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Design and methods of a double blind randomized placebo-controlled trial of extended-release naltrexone for HIV-infected, opioid dependent prisoners and jail detainees who are transitioning to the community

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ABSTRACT

Background: People with opioid dependence and HIV are concentrated within criminal justice settings (CJS). Upon release, however, drug relapse is common and contributes to poor HIV treatment outcomes, increased HIV transmission risk, reincarceration and mortality. Extended-release naltrexone (XR-NTX) is an evidence-based treatment for opioid dependence, yet is not routinely available for CJS populations.
Methods: A randomized, double-blind, placebo-controlled trial of XR-NTX for HIV-infected inmates transitioning from correctional to community settings is underway to assess its impact on HIV and opioid-relapse outcomes.
Results: We describe the methods and early acceptability of this trial. In addition we provide protocol details to safely administer XR-NTX near community release and describe logistical implementation issues identified. Study acceptability was modest, with 132 (66%) persons who consented to participate from 199 total referrals. Overall, 79% of the participants had previously received opioid agonist treatment before this incarceration. Thus far, 65 (49%) of those agreeing to participate in the trial have initiated XR-NTX or placebo. Of the 134 referred patients who ultimately did not receive a first injection, the main reasons included a preference for an alternative opioid agonist treatment (37%), being ineligible (32%), not yet released (10%), and lost upon release before receiving their injection (14%).
Conclusions: Study findings should provide high internal validity about HIV and opioid treatment outcomes for HIV-infected prisoners transitioning to the community. The large number of patients

Abbreviations: SUDs, substance use disorders; CJS, criminal justice system; cART, combination antiretroviral treatment; CD4, CD4+ T lymphocyte; VS, viral suppression; MMT, methadone; BMT, buprenorphine; NTX, naltrexone; XR-NTX, extended-release naltrexone; MAT, medication assisted therapy; NIDA, National Institute on Drug Abuse; NIH, National Institute of Health; STTR, seek, test, treat and retain; RCT, Randomized Control Trial; IRB, Internal Review Board; CTDOC, Connecticut Department of Correction; HCCC, Hampden County Correctional Center; OHRP, Office of Human Research Protections; CoC, Certificate of Confidentiality; ITT, intention-to-treat; IDN, Infectious Disease Nurse; ROI, release of information; RA, Research Assistant; MINI, Mini International Neuropsychiatric Interview; AUDIT, Alcohol Use Disorders Identification Test; SAFTEE, Systemic Assessment For Treatment Emergent Effects Intervention; CASI, computer-assisted survey; IDS, Investigational Drug Service; CR, Clinician Researcher; LFT, liver function test; COWS, clinical opioid withdrawal scale; MM, Medical Management.

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who ultimately did not receive the study medication may raise external validity concerns due to XR-NTX acceptability and interest in opioid agonist treatments.
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1. Introduction

The dramatic growth in the U.S. inmate population over the last three decades has resulted from the increased detention of individuals for drug-related offenses and recidivist offenders. As a result, those with substance use disorders (SUDs) with or at risk for HIV infection are concentrated within the criminal justice system (CJS). The prevalence of HIV and AIDS is 3- and 4-fold greater, respectively, among incarcerated persons compared to the general population [1,2]. In 2004, the U.S. Department of Justice reported that 53% of state prisoners met DSM-IV criteria for drug abuse or dependence, 56% reported regular use in the month prior to their offence, specifically, 13.1% reported using heroin and opiates [3,4]. In a study conducted in CT, among HIV-infected prisoners with SUDs, 61% met criteria for opioid dependence [5–8].

The revolving door of prisons and jails results in 12 million people being released annually to communities, oftentimes with undiagnosed or untreated medical conditions [9]; including one-sixth of the nearly 1.2 million people living with HIV/AIDS (PLWH) [2]. Though HIV-infected prisoners markedly reduce HIV-1 RNA levels and achieve markedly high levels viral suppression (VS) during incarceration due to the availability of combination antiretroviral therapy (cART) and the structure of the facilities [10–12], these benefits are lost soon after release [10,13,14], especially due to drug and alcohol relapse [15], especially heroin. The negative consequences of opioid relapse for HIV-infected patients include poor retention in care [14,16–18], cART adherence [5,6] and increased recidivism to prison/jail [19,20]. This is in addition to the increased early mortality risk upon release [21–27], mostly associated with opioid overdose [22,25–27], affirms the need for evidence-based transitional interventions.

According to the International Association of Physicians in AIDS Care (IAPAC) guidelines, only directly administered antiretroviral therapy (DAART) is effective for transitioning HIV-infected prisoners [28]. One randomized controlled trial (RCT) of DAART for released prisoners, however, showed that for the subset meeting criteria for opioid dependence, those retained on buprenorphine post-release markedly increased their likelihood of achieving VS [7,8], suggesting that medication-assisted therapies (MATs) might be a more effective and less costly strategy for released prisoners with HIV and opioid dependence. Despite there being three FDA-approved pharmacological treatments for opioid dependence, methadone (MMT), buprenorphine (BMT) and extended-release naltrexone (XR-NTX), with rare exception, have they not been empirically tested as transitional care for released prisoners [29–33]. Despite preliminary successes using MAT among HIV seronegative subjects [31,32,34,35], these treatments have not been deployed systematically within the CJS [36–39] nor deployed to optimize HIV treatment, as recommended by the IAPAC for PLWH and SUDs in the community[28].

As part on the National Institute of Drug Abuse's (NIDA) initiative to examine the impact of the seek, test, treat, and retain model of care (STTR) for criminal justice populations [40], this study directly examines the ability of XR-NTX to effectively "treat and retain" opioid dependent prisoners through the post-release transitional period. To test whether XR-NTX effectively stabilizes patients through this precarious post-release period, we have implemented a novel double-blind, placebo-controlled RCT of XR-NTX among opioid dependent HIV-infected prisoners and jail detainees transitioning to the community, with an examination of both HIV and substance abuse treatment outcomes.

2. Methods

2.1. Study design

Project NEW HOPE (Needing Extended-release Wellness Helping Opioid dependent People Excel) is a multi-site, double-blind, placebo-controlled RCT of XR-NTX among opioid dependent HIV-infected prisoners and jail detainees transitioning to the community. The study design is shown in Fig. 1.

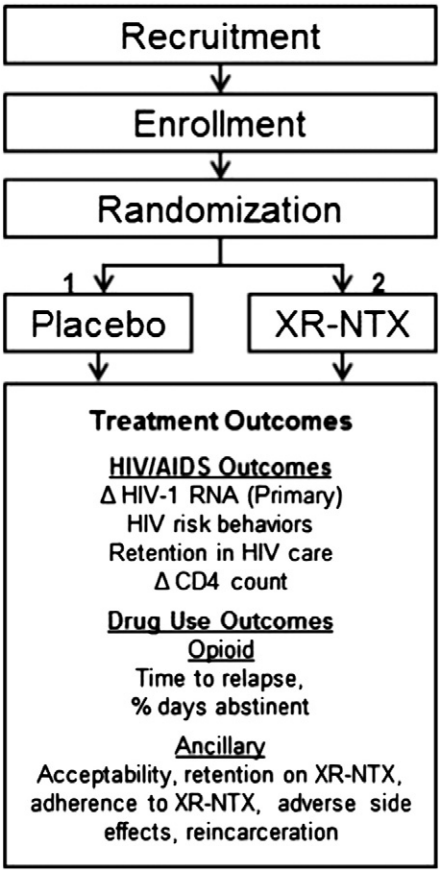

Fig. 1. Study design.

2.2. Ethical oversight

Institutional Review Boards (IRB) at Yale University, Waterbury Hospital and Baystate Medical Center, and research committees at Hampden County Correctional Centers (HCCC) and the Connecticut Department of Correction (CTDOC) reviewed and approved all study procedures. The study is registered at www.clinicaltrials.gov (NCT01246401). Additional protections were provided by the Office of Human Research Protections (OHRP) at the Department of Health and Human Services and a Certificate of Confidentiality (CoC) was obtained.

2.3. Research goals

Given the high rate of relapse to opioid use upon release [41] and its association with poor HIV treatment outcomes [15,42], this study's aim is to examine if using an evidence-based treatment for opioid dependence improves HIV and substance abuse treatment outcomes in the post-release period. Outcomes include HIV-related outcomes (HIV-1 RNA levels, including VS, CD4 count, cART adherence, retention in HIV care); substance abuse outcomes (time to opioid relapse, percent of opioid negative urine screens, opioid craving); recidivism and re-arrests; adverse side effects; and HIV risk behaviors (sexual and drug-related risks). The primary outcome is the proportion achieving VS (HIV-1 RNA < 400 copies/mL) 6 months post-release. Additional detail regarding the outcomes of interest can be found in the Analytical Plan section.

2.4. Sample size and power calculations

Sample size calculations were based on the primary outcome of the proportion of participants who achieve VS 6 months after release, based on 2:1 randomization; increased allocation to the XR-NTX arm was justified to assess for adverse side effects. Sample size requirements for a Type I error rate of 0.05 and power of 80% estimated by preliminary data from our prison-release data suggest that approximately 60% of inmates leave prison with VS [10]. Of note, more recent data suggest that VS upon release is 70% [12]. Using an intention-to-treat (ITT) analysis and assuming a baseline VS of 60% [10], 150 subjects would be required to a difference of 25% between the two treatment arms if randomized 2:1 (XR-NTX = 100 and placebo = 50).

3. Study procedures

3.1. Recruitment and screening

Recruitment started in 2011 and will continue until 2015 in all prisons and jails by Infectious Disease Nurses (IDN), who coordinate all HIV-related care for HIV-infected inmates. Initial study criteria includes: 1) being HIV-seropositive; 2) returning to three sites in Connecticut (New Haven, Hartford, Waterbury [2012 and 2013 only] or Massachusetts (Springfield only); 3) meets DSM-IV criteria for opioid dependence (using the Rapid Opioid Dependency Scale) based on information 12 months prior to their current incarceration [43]; 4) able to provide informed consent; 5) speaks English or Spanish; and 6) 18 years or older. Those meeting screening criteria were asked to sign a release of information (ROI) so that research staff can meet and inform them about the research study and undergo informed consent procedures. For PLWH and released to the community without being assessed, referrals from the community were allowed from HIV clinicians and drug treatment providers, case managers and through self-referrals using approved flyers and advertisements if made within 30 days of release to the community.

3.2. Eligibility process

After receiving the ROI, Research Staff scheduled an appointment with the inmate in a confidential setting to assess additional eligibility criteria. If the inmate was eligible for the study, the study staff member described the study and enrolled the participant. Additional inclusion criteria include: 1) not participating in a pharmacotherapy or adherence trial in the previous 30 days; and 2) within 30 days of release from prison or jail. Exclusion criteria included: 1) threatening behavior toward study staff or other participants; 2) pending federal charges; 3) prescription of opioid pain medications or expressing a need for them; 4) known hypersensitivity to naltrexone, PLG (polylactide-co-glycolide), arboxymethylcellulose, or any other components of the diluent; and 5) medication contraindications that included: a) already enrolled in an opioid substitution therapy program; b) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations (>5× upper limit of normal); c) evidence of Child Pugh Class C cirrhosis; or d) breastfeeding, pregnant or unwilling to use contraception (women).

3.3. Informed consent and enrollment

Upon completion of eligibility determination, the study research member completed informed consent procedures and assessed the participant's willingness to enroll in the study, including receiving six monthly injections, where the first was administered approximately 7 days prior to release and then attend monthly interviews over twelve months post-release. To ensure that there was no real or perceived coercion for enrollment during incarceration, all participants underwent a second written informed consent process upon release from the correctional facility to confirm their interest in study participation. For those that were referred from the community or were released unexpectedly, the initial injection was administered at the study sites after completing the baseline interview and medical chart review.

4. Covariate and outcome measures

4.1. Screening and intervention measures

After informed consent completion, all enrolled participants underwent baseline assessments, follow-up interviews and laboratory assessments monthly for 12 months. Please refer to Table 1 for the measures, main outcomes assessed, and the study timeline.

4.2. Process measures

In addition to the measures noted in Table 1, qualitative information was assessed to address:

Table 1
Study activity and measures.

Study activity	Study time point in months from day of release from incarceration														
	−3	−1 week	0	1	2	3	4	5	6	7	8	9	10	11	12
Study activity															
Screening for Eligibility	X														
Medical Chart Review		X													
Randomization		X													
Injection and Clinical Interview		X		X	X	X	X	X							
Research Interview	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic information															
Demographic Questions*	X														
Housing Questions*	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Health care status															
HIV quality of life (SF-12)* [71]	X					X			X			X			X
Current Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prescription Refill	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prison Medical Record (Medication, cART regimen, HCV antibody, medication allergies)		X													
Visual Analog Scale [51]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Previous Experience with Alcohol and Drug Treatment	X														
Mental health															
Mini International Neuropsychiatric Interview (MINI)* [72–74]	X														
Correctional Medical Record Diagnoses		X													
Brief Symptom Inventory-18 (BSI-18) [75–77]	X					X			X			X			X
Drug and alcohol use															
Rapid Opioid Dependence Screen [43]	X														
Addiction Severity Index Lite* [78–80]	X					X			X			X			X
Drug Urine Toxicology Screening		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alcohol Use Disorder Identification Test* [54,81–82]	X														
Timeline Recall [83,84]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Opioid Craving	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DSM-IV Criteria using MINI [73]	X														
Blood Alcohol Content via Breathalyzer			X	X	X	X	X	X	X	X	X	X	X	X	X
HIV risk behaviors															
Sexual Risk Behaviors* [85]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
HIV biological outcome measures															
HIV-1 RNA level*		X				X			X			X			X
CD4 Count*		X				X			X			X			X
HIV genotype*			X												X
Other laboratory tests															
Liver Function Tests (AST, ALT)		X	X	X	X	X	X	X							
Renal Function Tests (BUN, Creatinine)		X	X	X	X	X	X	X							
Side effects															
Systemic Assessment for Treatment Emergent Effects Intervention (SAFTEE) [44,86]			X	X	X	X	X	X	X						
Payments															
Research Interviews**	$20		$20	$20	$20	$40	$20	$20	$40	$30	$30	$60	$30	$30	$60
Clinical Interviews**		$10		$10	$10	$10	$10	$10							

Legend: cART = combination antiretroviral therapy; CJS = criminal justice system; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urine nitrogen.
* Seek, test, treat & retain harmonized measure.
** Payment for interviews completed in the correctional facilities were paid after release.

(1) *Acceptance of study involvement* to determine if this injectable, long-acting opioid dependence treatment would be acceptable given the other treatments available in the community, yet not available during incarceration. Of the initial 199 participants referred to the study, 132 (66%) signed consent forms while still incarcerated. The main reason for ineligibility was not meeting criteria for opioid dependence during the screening process (47%) (Table 2). Of the 132 that signed informed consent forms, 106 (80%) completed baseline interviews, providing insight into the acceptability of involvement in this study and potentially for XR-NTX as an intervention to prevent relapse (see Fig. 2).

(2) *Acceptability of opioid antagonist treatment* in persons with experience with opioid agonist treatments and thus evaluating whether this FDA-approved treatment will be accepted by those with experience with prior opioid agonist treatments. The main reason for refusal in the different stages of enrollment in this study was a preference for another form of MAT (34%) (Table 2). Thus far, 79% (79/100) of the participants in the study have self-reported previous experience with MMT or BMT (Fig. 3).

(3) *Acceptability of injections* by assessing how many participants who agree to participate in the study and complete baseline interviews will actually agree to receive

Table 2
Reasons for refusal or ineligibility of study participation.

Before initial consent	
Total not screened	5
Refused screening, does not want treatment	2
Released before being seen	1
Refused without a reason given	1
Not interested in participating a study	1
Total ineligible	34
Does not meet DSM-IV criteria for OD	16
Enrolled in another research study	1
On methadone + refused	1
Will be released out of catchment areas	7
Medical need for pain medication	8
Cirrhosis + refused	1
Total refused	28
Wants another form of treatment	8
Refused to sign consent — may want BMT on release	1
Study fatigue	2
Does not want injections	1
Concerned about current health issues and possible complications	2
Does not want treatment	2
Afraid of needles and does not want treatment	1
Does not want placebo	2
No reason given/not interested	3
Does not want NTX	1
No reason for refusal + Elevated LFTs	1
Released before consented, wanted to think about it	1
Refused + being released out of area	3
After initial consent, prior to release from prison	
Total disenrolled	2
Behavior issues	1
Passed away in prison (unrelated to study/health)	1
Total refused	13
Wants another form of treatment	5
Advised by family not to enroll, released out of area, possible need pain meds	1
Does not think he needs treatment, and will not be released early	1
Does not have time, does not need the money	1
Concerned about current health issues doesn't want complications	1
"I don't want to feel like a lab rat"	1
Refused — no reason given	3
Total ineligible	6
Liver Failure/Elevated LFTs	2
Found to be unable to consent (memory/cognition issues)	1
Cirrhosis, wants methadone & medical need for pain meds	1
On methadone	2
After initial consent, after release from prison	
Total lost upon release, reasons missed injections	13
Released too quickly post referral	1
Refused injection in prison, and moved upon release	1
Released to parole unexpectedly	3
Released unexpectedly	8
Total refused	7
Wants another form of treatment	3
Moving out of area	1
Transportation issues	1
No reason given	2

Abbreviations: OD, opioid dependence; BMT, buprenorphine maintenance treatment; NTX, naltrexone; LFTs, liver function tests.

an initial injection. Thus far in this on-going trial, of those who have completed baseline interviews 84% (89/106) were released from incarceration, and 73% (65/89) received their initial injection near the day of release.

(4) *Attrition from intervention*, to assess whether participants will remain in the assigned study arm and adhere to the study medication, thus focusing on persistence of monthly injections in a placebo-controlled trial. For participants wishing to switch to another form of treatment, including but not limited to another form of MAT or inpatient treatment, s/he will be continuously followed for the duration of the study but will receive no further study injections.

(5) *Tolerability and adverse event monitoring* is assessed by recording the number and frequency of adverse events monitored using the Systemic Assessment For Treatment Emergent Effects Intervention (SAFTEE) [44].

(6) *Ancillary encounters*, are assessed and include additional services that participants may request including clinical/medical services, counseling and case management services such as food, shelter, insurance, drug/alcohol counseling or detoxification, mental illness treatment, and medical insurance enrollment.

(7) Constant *communication* with study staff at all study sites is recorded with CTDOC and HCCC personnel, and participants.

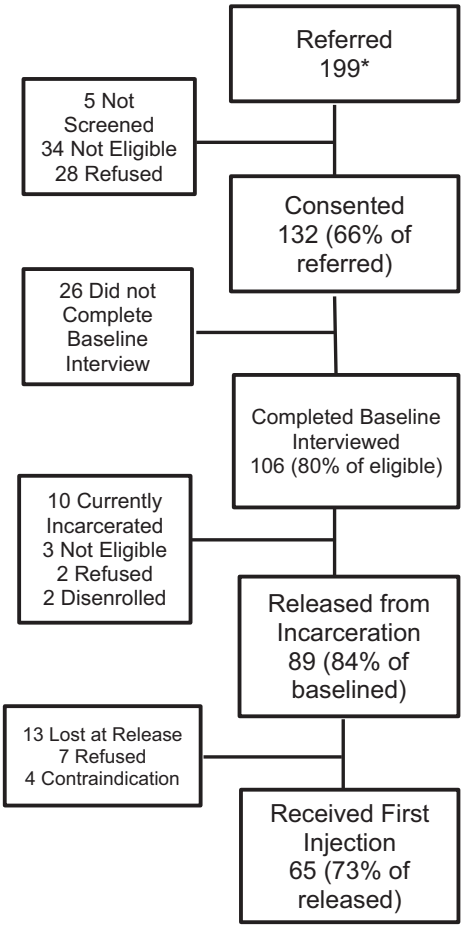

Fig. 2. Study flow of current acceptability. *Study is still recruiting.

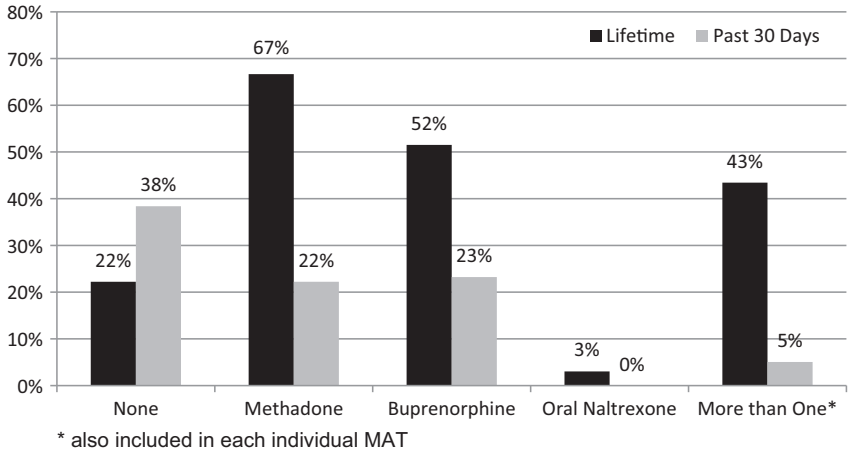

Fig. 3. Previous experience with medication assisted therapy (N = 99).

5. Randomization and dispensing

All study medication packages (active drug and placebo) were provided and prepared by Alkermes, Inc. and randomized and dispensed by the Yale-New Haven Hospital or Baystate Medical Center Investigational Drug Service (IDS) pharmacists in a blinded manner. Participants were randomized 2:1 prior to their release from the correctional facility by the IDS pharmacist, to XR-NTX or placebo. IDS pharmacists stored, distributed and labeled study medications using participant identification numbers. To maintain the double-blinded condition of the study design, placebo microspheres were used instead of naltrexone, and vials containing the microspheres were tinted amber to mask the color differences in the solution. To control for covariates potentially associated with the outcomes, covariate adaptive randomization was used [45–47]. These covariates included: 1) community release site (greater New Haven, Hartford, or Springfield areas); and 2) being prescribed or not prescribed cART.

6. Intervention

6.1. Study procedures

Injections were optimally initiated prior to correctional release, thereby introducing specific challenges and issues during the implementation process. These issues are later described in this paper and in Table 3. After release, participants are followed for 12 months, receiving an additional 5 injections and 13 interviews. Please see Table 1 for the study timeline for study and injection interviews.

(1) *Pre-Release*: After enrollment, a baseline interview was completed using a computer-assisted survey instrument (CASI) [48,49]. To ensure participant confidentiality, CASI was selected based on our previous prison studies [50] to allow inmates to respond to sensitive questions about drug and alcohol use and HIV risk behaviors. See Table 1 for the list of instruments administered during the baseline interview. Before final enrollment and the first injection, a clinical researcher (CR) reviewed the inmate's medical record to ensure s/he does not have Child Pugh Class C cirrhosis or other contraindications to XR-NTX and administered the study medication. In order to ensure that the correctional facility was aware of the inmates' enrollment and administration of the study medication, a sticker and "order" were placed in the medical chart with a brief summary of the study drug's possible side effects and the toll-free number to call should an inmate experience any perceived side effects. If a participant was released without receiving an injection prior to release or was referred from the community, the study medication was administered within 30 days post-release, including those who relapsed to opioids before the first injection.

(2) *Day of Release*: On the expected day of release the research assistant (RA) met and transported the participant to the study site. Additionally, participants completed a brief interview to document any change in their health and behaviors while they were in the correctional facility including study drug injection experience and potential side effects, as well as undergoing phlebotomy, alcohol breathalyzer assessments, drug urine screening, and update their contact information. To improve retention, participants were paid a "bonus" payment for showing up immediately after release (see Table 1), and a RA accompanied the participants to a site of their preference (home, shelter, short-term housing, etc.) and inquired about any other local spots where they are likely to spend time during the course of the study.

(3) *Monthly Research Visits*: Over 12 months, participants meet the RA every month for CASI interviews, phlebotomy, drug urine screens, urine pregnancy tests for female participants, alcohol breathalyzer assessments, and cART adherence assessments using the Visual Analog Scale (VAS) [51]. During the intervention phase (6 months) of the study, adverse side effects were assessed and all participants received a brief 15-minute medical management (MM) counseling intervention [52].

(4) *Injection Procedures*: Following the initial injection, five total injections are administered, each approximately 28 days apart. At each visit, participants met with a CR who assessed side effects from the previous injection,

Table 3
Study implementation issues.

Obstacle	Action taken	Knowledge gained
Harmonized data measures & multisite data transfers		
1) Creating interviews using harmonized data measures	Collaboration with NIDA and 11 additional grantees on selecting and implementing harmonized measures. http://www.drugabuse.gov/researchers/research-resources/data-harmonization-projects/seek-test-treat-retain.	Strong communication and attention to detail was needed to ensure the correct measures were collected at the appropriate times. Study participants complained that surveys were too long.
2) Deidentification of data	In order to comply with HIPAA regulations, all data were deidentified before data transfers to NIDA and from Baystate to Yale. Yale Information Technology Services (ITS) and Human Research Protection Program were consulted ensure all data transfers meet HIPAA regulations.	Prior to data collection, Yale Human Research Protection Program policies were explored to ensure data collected for the harmonization was compliant with HIPAA regulations and ensured that all data to be transferred was deidentified as required. Each site maintained a link between study number and personal identities.
3) Multisite data collection	To ensure all data was properly protected, the Yale ITS encrypted file transfer was used on a quarterly basis to transfer data from Baystate Medical Center to Yale AIDS Program. Once the data was received into the office, it was saved on the Yale secure server.	Collaboration from different departments within Yale University and updates of new services to safeguard protected data. Yale ITS and Baystate ITS needed to ensure that computers and programs were compatible with encryption software and interview software.
4) Coordination of multiple review boards and approval	Upon creation of the study protocol to be submitted, reviewed and approved by multiple review boards, a review of the different institutions' policy to reduce the number of amendments and changes required before approval. Communication with Yale IRB (as primary site) to assist with coordination of federal approvals required for this vulnerable population.	Approval from the primary institution was required before other approvals were able to be gained. Communication with the different institutions before a final protocol is submitted is essential to receive the appropriate approvals in a timely manner. This resulted in a process that approached 12 months.
Recruitment and facility staff trainings		
5) Educational sessions on medication assisted therapies	Interactive information sessions were conducted throughout the study to inform the correctional staff of newly FDA approved injectable formulation of NTX and of other pharmacotherapies approved for the treatment of opioid dependence. Addressing concerns and questions regarding the different treatments.	Correctional staff was updated and given a refresher of current treatments for opioid dependence. This opened another line of communication with the correctional staff.
Changes in department of corrections policies		
6) Methadone Maintenance Program in two facilities	In CT one of the men's facilities and the women's facility offered those with a short sentence entering the facility on a methadone maintenance program to continue during their incarceration. Additional attention was paid to those on methadone and some participants became ineligible for the study. This change went into effect July 2012.	Changes in availability of alternative medication assisted therapies altered willingness to participate in the study.
7) XR-NTX initiation and referral	A pilot program for XR-NTX starting prior to release with community maintenance was created and made available for residents with alcohol or opioid addictions in the addiction treatment facility of the HCCC starting in April 2013. Prior to this, education of staff and residents on options for medically assisted treatment and community treatment sites was done in all the HCCC facilities.	In the few instances where routine XR-NTX treatment and placebo controlled trial were both immediately available, patients elected the routine treatment, suggesting that patients' preferences may influence outcomes.
8) Naloxone in MA	Routine overdose prevention education including intranasal naloxone training and access was expanded in the HCCC facilities and after incarceration program.	Overdose prevention and naloxone training was welcomed by this population. Concerns about overdose if participants were late for injections should include naloxone prescription and availability.
9) Change in sentences from Risk Reduction Earned Credit program	Changes in policy changing the release date unexpectedly for participants. Increased monitoring and communication with the DOC was needed to ensure changes in a participant's release date were known and interviews and injections could be administered before he/she was released. This change went into effect October 2011. There was also a change in earned days from 5 to 10 in MA.	Communication with the DOC staff is essential to the implementation and continuation of a study that initiates in the correctional facility.
10) Reduction in the number of HIV-infected inmates	Recruitment to those on parole or probation was expanded in 2013 in an attempt to increase enrollment numbers.	With decreasing numbers in general inmate populations and increase in various medication-assisted therapies for HIV-infected inmates and alternative correctional programs (halfway houses and drug programs), alternative recruitment strategies are needed to capture those involved in the criminal justice system.
Participant health		
11) Required DSMB	A DSMB was created with three board certified Infectious Disease doctors at Yale to ensure the safety of the study participants and study performance.	
12) Education of overdose	Education tools were developed to protect against overdose	These educational sessions and tools, allowed to

Table 3 *(continued)*

Obstacle	Action taken	Knowledge gained
risk	at the end of the injection period and if a participant missed an injection. This protocol contained a treatment agreement and visual aid reviewed and signed by the participant acknowledging the education received from the risk education.	participants to fully understand the severity of the risk to overdose and death if they should relapse. Treatment agreements were used a treatment plans.
13) Relapse to opioid use	To protect against withdrawal symptoms, should a participant relapse to opioid use before his/her next injection an extensive protocol was developed utilizing self-reported opioid use, urine toxicology screen results, an antagonist challenge and if needed a community buprenorphine detoxification.	These protocols have been modified for community based administration of XR-NTX.

Legend: NIDA = National Institute on Drug Abuse; DOC = Department of Correction; CR = Clinical Researcher; CMHC = Correctional Managed Health Care; XR-NTX = Extended-release naltrexone; HCCC = Hampton County Correctional Center; IRB = Internal Review Board; DSMB = Data Safety Management Board.

conducted a brief physical assessment focusing on signs of liver damage, pertinent medical history, review of liver function tests (LFTs) and assessment of other contraindications for XR-NTX including potential opioid use, acute hepatitis, current prescription of opioid medications, anticipated need for prescription opioid medications, pregnancy, and breastfeeding. *Given that this study is focused on opioid dependent individuals, some of whom were receiving placebo, special attention was paid to participants actively using opioids.* We also showed participants a time-dependent graph, provided by Alkermes, Inc., to illustrate the risk of overdose given the falling blood levels of XR-NTX. Participants then signed a study agreement acknowledging their understanding of an increased risk of injury or death due to opioid overdose if they did not receive their next injection at or around 4 weeks after the previous injection.

(5) *Recent Opioid Use Protocol*: All CRs were trained in the study protocol that included extensive protections for participants to avoid precipitating opioid withdrawal (see Fig. 4). For participants actively using opioids (within 7 previous days) but is not found to be physically dependent, s/he was given an antagonist (naloxone) challenge (0.4 mg intramuscular) and if there were no signs of withdrawal in 10 minunites an additional dose (0.8 mg) was administered. Opioid withdrawal signs and symptoms are monitored using the Clinical Opioid Withdrawal Scale (COWS) [53]. If the antagonist challenge caused opioid withdrawal symptoms, participants undergo a 5-day buprenorphine supervised withdrawal protocol. If the antagonist challenge does not precipitate withdrawal, the injection of the study medication is administered if no other contradictions were present. The community detoxification protocol used was based on the Substance Abuse and Mental Health Services Administration (SAMHSA) Tip 40 for a 5-day buprenorphine detox protocol (8 mg BID on day 1; 16 mg QD on day 2; 12 mg QD on day 3; 8 mg on day 4; and then 4 mg on day 5) then off of buprenorphine for 3 to 5 days, with daily monitoring on the days off buprenorphine. Upon completion of the supervised withdrawal procedures, participants are then reassessed for injection of the study medication.

(6) *Counseling Visits*: Irrespective of randomization during the intervention phase (6 months post-release), as part of the 45-minute injection preparation process, all participants receive a standardized monthly brief counseling intervention for opioid dependence, modified from the Medical Management (MM) procedures used in the COMIBINE trial for alcohol dependence [52,54,55]. This modified 15-minute MM, conducted by the CR, reviews medication and health information including opioid pharmacotherapy, laboratory results, drug use and prior counseling in addition to briefly counseling patients about the hazards of using opioids. If participants were perceived as failing the existing treatment program, they were referred to more intensive community-based counseling and/or treatment by our on-site substance abuse counselors. In addition, all participants are offered voluntary weekly 12-step counseling sessions held at all of the study sites as well as individualized cognitive behavioral counseling sessions by a licensed behavioral health specialist [56–58]. Use of the voluntary cognitive behavioral counseling interventions is monitored for final study analysis.

7. Payments

Please refer to Table 1 for subject compensation. Participants were paid for contributing their time to the research activities and not for receiving study medication. The form of participant payment was changed from gift cards to cash in 2013 in response to patient preferences for payment.

8. Specific safety protocols

During the intervention phase of the study, participants are monitored regularly for injection-related side effects, changes in LFTs and renal function, and new contraindications to XR-NTX including pregnancy and opioid relapse and withdrawal [59]. Prior to administration of the study medication, the CR reviews his/her current medications, medical diagnoses, laboratory and drug urine screening results. If a participant develops Grade 4 hepatotoxicity (defined as LFTs >10 times the upper limit of normal with clinical symptoms or signs of hepatotoxicity), Child Pugh Class C cirrhosis, or becomes pregnant, then injections are stopped and the participant is unblinded. As an additional safety precaution, all participants' primary care providers are sent letters confirming study enrollment, including basic study information that the participant may be

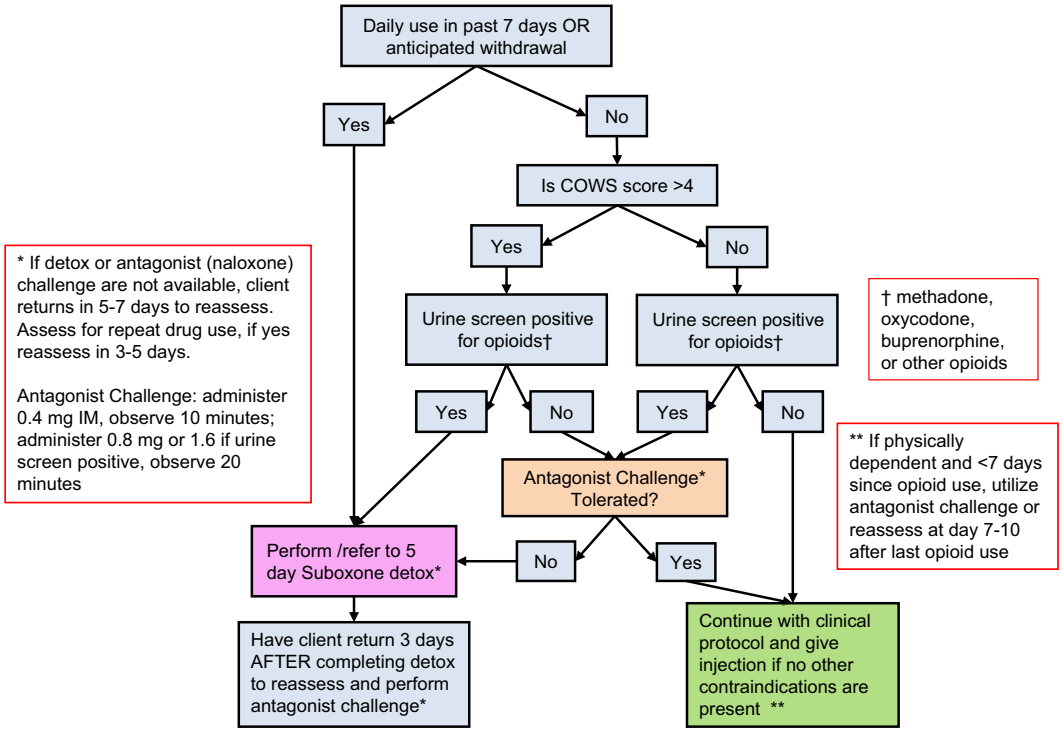

Fig. 4. Clinical management of study participants and ongoing opioid use.

receiving XR-NTX or placebo, length of study enrollment, date of initial injection, possible side effects, a statement that opioid pain medication should be avoided, and contact information should s/he have any questions or concerns. Given that two thirds of participants receive XR-NTX, safety wallet cards are provided to all participants to give to any healthcare providers should they require emergency pain medications in the setting of a possible opioid antagonist effect from XR-NTX and possible requirements of pain medication during an emergency. For individuals found to be actively using alcohol and/or drugs, they are referred for additional community-based drug or alcohol treatment.

9. Analytic plan

The analytic plan for this study is similar to another similarly designed XR-NTX trial that focuses on pre-release prisoners with HIV and alcohol use disorders [60]. Below is a brief description of the planned analysis.

9.1. HIV treatment outcomes

The *primary* study outcome is to compare the proportion of participants achieving VS under the threshold of <400 copies/mL and <50 copies/mL at study month 6 (end of the intervention) using chi-square tests and odds ratios with 95% confidence intervals in the two groups. All participants that completed a baseline interview are considered enrolled and followed for the 12 months, using an ITT analysis, all those with missing values will be imputed as failure (no VS). The trial is on-going and thus results are not currently known.

Secondary HIV treatment outcomes include: mean change in CD4 count and HIV-1 RNA level as a repeated measure at all time points post-release. Changes in $\log_{10}$ HIV-1 RNA will be fitted to a linear regression with interval censoring to account for the large number of censored values owing to HIV-1 RNA at the lower limits of detection at baseline and at follow-up. Missing values will be imputed depending on whether values meet missing at random assumptions. A general linear model including baseline CD4 count and HIV-1 RNA as covariates will assess mean change in the $\log_{10}$ CD4 count from baseline to follow-up month 12.

Similarly, *CD4 counts* have been strongly associated with survival and risk for development of opportunistic infections. Therefore, it is the goal to maintain or improve CD4 count. It will not, however, be a primary endpoint as CD4 count benefits may persist after loss of adherence. Analysis of change in mean/median CD4 count from baseline to months 6 and 12 will use the Wilcoxon rank test, stratified by variables such as cART experience. Spearman's rank correlation will test for associations between a wide range of variables with a binomial distribution.

9.2. Substance abuse outcomes

Several drug relapse variables will be examined. The first drug use variable will be “time to opioid relapse”. Subjects are interviewed monthly using timeline followback (TLFB) [61]. Multiple variables will be used to determine opioid use including drug urine screens, positive naloxone challenge results, and the TLFB method to ascertain the date of first use. Both a median time-to-relapse will be calculated as well as Kaplan–Meier time-to-event analysis performed. Significance will be tested using the log rank test and Wilcoxon statistics. The second

variable will be a calculation of mean duration of time being drug-free. Each month, a recall of days where illicit drugs were used will be calculated from the TLFB method. For each individual, a mean drug-free interval will be calculated. These drug variables will be calculated for opioids, cocaine and for "any" drug as an exploratory analysis. Last, the proportion of positive drug urine screening results over the 6 months of the intervention will be measured. Missing drug urine screen results will be adjudicated in the following sequential manner: 1) self-report at monthly visits; and 2) last value carried forward if no self-report was available and the next value was the same as the previous one; 3) alternative strategies will explore missing values as positive as well as imputing values based on whether data are missing at random or not. The percent of opioid-free urine screenings over the six-month examination period will be compared between the two groups after transforming outcome to means and compared statistically using Mantel–Haenszel Chi Square.

10. Implementation issues

When working with the CJS there are unique implementation and logistical concerns that were overcome during the course of this study. Various concerns were addressed in a similar study but were again encountered here [60]. Listed below and in Table 3 are some of the additional barriers that were encountered and overcome during this study.

- *Review Board Protocol Approval*: Multiple submissions to the Yale IRB, Baystate Medical Center IRB, the Director of Research at HCCC, CTDOC Research Advisory Committee, and Waterbury Hospital IRB were required to ensure that each facility was operating under the same systematic study protocol, and to ensure that any and all issues were addressed by the each institution. Although initial approval from all of the review boards was approximately 6 months, a total of 12 months was needed to coordinate the changes and obtain final OHRP approval and a CoC (see Obstacle 4 in Table 3).
- *Data Safety Monitoring Board (DSMB)*: Per NIDA request, a DSMB, expanded and more stringent than the original Data Safety Monitoring Plan, was created which included three board certified Infectious Disease doctors at Yale Medical School to conduct interim monitoring of the study's risk. Also included in the DSMB was a protocol detailed with the precautions used in the study to monitor for side effects, liver damage, risk of overdose, and other aspects of the study. Responsibilities of the DSMB include reviewing the study performance, evaluation of study quality, and recommending the continuation of the ongoing study (see Obstacle 11 in Table 3).
- *Correctional Facility Information Sessions*: Board-certified Addiction Medicine physicians conducted information sessions throughout the study regarding XR-NTX and other pharmacological treatments available in the community for those with opioid dependence. These interactive sessions allowed the correctional staff to learn about the differences in the treatments, how they are administered, safety information, and updates of treatment use. When this study was initiating recruitment, XR-NTX was newly approved by the FDA for opioid dependence; questions from the staff were expected and addressed (see Obstacle 5 in Table 3).
- *Coordination Between Multiple Sites*: In order to ensure timely and secure data transfer, a quarterly schedule was created for data transfers from Baystate Medical Center. Encrypted data transfer systems provided by Yale University Information Technology Services were used to ensure that participants' information was protected in a HIPAA approved manor (see Obstacles 2 and 3 in Table 3).
- *Reduction of HIV-infected Inmate Population*: During the study submission process, the average daily census of HIV-infected inmates in the CTDOC, where a majority of the participants were recruited was 320 [62]. This number was substantially reduced by 16.6% over the time of the study (personal communication, C. Gallagher CTDOC, September 4, 2014) as a consequence of several other projects that aimed to reduce recidivism by providing other MAT for HIV-infected inmates transitioning to the community (see Obstacle 10 in Table 3).
- *Changes in Department of Correction Policy*: At the end of 2011 and beginning of 2012 two major changes occurred in the CTDOC policy. MMT was made available in one of the men's jail facilities, the women's correctional facility in CT for those with a short sentence and entered the facility while on MMT. A pilot program in the Massachusetts drug and alcohol rehabilitation facilities supervised by the HCCC began to offer XR-NTX treatment. Additionally, those incarcerated with specific non-violent charges were given the ability to earn five days off of their sentence for each month of "good behavior" with the Risk Reduction Earned Credit program. In HCCC there was an increase in number of sentence reduction days earned from 5 to 10 days (see Obstacles 6–9 in Table 3).

11. Summary

It is possible that the negative attitudes by correctional providers, stigma, diversion concerns, poor adherence, and additional restrictive licenses of using an opioid agonist for treating opioid dependence may be possible reasons why they are not widely deployed in the CJS [29,33,63]. XR-NTX provides an alternative treatment as an opioid antagonist, which does not require additional certifications or licenses to administer and store these medications unlike agonist treatments [64,65]. The monthly dosing schedule of injections could potentially reduce adherence concerns with daily oral medications and eliminate the concerns of diversion. Additionally, the protective properties of XR-NTX and the long-acting half-life may reduce the risk of overdose upon release from the correctional system when administered prior to release. Although other forms of MAT are widely available in the U.S., including BMT, MMT, and XR-NTX, no studies have compared these MATs for released prisoners and MMT must be initiated ~6 months pre-release in order to achieve effective doses [66,67]. For most prisoners who are not tolerant to opioids upon release, BMT and XR-NTX are preferred options. Both medications, however, differ with regard to pharmacology, route of administration (sublingual versus injection), duration of effect (daily versus monthly), benefits on alcohol disorders (XR-NTX) and opioid craving (BMT), side effects, cost, impact on retention and patient preferences. Moreover, prison administrators favor XR-NTX over BMT due to its lack of dependence ("being addicted"), but patients may reject it for other reasons. Thus comparative effectiveness studies are urgently needed to inform patient-

centered treatment options that involved informed patient decision-making.

As part of the STTR model by NIDA, this is the first double-bind, placebo-controlled clinical trial of XR-NTX for opioid dependent, HIV-infected persons involved in the CJS. The novel use of XR-NTX within the CJS as a conduit for HIV care will strengthen the current evidence of the effectiveness of XR-NTX. Concerns regarding hepatic safety of XR-NTX have been expressed prior to initiating this intervention given the impact of cART on liver function and the high rate of Hepatitis C virus co-infection. New evidence, however, now provides assurances of XR-NTX safety in HIV-infected patients on cART [68,69]. Given the consequences of relapse to opioid use after release from the correctional system, XR-NTX can prevent relapse, and prevent the spiral of poor care leading to increased HIV risk behaviors, poor adherence to cART, and possible risk of infecting those in the community.

Findings from this study may show the benefits of initiating opioid treatment prior to release as a way to improve HIV treatment by preventing and reducing drug use. Also of note, this study provided an opportunity to develop a safety and clinical protocol for the use of XR-NTX for opioid dependence within the community including the monitoring of opioid relapse and opioid withdrawal and use of a community detoxification protocol with buprenorphine prior to reinitiating injection with XR-NTX that may be used by others in similar research settings or for routine clinical use. Additionally, the preliminary findings of acceptability for this form of opioid dependence treatment may not be generalizable to all those involved in the CJS.

This study was designed to provide good internal validity by controlling known confounders, by having a target sample powered to detect the difference in primary outcome using a similar sample, using validated measurements, and by using statistical methods that have been proven to reduce Type I and Type II errors. The nature of this population may lead to a threat to the external validity of this study as seen in the modest acceptability of XR-NTX thus far in this on-going study. Given the large number of those who refused at different stages of the study there is a potential threat to the external validity of the treatment and desire to enroll in the study. Unlike the initial large clinical trial where other forms of MAT are not available [70], a large percentage of the population (79%) reported a previous experience with other forms of MAT and the main reason for refusal was 'the desire for treatment using another form of MAT. This "choice" allows for the opportunity to participate in an informed decision regarding their form of MAT prior to release, which may reduce opioid relapse and the negative consequences that occur from active drug use thereby increasing the external validity of the study. With the recent changes to the DSM-V and the availability of newer, office-based treatments for opioid use disorders, we now require a reassessment of transitional care for opioid dependent patients in the CJS.

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