

As described in the eligibility criteria, participants will be excluded if there is a need for ongoing opioid analgesic treatment. The study 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 – XR-NTX arm only) 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 (e.g., prochlorperazine) as needed.

as undesirable as lack of suppression, “unsuppressed” will be assigned as a status value for visits subsequent to death. A secondary sensitivity analysis will explore the extent to which trial conclusions need to be changed as the missingness assumption approaches MAR.

17.3 Secondary Outcome Measures

1) Secondary HIV outcomes variables:

a. VACS Index. Change in VACS Index score at 24 weeks compared with randomization (continuous; laboratory assays and demographics).

b. CD4 Count. Change in CD4 count at 24 weeks following treatment initiation compared with randomization (count; laboratory assay).

2) Engagement in HIV Care Variables:

a. ART prescribed. Proportion of participants prescribed ART within 24 weeks following randomization (binary; medical record abstraction).

b. ART Adherence. Proportion of participants taking 100% of prescribed ART doses in the past month at 24 weeks for those prescribed ART at any point during the 24 week trial (binary; self-reported medication adherence measure).

c. Retention in HIV Care: Proportion of participants with at least 1 HIV primary care visit in the past 12 weeks, measured at week 24. Adherence to HIV clinic visits in the year after ART initiation predicts HIV disease progression and death [164] (binary; medical record abstraction).

d. HIV Risk Behaviors. Past 30 day injection drug use, unprotected sex, multiple sexual partners as measured by the RAB at week 24 (binary; self-report).

e. Quality of life. Past 30 day health-related quality of life as measured by EQ-5D at week 24.

3) ART Adherence Mediation Variables:

a. Days of Opioid Use. Number of days of opioid use since baseline, measured by Timeline Followback at 24 weeks (count; self-report).

b. Opioid Abstinence. Past 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 24 week trial (binary; self-report + UDS).

17.4 Sample Size and Duration of Recruitment Phase

The CTN-0067 CHOICES scale-up trial will randomize 350 participants with opioid use disorder who are unsuppressed at baseline from no more than 8 sites over approxmiately 22 months for a power of 80%. Justification for this decision follows.

The trial will be powered as a non-inferiority trial since the overall goal of the research is to add to rather than to supplant the available effective opioid agonist treatment options currently available.

17.5 Substantive Justification for a Non-Inferiority Design.

A non-inferiority trial and the attendant choice of margin must be justified not just statistically, but also on substantive grounds. A non-inferiority trial design is justified when the active control is well-established and effective, and when a non-active control would be unethical, as in the case of treatments for HIV infection [165]. Both conditions are salient to the CTN-0067 CHOICES scale-up study in that opioid agonist therapy with buprenorphine or methadone is considered the standard of care for treatment of opioid dependence in HIV infected patients [104], and placebo treatments for either opioid use disorder or HIV infection are unethical.

Reporting of non-inferiority methods must include [165, 166]:

- Non-inferiority margin (delta)
- Sample size calculation must take into account the margin
- Both ITT and per-protocol analyses must be presented
- Confidence intervals for the results must be presented
- Justification of the margin

The first 4 points have been addressed in other parts of this statistical section. The following section describes the justification for the margin.

17.6 Justification of the Non-Inferiority Margin

Little data exist to inform justification of non-inferiority margins. Given that our primary outcome measure is viral suppression, we reviewed recent non-inferiority trials comparing two antiretroviral regimens with viral suppression as the outcome. Noninferiority margins in these trials ranged from 10% to 15% [114, 167-169], though no published justification is provided for these estimates.

The only study to estimate virologic suppression in HIV-infected participants receiving BUP/NX was the BHIVES collaborative. BHIVES was an observational study of HIV-infected participants with opioid use disorder receiving office-based BUP/NX from their HIV providers. Participants not already on ART baseline were offered ART regimens available in 2004-2007, which were less potent than currently available regimens. Among 64 participants who were not prescribed ART at baseline and who were prescribed BUP/NX for at least 3 quarters, 57.3% achieved HIV viral suppression by 6 months (a timeframe comparable to CHOICES 24-week outcome) [29]. More information about the choice of margin is given in the following section on Power results.

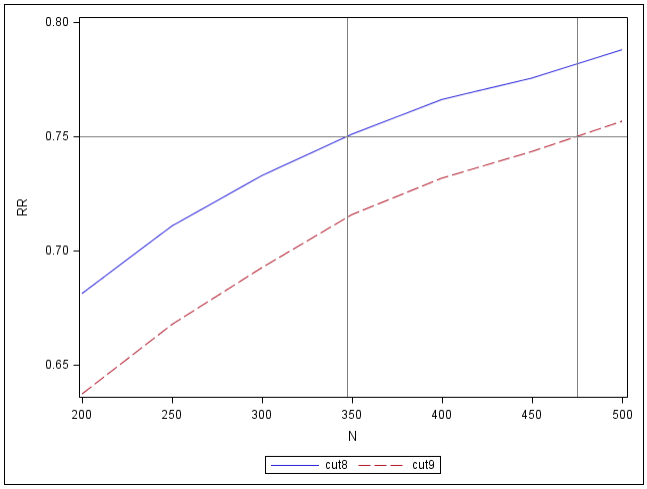
17.7 Rationale for Sample Size

Figure 4 shows the non-inferiority margin required for power of (0.8, 0.9) (using the lower tail of the two-sided 95% confidence interval) as a function of the sample size for the non-inferiority test of XR-NTX versus TAU at 4 months, as estimated from data “random-assignment-bootstrapped” from the (opioid + overlap) group who were unsuppressed at baseline in the pilot study (CTN-0055). There are only 9 participants in the bootstrap population: 7 in Core and 2 in UBC. The random-assignment bootstrap approach was used at 4 months as a conservative way to estimate power in the scale-up (see appendix). The margin is expressed in terms of the risk ratio (RR), that

is, Pr(suppressed | XR-NTX) / Pr(suppressed | TAU)[1]. A horizontal reference line in **Figure 4** marks RR = 0.75, and vertical reference lines mark the intersection of the horizontal line with the power curves for (0.8, 0.9). The vertical lines intersect the N axis at sample sizes of about (350, 480). For a given sample size, use of a margin at or below the one specified by the relevant curved line will grant power in excess of that depicted by the line. For example, an RR margin less than or equal to 0.75 will grant a power of at least 90% for total sample size (both arms together) of about 480, and will grant a power of at least 80% for total sample size of 350. We have chosen this last point upon which to base our sample size.

This particular example is calculated using the Rose et al. binary RMVL model. The fixed effects in the model are treatment, visit number (continuous), time by treatment interaction, baseline alcohol, and site (categorical). The data for each participant are assumed to have an exchangeable correlation structure. Missing data are assumed to be unsuppressed. Note that cases in which the model failed to converge or converged but SAS flagged the result as questionable have been dropped from this analysis. The number of analyzed iterations was (9020, 9492, 9696, 9819, 9848, 9869, and 9911) for n = (200, 250, 300, 350, 400, 450, 500), respectively. With the assumptions above, a non-inferiority sample size calculation was performed using commercial software PASS and got very similar results.

17.7.1 Figure 4. Non-inferiority margins granting power = 0.8 and 0.9 as a function of sample size



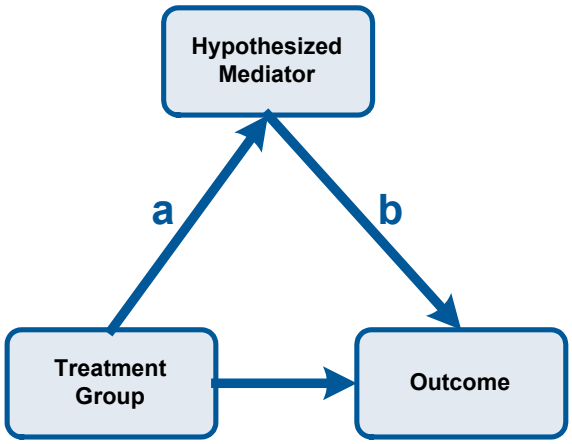
Additional Comments Concerning Choice of RR margin

The reasoning in the non-inferiority margin calculation of a RR of 0.75 is as follows:

[1] As we define it here, RR might better be termed a “benefit ratio,” but we shall retain the common usage.

Analyzed via rank-based methods such as Wilcoxon rank-sum tests. Covariates can be considered via the cumulative logit model.

Mediation Analysis



Mediation will be tested using structural equation modeling with Mplus 7.3. These models estimate the effect of the intervention on the potential mediator (path a, e.g., the effect of intervention on *substance use*) and the effect of the mediator on the outcome or next proximal intermediate outcome (path b, e.g., the effect of *substance use* on *HIV medication adherence*). Longer mediation pathways can also be tested (e.g., a*b*c), and therefore the entire mediational path depicted in section 1.2.1 can be assessed in this framework. There is significant mediation if the product of these two paths (a*b) is greater than zero (or the product of more pathways in a longer mediational chain). Statistical significance will be assessed using bias-corrected bootstrap confidence intervals on the product terms [171]. This test is by far the most powerful test of mediation [172] and can test multiple mediating pathways within a single structural model. Using the tables in Fritz and MacKinnon [171], we should have over 80% power for mediation when the standardized path coefficients (a and b) are .164, which corresponds to approximately 2.7% shared variance between the outcome and predictor variable (e.g., treatment and substance for the a-path in the example given above.) We will also examine whether there are differences in strength of mediational pathways across the opioid and alcohol disorder subgroups.

Qualitative Analysis of Implementation Data The qualitative team creates a coding scheme, practices coding, and revises in an iterative group process. Each transcript is coded and check-coding is completed with 20% of transcripts to ensure inter-coder reliability. The analysis uses a deductive approach to focus on themes related to select CFIR inner and outer setting, provider characteristics, and implementation characteristic domains. Iterative analyses assess convergence of CFIR patient, provider and organizational dimensions on study measures as well as the context of the policy subsystems, cross-system interactions, and resource allocation. A five phase strategy guides the analysis: describe themes, organize and structure data, connect codes and themes, corroborate and triangulate, and condense and summarize findings [173]. Site structural data will be triangulated with staff and patient qualitative interviews to integrate an environmental perspective.

17.9.1 Additional Statistical Tests of the Secondary Outcomes

In addition to the methods described after each secondary outcome, statistical modeling will be done using generalized estimating equations (GEEs) models as employed by Liang and Zeger [174] to allow covariate adjustment in factors such as concomitant alcohol use disorder and severity of opioid and alcohol use disorder. Those secondary outcomes that are binary will be tested with a binomial distribution and logit link as implemented in SAS; whereas those secondary outcomes that involve either continuous or ordinal variables will utilize the appropriate distribution and link function. Note that the exact method of analysis will depend on the realized distribution of the particular outcome in this trial. For example, an expected count data variable may need to be modeled using a zero-inflated Poisson regression rather than a standard Poisson regression if there are too many zero observations to fit the standard Poisson. If there is over-dispersion, a

negative binomial (or zero-inflated negative binomial) regression may be appropriate. For these secondary analyses, the overall Type I error will not be controlled.

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

Analysis will be ITT in the sense that participants will be analyzed as being members of the arm to which they were originally randomized. With one exception, we plan in the primary analysis to recode missing data to “unsuppressed” because, in this setting, this seems more realistic than assuming that missingness is non-informative for suppression. The exception is that, if missing data are flanked on both sides by “suppressed” values, we will impute the missing data to be suppressed. Sensitivity analyses will secondarily explore the implications of this MNAR imputation, and outcomes according to treatment received. Per-protocol sensitivity analyses will compare outcomes among those who initiated at least one dose of XR-NTX compared with those who initiated at least one dose of buprenorphine or methadone.

17.11 Interim Monitoring of Primary Efficacy Endpoint

Interim monitoring will be performed of the primary alternative hypothesis that XR-NTX is non-inferior to TAU at 6 months of follow-up, using a non-inferiority risk ratio of RR = Pr(suppressed|NTX)/Pr(suppressed|TAU) = 0.75. There will be no interim efficacy monitoring before 1/3 the participants have attained 24 weeks of follow-up and a sample size-re-estimation is performed (see the sample size re-estimation section below). Assuming the re-estimation does not call for a change in sample size (which would have to be ratified by the DSMB and approved by NIDA), we will on every subsequent DSMB meeting perform interim efficacy monitoring. All interim monitoring will use an O’Brien-Fleming-type boundary with information fraction equal to the proportion of the target sample size with primary outcome, and alpha = 0.025, one-tailed.

Before recommending early termination, the DSMB will consider:

- Internal consistency of primary and secondary results.
- Internal consistency of primary and secondary results by subgroups defined by baseline characteristics.
- Distribution of baseline prognostic factors among the two groups.
- Consistency of primary and secondary results across sites and among sites enrolling larger numbers of participants.
- Possible bias in assessment of primary and secondary response variables.
- Possible impact of missing data from missed participant visits for assessment of the primary and secondary response variables.
- Possible differences in concomitant interventions or medications.

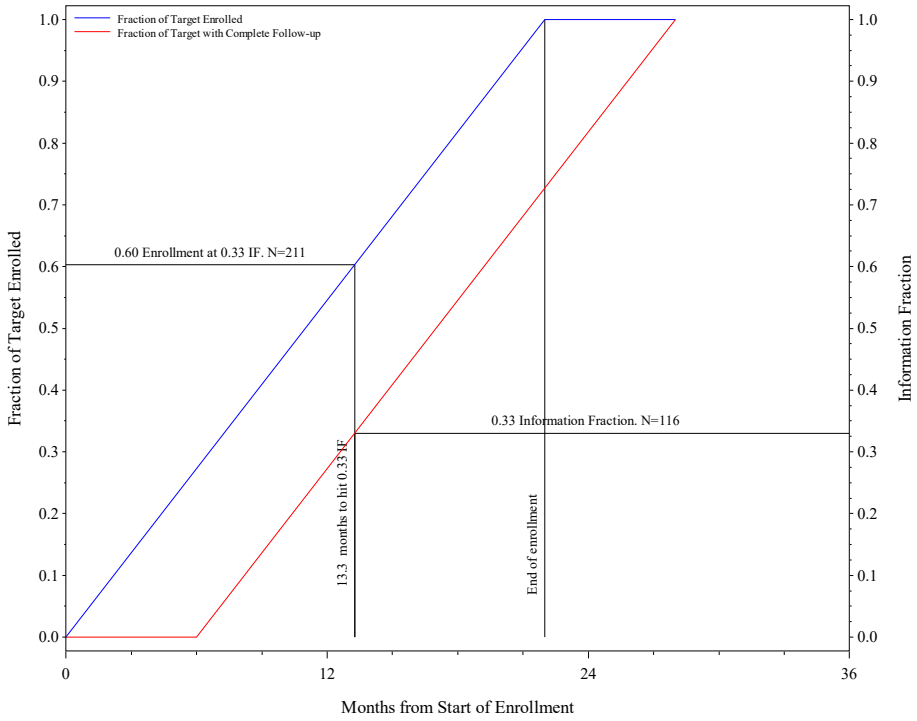
Sample Size Re-estimation

We plan to also perform a sample size re-estimation after about 1/3 off the total expected number of participants (n=116) attain their 24 week outcome, which is approximately 13 months into enrollment. The motivation for sample size re-estimation is that the original sample size calculation was based not only on a hypothesized treatment effect, but also on assumptions about nuisance parameters such as variances and attrition. In the case of CTN-0067, these nuisance parameter estimates are implicitly contained in the Random Assignment Bootstrapping approach we adopted for our sample size calculation, based on pilot data from CTN-0055. It seems reasonable to supplant that calculation with one based on ~100 actual CTN-0067 observations.

The Randomized Assignment part of the Bootstrap approach, when applied to these observations, will automatically suppress the observed treatment effect in favor of one representing the design alternative.

The timing of the sample size re-estimation is based on a number of factors: recruitment rate, timing of primary outcome, and time to perform the sample size re-estimation. For CTN-0067, we use the graphical tool presented in **Figure 7** to assist in assessing the appropriate timing of sample size re-estimation. To illustrate, **Figure 7** shows in a picture the timing of re-estimation when 33% of the participants have outcome data [information fraction = 0.33 (N=116) on the red line] and assuming enrollment (blue line) in CTN-0067 of 350 participants over a 22-month period. This time period to perform the sample size re-estimation corresponds to approximately 13 months after enrollment into CTN-0067 has started, at which point, the study will have enrolled about 60% of the target sample size. If recruitment takes longer or shorter than expected, modifications can be made to the timing of the sample size re-estimation.

17.11.1 Figure 7. Information Fraction and Fraction of Target Enrollment for Proposed Sample Size Re-Estimation Based on Months from Start of Enrollment



17.12 Conditional Power and Futility

Unless otherwise requested, we will perform a futility/conditional power calculation every time we do interim monitoring. If at any DSMB meeting the conditional power falls below 0.3 (when hypothetical future observations are generated under the design alternative RR=1 but tested under the null RR ≤ 0.75), this will stimulate a discussion among the DSMB members about whether we should stop for futility. The conditional power calculation may be carried out via Random Assignment Bootstrapping, similar to the sample-size re-estimation procedure, except that in conditional power, one uses the data already gathered in two ways: first, one includes it in every iteration unchanged as part of the simulated final sample, and second, one Random-

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, mild (Grade 1) and unrelated Adverse Events will not require reporting in the data system. All adverse events will be tracked on a manual (paper only) Adverse Event Log, regardless of severity, seriousness, relatedness, or expectedness.

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.

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

2) Admission for labor and delivery (documented instead on the Confirmed Pregnancy and Outcomes form).

3) Admission for elective or pre-planned surgery.

The Lead Node will report all other SAEs on the Serious Adverse Event form in the data system Sites must determine if local IRBs will require annual or other SAE reporting.

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 has 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 will be captured on study-specific forms and not duplicately reported as an adverse or serious adverse event. All hospitalizations for other (non-HIV, non-substance-use related) medical, surgical and psychological reasons and deaths will be reported on AE/SAE forms. 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. Advantage eClinical, 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 site will be specified by the DSC and outlined in the Advantage eClinical 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 sites, 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 Advantage eClinical system in accordance with the Advantage eClinical User's Guide. Only authorized individuals shall have access to eCRFs.

20.6 Data Editing

Completed data will be entered into Advantage eClinical. 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 Advantage eClinical.

20.7 Database 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 site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

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.

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.

23.3 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 pre-existing conditions, such as arthritis, which are present prior to clinical trial entry, are not considered to be AEs unless the medical clinician deems that the condition has worsened in intensity and/or frequency during the course of the study.

23.4 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 with the lead team 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 when operating under an IRB Authorization Agreement.

Site staff is required to enter reportable AEs and SAEs in the Advantage eClinical 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 of records or information necessary to provide a complete and clear picture of the SAE as well as events preceding and following the SAE. 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.

23.5 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.

23.6 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.

23.6.1 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?

Please note that for the purposes of this protocol, events assessed to be mild (Grade 1) and unrelated, though reportable on the manual adverse event tracking log, are ***not*** reportable in the electronic data capture system.

23.6.2 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 may 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.

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

A NIDA-assigned Medical Monitor/Safety 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/Safety Monitor in Advantage eClinical 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/Safety Monitor in writing for review by the sponsor and DSMB.

23.7 Regulatory Reporting for an IND study

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

23.8 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.

23.9 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, or the participant has been removed from the study, the participant will be asked to complete an end of study visit to assure safety and to document end of treatment outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.

24.0 APPENDIX B - Data Safety and Monitoring Plan (DSMP)

24.1 Brief Study Overview

The Primary Objective of the CTN-0067 CHOICES scale-up study is to compare the effectiveness of HIV clinic-based XR-NTX in decreasing substance use and increasing HIV viral suppression in HIV-infected participants with opioid use disorder to treatment as usual (TAU) in this population. Details for the definitions and reporting of safety events are found in the protocol (Appendix A).

24.2 Oversight of Clinical Responsibilities

24.2.1 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, 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).

24.2.2 Medical Monitor/Safety Monitor

The NIDA Clinical Coordinating Center (CCC) Medical Monitor/Safety 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 Medical Monitor/Safety Monitor will discuss the event with the site. Reviews of SAEs will be conducted in the Advantage eClinical data system and will be a part of the safety database. All AEs are reviewed on a regular basis to observe trends or unusual events.

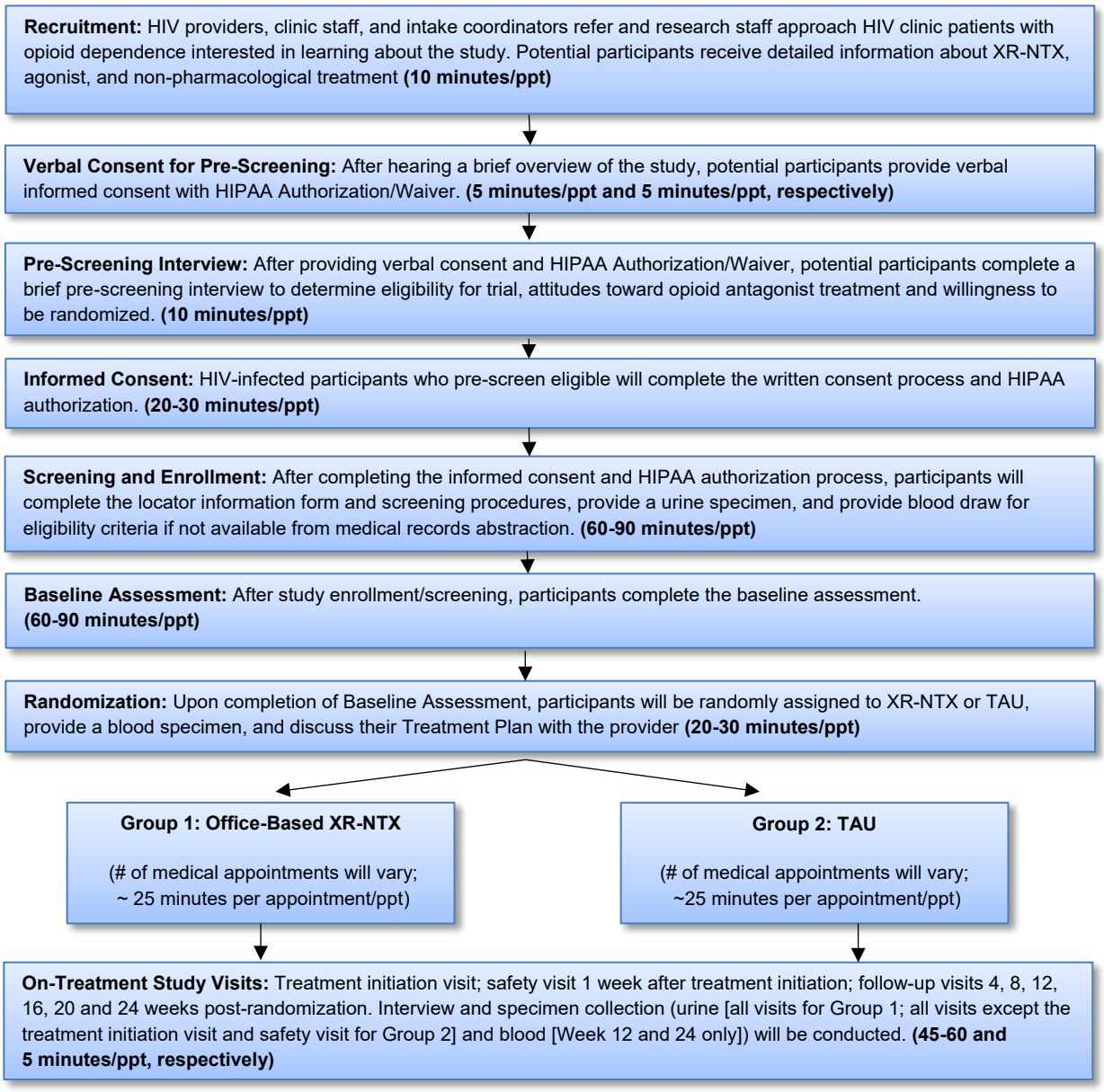
Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

24.2.3 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 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)

Abbreviation	Definition
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PLWHA	Persons Living with HIV/AIDS
PLG	Polylactide-co-glycolide
PWID	People Who Inject Drugs
QA	Quality Assurance
RAB	Risk Assessment Battery
RMVL	Repeated Measure of Viral Load
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SC	Subcutaneous
SOP	Standard Operating Procedures
TAU	Treatment as Usual
TLFB	Timeline Follow-Back
UDS	Urine Drug Screen
VACS	Veterans Aging Cohort Study
XR-NTX	Extended-Release Naltrexone (Vivitrol®)

3.0 STUDY FLOW CHART



an expanded palette of treatment options for opioid use disorder in HIV clinics is greatly needed. Only a minority of HIV-infected patients with substance use disorders receive addiction treatment [3, 46]. For those who receive pharmacologic treatment for opioid use disorder, 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 [47-49] and increases in buprenorphine levels [50, 51] that complicate methadone and buprenorphine dosing and ART choice. 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 [32].

Naltrexone Treatment of Opioid Use Disorder. 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 [52, 53]. Two recent studies of XR-NTX: 1) Comer et al. [54], testing Depotrex®, Biotech Inc., in New York City and Philadelphia; and 2) Krupitsky et al. [55], 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, 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" [56]. 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, implementation issues, safety, and costs of XR-NTX in U.S. HIV-infected populations.

Naltrexone for Treatment of Comorbid Alcohol Use Disorder. The CTN-0055 CHOICES pilot study demonstrated that 16% of participants with opioid use disorder had comorbid alcohol use disorder. Oral naltrexone received FDA approval in 1994 for treatment of alcohol use disorders and systematic reviews support its efficacy compared to placebo [57-61]; however, its success is limited by suboptimal adherence to daily dosing requirements [62, 63]. 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 [64], improved quality of life [65], and decreased holiday drinking [66]. In a post-hoc analysis limited to those with higher severity alcohol dependence, XR-NTX reduced heavy drinking days by 37% and compared with a 27% reduction for placebo-treated participants' improved maintenance of abstinence [67]. Treatment responses were highest among participants with at least 4 days of voluntary alcohol abstinence prior to their first dose of XR-NTX [64, 68], and were rapid in onset, with significant reductions in alcohol use observed after only 2 days [69]. XR-NTX did not significantly increase counseling or support group participation [69].

communication, practice culture, and implementation climate), provider characteristics (e.g., self-efficacy for XR-NTX treatment) and the implementation process (e.g., engaging, executing, evaluating) [90, 119]. Not all questions will be asked of all informants.

Audio-recorded interviews will be professionally transcribed, reviewed and summarized. Transcriptions will be password protected, stored on a secure network and uploaded into qualitative analysis software (Atlas.ti™) which organizes data and facilitates coding and thematic analysis.

Qualitative data will be supplemented with a brief survey of participating sites (*n* = no more than 8), completed prior to study initiation, to document local treatment environment (e.g., availability of clinic-based buprenorphine, state Medicaid support for medication-assisted treatment, amount of Ryan White Care Act funding, community referral resources, etc.).

information form will take approximately 5-10 minutes to initially complete and content will be checked at future study visits.

9.1.6 Medical Record Release Form

Participants will complete the form(s) as applicable during screening and throughout the study 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 opioid overdose events. Records review/abstraction will occur throughout the study (as needed) and up to 52 weeks post-randomization.

9.1.7 Collection of Biological Specimens

Study staff will collect blood specimens at screening, randomization, 12 weeks, and 24 weeks to confirm eligibility and assess the primary outcome of HIV-1 RNA PCR and secondary outcomes of CD4 count, VACS Index, and hepatotoxicity. CBC, serum creatinine, LFTs (AST, ALT), INR, and HIV-1 RNA blood specimens will be collected during screening. CD4, Hepatitis C, Hepatitis B, and PBMC specimens will be collected and processed only after the participant has been randomized. Study staff will collect urine specimens during screening and at treatment initiation (XR-NTX arm only), safety visit (XR-NTX arm only), and at 4, 8, 12, 16, 20, and 24 weeks to confirm eligibility and assess secondary outcomes and pregnancy. Screening and randomization labs (CD4, HIV-1 RNA, and hepatitis B and C serologies) drawn in the 90 days prior to date of informed consent may be abstracted from participant medical records, when available. Other screening lab tests may be abstracted from medical records if drawn within 30 days prior to the date of informed consent, with the exception of urine specimens, which must be collected by study personnel. Some participating sites may require that copies of some or all lab results collected for study purposes be filed in participants' medical records.

9.1.8 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 either through a computer-assisted data collection instrument or a paper version of the CRF. 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, current health status, and other baseline characteristics. The baseline assessment will take approximately 60-90 minutes to complete.

9.1.9 Randomization

The timing of randomization will follow shortly after baseline assessments and final confirmation of eligibility. Participants will be encouraged to initiate treatment within 28 days of randomization. If a participant is unable to initiate treatment within 28 days, he or she may initiate XR-NTX study drug at any time until week 20 and may initiate TAU at any time during the trial. Initiation of 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. Randomization will be stratified only by site. Participants who meet DSM-5 criteria for both opioid and alcohol use disorder (16% of CTN-0055 CHOICES pilot study participants) will be included, in addition to participants with OUD, alone.

Assessment/Activity	Pre-Screening	Screening	Baseline	Random-ization^^	Treatment Initiation	Safety Visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	End of Study (≠Week 24)	As Needed
Risk Assessment Battery			X				X	X	X	X	X	X	X	
Tobacco Use History and Substance Use History, from PhenX			X									X	X	
Timeline Follow Back			X		X		X	X	X	X	X	X	X	
Treatment Plan				X			X	X	X	X	X	X	X	
Treatment Initiation***													X	X
XR-NTX Non-Initiation*														X
Treatment Satisfaction Survey												X	X	
Treatment Services Review			X		X		X	X	X	X	X	X	X	
VACS Index				X								X	X	
Visual Analog Scale			X				X	X	X	X	X	X	X	
PHQ-9 Depression Symptoms			X						X			X	X	
Suicidal Risk														X
Criminal Justice			X						X			X	X	
Participant Treatment Preference			X											

** Only for participants randomized to the XR-NTX arm.*

***At randomization, HCV PCR confirmation is required when HCV ab is positive. At 24 weeks, collect HCV ab if participant tested HCV ab negative at randomization or if HCV ab result was not obtained at randomization. At 24 weeks, collect HCV PCR confirmation if: HCV antibody is positive at randomization, but HCV PCR was not obtained at randomization or HCV antibody was negative at randomization, but HCV antibody is positive at Week 24.*

**** Only for participants randomized to TAU arm.*

± Height and weight only for BMI calculations.

++ Not captured in eClinical.

^Urine pregnancy test required for XR-NTX group only; remainder of Pregnancy and Birth Control Assessment required for all participants.

^^Assessments performed at randomization correspond with Week 0 requirements in the eClinical system.

12.0 GENERAL MEASURES

12.1 Inclusion/Exclusion

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

12.2 Locator Form

A locator form will be used to obtain information to assist in finding participants during screening/baseline and at follow-up. This form will collect participants' current address, email address, and phone number(s). In order to facilitate locating participants if direct contact efforts are unsuccessful, we will attempt to 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.

12.3 PhenX Core Tier 1 Forms

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. The Core Tier 1 collection includes measures for demographics (age, ethnicity, sex, 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. Core Tier 1 assessments will be completed at baseline only, with BMI and tobacco use questions repeated at week 24 or the end of study visit, if not week 24.

12.4 Demographics Form

The demographics form will collect information about demographic characteristics of the participant, including sex, 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.

12.5 Treatment Satisfaction Survey

Satisfaction with treatment will be recorded on the Treatment Satisfaction Survey completed at week 24 visit or the end of study visit, if not week 24.

12.6 Treatment Plan

This form will be used once the participant is randomized. After randomization, the participant will meet with the study clinician to develop a plan that will determine the activities the participant should engage in, including addiction pharmacotherapy (e.g., methadone, buprenorphine, XR-NTX) during the active treatment phase of the protocol. This meeting and form should be completed the same day the participant is randomized. The Treatment Plan will be reviewed at follow-up visits 4, 8, 12, 16, 20, and 24 or the end of study visit, if not week 24.

13.0 SAFETY AND MEDICAL MEASURES

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

13.1 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.

13.2 Physical Examination

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 clinician will examine the planned injection sites to ensure adequacy for XR-NTX gluteal intramuscular injection of naltrexone with the supplied needle.

13.3 Vital Signs

Study personnel will complete vital signs (blood pressure, pulse, temperature, height, and weight) at screening to inform overall medical fitness for participation, along with the physical exam. Height and weight only will be collected at week 24 or the end of study visit, if not week 24.

13.4 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.

13.5 Clinical Laboratory Tests

Trained staff will be responsible for collecting and processing biologic specimens. Local laboratories at participating sites will be used to conduct all laboratory tests with the exception of the PBMCs. Laboratories must participate in the Clinical Laboratory Improvement Act of 1998 (CLIA) or be accredited by the College of American Pathologists (CAP). If neither CLIA nor CAP is available, equivalent evidence of laboratory certification may be acceptable and must be discussed on a case-by-case basis with the Lead Team. Laboratories should provide reference ranges and proof of laboratory certification.

HIV-1 RNA PCR: will be drawn at screening, 12, and 24 weeks (or the end of study visit, if not week 24) for outcomes assessment. At screening, results of laboratory tests conducted within 90 days prior to date of informed consent will be acceptable.

CD4 Count (T-helper cells): will be drawn at randomization and at 12 and 24 week visits or the end of study visit, if not week 24, for secondary outcomes assessment. At randomization, results of laboratory tests conducted within 90 days prior to date of informed consent will be acceptable.

Peripheral Blood Mononuclear Cells (PBMCs): For all randomized participants (both TAU and XR-NTX), we will collect four 8mL or eight 4mL CPT tubes for PBMC analysis at randomization,

using the 3-item PEG [151]. 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.

17.0 STATISTICAL ANALYSIS

17.1 Primary Objective of the Analysis

The Primary objective of the CTN-0067 CHOICES scale-up study is to discover whether HIV clinic-based XR-NTX is non-inferior to TAU with respect to HIV viral suppression in HIV-infected participants with opioid use disorder. We have chosen a non-inferiority margin of 0.75. That is, we will reject the null hypothesis of inferiority of XR-NTX to TAU in favor of non-inferiority if the lower 95% confidence limit for the ratio $\frac{\Pr(suppresed|NTX)}{\Pr(suppressed|TAU)}$ is strictly greater than 0.75. We anticipate a sample size of 350 (175/arm) will grant at least 80% power for the non-inferiority conclusion.

17.2 Primary Outcome Measure

The primary outcome measure for CTN-0067 CHOICES scale-up study is HIV viral suppression. HIV viral suppression is defined as an HIV-1 RNA ≤ 200 copies/ml at 24 weeks from time of randomization.

The binary RMVL model of Rose et al. will be used to predict the log of the risk ratio (not the log of the odds) for suppression via a generalized estimating equation with an exchangeable covariance structure for all the values of a single participant. Baseline alcohol use disorder and sites are included as fixed effects. The fixed effects part of the model is thus:

$$\log(p_{ij}) = \alpha + \beta * trt_i + \gamma * month_j + \theta * trt_i * month_j + \tau * alc_i + \delta_1 * site_{1i} + \cdots + \delta_k * site_{ki}$$

where p_{ij} is the probablility of suppression of participant *i* in month *j*, *trt* is the indicator for treatment, months enter linearly, there is a time by treatment interaction, *alc* is an indicator for baseline alcohol use disorder, and $site_1, \ldots, site_k$ are site indicator variables. The model will incorporate 2 time points for each patient (months 3 and 6), with a contrast used to estimate the treatment effect at month 6. The following SAS fragment shows how to implement this analysis:

```
proc genmod data = visits descending;
class suppressed trt site projid alc base;
model suppressed = trt | month alc site / dist = bin link = log;
repeated subject = projid / type = exch;
estimate "6M trt eff" trt 1 -1 trt * month 6 -6
run;
```

Note that the estimate statements assumes the following coding: trt= (ntx, tau) month = (3, 6).

The RMVL is a type of longitudinal model. In theory, longitudinal models can accommodate missing data better than non-longitudinal models because they incorporate all non-missing data points. But this approach assumes that missing data are not informative, that is, that missing values are probably similar to corresponding non-missing values with the same set of other predictors. For trials of substance-using individuals, missing at random (MAR) is less likely than missing not at random (MNAR) alternative: if data are missing, it is probably because the participant is unsuppressed. So, for the primary analysis, “unsuppressed” will be substituted for missing suppression status values. An exception is that, if missing data are flanked on both sides by “suppressed” values, we will impute the missing data to be suppressed. Since death is at least

Recall from above that, in BHIVES, 57.3% achieved HIV viral suppression. Let us assume that, in the absence of any treatment for OUD, the suppression rate will be about 15%, so that the treatment effect of the active control in CHOICES is about 42%. It makes intuitive sense that the non-inferiority margin should be some fraction of this, and this general approach is discussed by the FDA in their Guidance for Industry on Non-inferiority Clinical Trials [170]. We have chosen 1/3 as the clinically reasonable fraction. That is, if XR-NTX preserves 2/3 or more of the effect of BUP/NX over placebo, we will consider XR/NTX to be non-inferior to BUP/NX. This implies a margin of 14%. With this margin, we are implicitly saying that, if the true suppression probability for BUP/NX is 57%, then we consider any true XR/NTX suppression probability greater than 43% to indicate that XR/NTX is not inferior to BUP/NX.

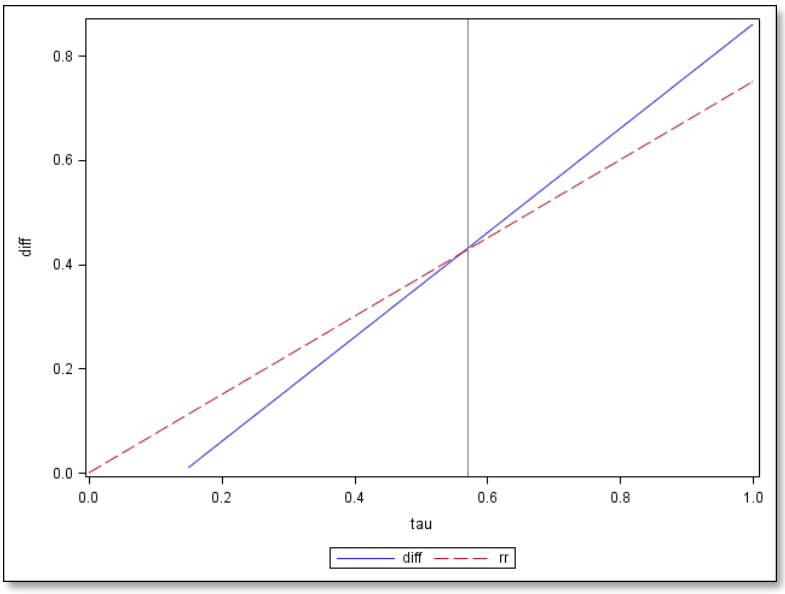
To turn this reasoning into a RR calculation, NTX is non-inferior if the observed risk ratio significantly exceeds 43/57=0.75.

The RR we can be derived from the pilot study data. There are 9 in the opioid + overlap group who started out unsuppressed. Their last non-missing suppression status is as follows:

	TAU	NTX
Suppressed	3	2
Unsuppressed	2	2

The suppression rates from the CTN-0055 pilot study are (TAU, NTX) = (60%, 50%). To call NTX non-inferior, NTX needs to preserve at least 14 percentage points of the TAU suppression rate, which means an NTX suppression rate of at least 60%-14% = 46% is needed. This means a RR of at least 46/60 = 77%. This is not much different from the 43/57 = 75% discussed above. Note that data paucity militates against a more precise calculation of pilot study RR.

17.7.2 Figure 5. Implications for probabilities of fixing RR = 0.75 versus fixing a probability difference of 0.14



Assignment Bootstraps from it to form the rest of the simulated final sample. In contrast, when one re-estimates the sample size, the entire simulated final sample of each iteration is drawn from the already-gathered sample via Random-Assignment Bootstrapping.

17.13 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.

21.0 PROTOCOL SIGNATURE PAGE

SPONSOR – CCTN SCIENTIFIC OFFICER OR DESIGNEE

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 5.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.

- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.

- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.

- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.

- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (HHS), the state, and the IRB.

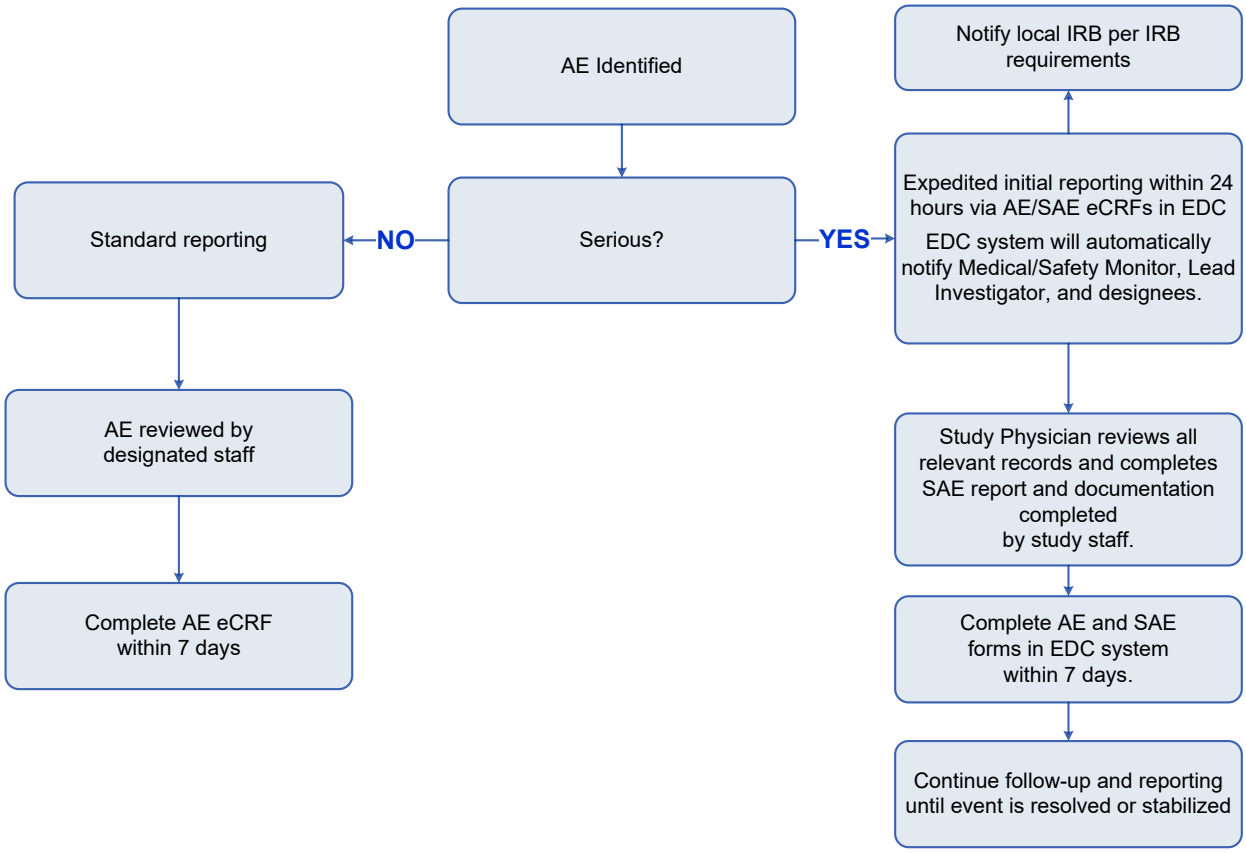
SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

23.10 Adverse Event Reporting Chart



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.

24.2.4 Quality Assurance (QA) Monitoring

The monitoring of the study site will be conducted on a regular basis using a combination of NIDA CCC contract monitors and the local Node QA monitors. Investigators will host periodic visits for the NIDA CCC contract monitors and Node QA monitors. 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 forwarded to the site Principal Investigator, the study Lead Investigator and NIDA.

24.2.5 Management of Risks to Participants

24.2.5.1 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.

24.2.5.2 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.

24.2.5.3 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 study visit to assure safety and to document end of treatment outcomes.

24.2.5.4 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.