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Extended-release naltrexone opioid treatment at jail reentry (XOR)

Ryan D. McDonald^a, Babak Tofighi^a, Eugene Laska^b, Keith Goldfeld^a, Wanda Bonilla^a, Mara Flannery^a, Nadina Santana-Correa^a, Christopher W. Johnson^c, Neil Leibowitz^c, John Rotrosen^b, Marc N. Gourevitch^a, and Joshua D. Lee^{a,d,*}

^aDepartment of Population Health, New York University School of Medicine, United States

^bDepartment of Psychiatry, New York University, United States

^cNew York City Health + Hospital Corporation, Correctional Health Services, United States

^dDivision of General Internal Medicine and Clinical Innovation, New York University School of Medicine, United States

Abstract

Background—Extended-release naltrexone (XR-NTX) is an injectable monthly sustained-release mu opioid receptor antagonist, which blocks the typical effects of heroin and other opioid agonists. Use of XR-NTX among opioid dependent persons leaving jails and prisons is increasing despite scant high-quality evidence regarding XR-NTX's effectiveness at re-entry.

Methods—This 24-week, open-label randomized controlled trial examines the effectiveness of XR-NTX as opioid relapse prevention at release from jail (N = 85) compared to enhanced treatment as usual (ETAU, N = 85). A third, non-randomized, quasi-experimental naturalistic arm of participants who have newly initiated a jail-to-community methadone treatment program (MTP, N = 85) allows for comparisons to a methadone standard-of-care.

Results—We describe the rationale, design, and primary and secondary outcomes of the study. The primary outcome is an opioid relapse event; the primary contrast is a time-to-relapse comparison of XR-NTX and ETAU over a 24-week treatment phase. Secondary outcomes are rates of: (a) post-release opioid treatment participation, (b) opioid, alcohol, and cocaine use, (c) injection drug use and HIV sexual risk behaviors, (d) overdose (fatal and non-fatal) and all-cause mortality, and, (e) re-incarceration.

Conclusions—XR-NTX is a potentially important, effective treatment and relapse prevention option for a large US population of persons with opioid use disorders leaving jails. This study will estimate XR-NTX's effectiveness relative to existing standards of care, including counseling-only treatment-as-usual and methadone maintenance.

*Corresponding author at: Department of Population Health, 227 E.30th St 712, NY NY 10016, United States. joshua.lee@med.nyu.edu (J.D. Lee).

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Conflicts of interest disclosures

Drs. Lee and Rotrosen receive in-kind study drug from Indivior in an additional study.

Keywords

Naltrexone; Extended-release naltrexone; Criminal justice; Opioid relapse prevention; Jail

1. Introduction and background

Extended-release naltrexone (XR-NTX), a long-acting, monthly injectable formulation, is indicated for the prevention of opioid relapse following detoxification. XR-NTX's applications within the US criminal justice system (CJS) are growing, as is evidence of XR-NTX's effectiveness as outpatient treatment [1]. Naltrexone is a mu opioid receptor antagonist, or 'blocker,' is not a controlled substance, has no known abuse or diversion liability, and can be prescribed in any general medical setting, in contrast to methadone and buprenorphine. The extended-release formulation blocks the euphoric and reinforcing effects of opioids (e.g., heroin, oxycodone) for about 30 days [2]. Cravings, heroin use, relapse rates are substantially lower on XR-NTX vs. placebo [3]. Among persons leaving jails and prisons and at high risk for opioid relapse, overdose, and death [4,5], there is a clear rationale in this and other studies for XR-NTX at reentry [6,7,8].

As part of the NIDA Studies of Opioid Medication Assisted Treatments in Correctional Settings (SOMATICS) collaborative, XOR is set in a municipal jail characterized by short stays, high turnover, and a disproportionately high prevalence of heroin and other opioid use disorders. The New York City Department of Corrections, including ten individual facilities on Rikers Island, averages a daily census of 12,000 inmates and 80,000 new admissions annually (2014) [9,10]. Roughly 15% of adult NYC jail admissions are diagnosed with an opioid use disorder, primarily heroin, and most will leave jail out-of-treatment [11]. Opioid users leaving jails are highly likely to relapse and at great risk of overdose [4,5,6,12,13]. Unintentional drug poisoning is the third leading cause of premature death in NYC (2013); 77% of all deaths involve opioids [14]. Developing an increased menu of effective treatment options for heroin and other opioid users at reentry is a public health priority in NYC and nationwide.

US jails and prisons limit access to medication-assisted treatments (MAT, methadone, buprenorphine, and naltrexone) [15,16]. NYC jails are an exception, and offer methadone detoxification (13,532 persons, 2014) and methadone maintenance (3086 persons, 2014) as routine standards of care [11,17,18]. However, most detainees receiving methadone detoxification will not transition to methadone maintenance due to various logistic, regulatory, and patient-centered factors [19,20]. Thus, among heroin users out-of-treatment at arrest, most leave NYC jails detoxed but still out-of-treatment, alongside a much smaller number newly enrolled in methadone maintenance.

XR-NTX is not currently available in NYC jails, presenting an ideal opportunity to test the real-world, open-label benefits of XR-NTX compared to usual care and methadone maintenance. Our previous proof-of-concept 8-week randomized pilot (N = 34) of XR-NTX demonstrated good acceptability (16 of 17 randomized to XR-NTX received an initial injection) and significantly lower rates of opioid relapse at 4 and 8 weeks after release compared to counseling-only (38% vs. 88% relapsed at 4 weeks, $p < 0.004$) [6]. XOR now

seeks to replicate this initial signal of effectiveness in a larger sample and over a longer period, similar to a recent multisite RCT of XR-NTX for outpatient CJS-involved adults [1]. XOR aims to estimate the effectiveness of XR-NTX during the crucial and high-risk period of jail-to-community reentry.

2. Research design and study population

2.1. Study design

XOR is an N = 255 open-label, non-blinded, 24-week randomized trial assessing the effectiveness of XR-NTX (n = 85) versus a counseling-only, enhanced treatment-as-usual (ETAU, n = 85) condition among opioid dependent adults released from NYC jails (Fig. 1). In a third trial arm, participants newly established on methadone maintenance during incarceration and therefore not eligible for XR-NTX treatment are recruited into a quasi-experimental comparison cohort (MTP, n = 85), allowing a naturalistic comparison of XR-NTX and ETAU with MTP. The study's primary outcome is a post-release opioid relapse event, defined as 7 or more consecutive days of non-prescribed opioid use by self-report, or two consecutive bi-weekly urine samples positive for non-prescribed opioids or missing. The study's primary contrast is a time-to-relapse survival function comparing XR-NTX to ETAU. Long-term follow-up following the 24-week treatment phase occurs at week 52.

2.2. Research questions and hypotheses

The primary study aim is whether an opioid-dependent adult population assigned to XR-NTX will exhibit longer time-to-relapse following release from jail compared to ETAU. More generally, will XR-NTX generate lower rates of opioid use post-release (i.e. % days of use and number of positive urines)? We hypothesize XR-NTX will be associated with a significantly longer time-to-relapse vs. ETAU and lower overall rates of opioid use (i.e., more opioid-free weeks). Because of the availability of methadone for out-of-treatment inmates, we are also able to ask, will XR-NTX produce similar time-to-relapse rates compared to a quasi-experimental methadone cohort, who at study baseline are already maintained on methadone and otherwise ineligible for naltrexone?

Secondary aims are to examine opioid-related outcomes across the three arms, including retention in any study or community opioid treatment modality, opioid, alcohol, or other drug use, injection drug use and HIV sexual risk factors, drug overdoses and mortality, and re-arrest and re-incarceration rates. We hypothesize that the XR-NTX participants will have greater rates of post-release opioid treatment retention, report less continuous opioid, alcohol, and other illicit drug use, less IV drug use and HIV sexual risk behavior, less overdose events, and less frequent re-incarceration compared to ETAU participants. We hypothesize similar rates of these secondary outcomes between XR-NTX and MTP.

2.3. Study sites

Recruitment is taking place at two New York City Department of Corrections (NYC DOC) jail facilities within the Rikers Island complex: one for adult men (Eric M. Taylor Center) and one for adult females (Rose M. Singer Center). All interactions between study staff and participants occur within the jail health care clinics. Permission for study conduct and study

staff security clearance is obtained from NYC Health + Hospitals (previously from the NYC Department of Health and Mental Hygiene). Study staff work with jail Key Extended Entry Program (KEEP) staff, the jail opioid treatment program, to advertise the study among inmates, assess pre-screen eligibility, and schedule study visits. All post-release follow-up visits take place at Bellevue Hospital in Manhattan.

2.4. Study population and inclusion/exclusion criteria

Eligible participants across all three arms are adults currently incarcerated in a New York City jail with a known release date, meet criteria for DSM-V current opioid use disorder based on a Modified Composite International Diagnostic Interview, version 2 (CIDI-2) for Substance Use Disorders [21], and are of general good health.

Persons eligible for the XR-NTX vs. ETAU randomized trial are opioid abstinent with a urine sample negative for all opioids at randomization, and not intending agonist treatment (buprenorphine, methadone) at release. Most randomized trial participants will have completed a standard 6-day methadone detoxification following arrest and at admission to NYC jails. This has typically concluded well before XOR recruitment and enrollment, which occurs in the weeks prior to release.

Participants eligible for the MTP quasi-experimental arm have newly initiated methadone maintenance during the current incarceration and prior to XOR enrollment. These participants have positive methadone urine samples and are planning to continue methadone maintenance at release, thus they are ineligible for the XR-NTX randomized trial.

Prior exposure to opioid treatment across the three trial arms will vary; many will have previously been enrolled in community methadone or buprenorphine treatment. Common to all XOR participants is that at trial baseline, none are continuing methadone or buprenorphine treatment established prior to the index incarceration.

2.4.1. Randomized arms (XR-NTX and ETAU)—Inclusion criteria for the randomized trial are: 1) adults ≥18 years of age with a known release date; 2) DSM-V criteria current opioid use disorder [22]; 3) not currently in or planning to pursue agonist (methadone, buprenorphine) treatment at release; 4) currently opioid-free by self-report and with a negative urine for all opioids; and 5) general good health as determined by medical evaluation. Exclusion criteria for randomized arms (ETAU, XR-NTX) are: 1) pregnancy, lactation, or planning conception; 2) active severe medical or psychiatric illness (i.e., severe liver disease, psychosis) precluding safe participation; 3) history of allergic reaction to naltrexone or XR-NTX components; and 4) current chronic pain condition requiring opioid analgesia.

2.4.2. Quasi-experimental cohort (methadone, MTP)—Inclusion criteria for methadone participants are similar but target patients newly initiating methadone during the current incarceration: 1) adults ≥18 years of age with a known release date; 2) DSM-V criteria for current opioid use disorder; 3) initiated methadone maintenance treatment during the current incarceration; and 4) general good health as determined by medical evaluation. Exclusion criteria for the non-randomized methadone group (MTP) are: 1) pregnancy,

lactation, or planning conception; 2) active medical or psychiatric illness precluding safe participation; and 3) in community methadone treatment at the time of arrest and incarceration.

2.5. Recruitment

Recruitment, screening, and randomization visits take place at the two jail facility's health clinics, which are operated by the NYC Health and Hospitals Corporation (HHC) and use an electronic medical record (EMR) system, eClinicalWorks [23]. Automated reports list soon-to-be-released inmates with opioid use disorders, which are reviewed by opioid treatment program staff and study personnel to identify potentially eligible individuals. Flyers and business cards, detailing of jail staff, and word-of-mouth referrals generated by active study participants also drive recruitment. Potentially eligible inmates are scheduled for individual interviews in the clinic area to learn about the study and discuss informed consent and enrollment procedures. Every effort is made to maximize privacy and confidentiality during screening and randomization visits.

2.6. Informed consent

Individuals who appear eligible and express interest in study participation are scheduled for a screening visit. Per standard Good Clinical Practice guidelines, study staff obtains written informed consent and lead a discussion of potential risks and benefits and voluntary, confidential study participation. Interested participants must sign the informed consent form and complete a consent quiz. The consent quiz is implemented in order to ensure the participants' comprehension of study rationale, risks, procedures, and voluntary participation and is increasingly standard practice in addiction clinical research [1,24]. The quiz documents an assessment of the participant's understanding and voluntary participation. Incorrect answers prompt additional discussion, until the quiz is completed correctly.

2.7. Screening, randomization, and follow-up procedures

Screening consists of informed consent, urine toxicology, inclusion/exclusion checklist, and study registration (in that order). Study clinicians review the participant's medical and psychiatric status and confirm eligibility. Individuals not on methadone must test opioid-negative at randomization; this means that they could potentially test opioid-positive at screening but still later be randomized if they are opioid-abstinent at randomization during the week of scheduled release. Randomization is stratified by gender, 1:1 XR-NTX: ETAU, and by random permuted blocks of sizes 2 and 4. Statistical personnel independent of the study generated the random sequence and sealed consecutively numbered envelopes. Similarly, MTP participants provide informed consent, complete the screening visit, and initiate MTP cohort enrollment at a second visit within 1 week of release, a parallel to the randomization visit. All participants are given 2-sessions of enhanced counseling and a patient-drug educational handout that includes contact information to community treatment referrals. After randomization, all participants attend a total of 14 (ETAU and MTP arms) or 15 (XR-NTX) visits (see Table 1), with the XR-NTX group receiving one additional 'safety' follow-up visit one month post-treatment phase. A final follow up study visit at week 52 (12 months post-release, 6 months after the 25-week treatment trial) extends the tracking of opioid use and the secondary outcomes.

2.8. Data management

Study staff complete screening and randomization assessments at Rikers Island using written case report forms (CRFs) due to limited internet access and prohibition of study laptops and tablets in the jail facilities. Screening and randomization visit data is later entered electronically. Post-release follow-up visits are completed using written source documents and web-based data entry. Data is captured and warehoused on a secure NYUMC server using the REDCap (Research Electronic Data Capture) platform [25]. Programming of common assessments and data management has been standardized across the three SOMATICS studies using REDCap.

2.9. NIDA SOMATICS collaborative

The XOR study, conducted in NYC jails and Bellevue Hospital Center through New York University (NYU), is collaborating with two other jail-based opioid treatment studies as part of a National Institute of Drug Abuse (NIDA) research cooperative, Studies of Medication for Addiction Treatment in Correctional Settings (SOMATICS). The two other SOMATICS studies are Friends Research Institute (FRI) in Baltimore, MD, examining interim methadone and patient navigation (NCT02334215), and the University of California, Los Angeles (UCLA) – University of New Mexico (UNM) in Albuquerque, NM, examining XR-NTX and patient navigation (NCT02110264). The rationale and methods of the SOMATICS collaborative and the two partner studies are published elsewhere in this issue.

3. Approvals and data and safety monitoring

3.1. Approvals and certifications

NYU School of Medicine's Institutional Review Board approved the study protocol. Trial registration was completed at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01999946). Department of Human Services Office of Human Research Protections reviewed the approved protocol and certified the protocol has met standards for the ethical conduct of federal research among prisoners. A Certificate of Confidentiality protects from disclosure of participant data.

3.2. Data Safety Monitoring Board and interim analysis

The Data Safety Monitoring Board (DSMB) at the UCLA Integrated Substance Abuse Programs (UCLA ISAP) monitors data and safety events across all three SOMATICS studies. The XOR study team and principal investigator (PI) monitor recruitment, retention, and safety events in real-time and report annually to the NYU IRB and DSMB. Adverse events (AE) and serious adverse events (SAEs) are logged in sequential, open-ended fashion during monthly assessments using specific case report forms and AE and SAE logs. AE and SAE are determined to be medication- or study-related by the study clinician or PI. All SAEs are reported to the NYU IRB, the DSMB, the study sponsor (NIDA), and the manufacturer (Alkermes). There are no pre-specified trial stopping rules or planned interim analysis of clinical outcomes.

4. Study interventions

4.1. XR-NTX and medical management treatment visits

Participants randomized to XR-NTX treatment receive an initial injection within a week of the scheduled release date. The participant must report no opioid use in the last 7 days, provide an opioid negative urine sample (negative for buprenorphine, methadone, oxycodone, and morphine metabolites), and complete a negative naloxone challenge consisting of a 0.8 mg or more of IV, SC, or IM naloxone with a pre/post assessment of precipitated opioid withdrawal. The study clinician then administers a 380 mg intramuscular dose of XR-NTX (Vivitrol®, Alkermes) to the right upper outer gluteus (buttock). Subsequent injections occur every 4 weeks during the 24-week study treatment phase (6 or more monthly injections; XR-NTX can be given every 21 days if cravings or opioid use are increasing). Medical management (MM) counseling by the study physician addresses the rationale for continued naltrexone treatment for opioid dependence, possible side effects (e.g. injection site discomfort, nausea, malaise), self-help and community treatment participation, and relapse and overdose risk reduction counseling, all within typical ambulatory care office visits which include the XR-NTX injections [26]. In addition, during the screening and randomization visit, all participants receive the ETAU counseling intervention (below).

The 24-week XR-NTX treatment phase constitutes the active phase of the trial, and marks the endpoint for the primary outcome, time-to-relapse. XR-NTX participants are followed for an additional 4-week post-treatment follow-up period, which collects data on immediate post-XR-NTX safety and treatment outcomes (opioid relapse, AEs, and other treatment uptake). XR-NTX participants are encouraged by study staff to accept referrals to appropriate community aftercare, which may include continued naltrexone treatment.

4.2. Enhanced treatment-as-usual (ETAU)

ETAU consists of brief, 2-session education, counseling and community treatment referrals provided by the research staff at screening and randomization to all participants. ETAU ensures all participants in the trial are offered tangible health benefits above and beyond those expected during a usual jail incarceration episode, in accordance with DHS federal research standards for prisoners. Throughout the trial, and particularly if relapse occurs, counseling in support of appropriate community treatment involvement continues across all arms.

4.3. Quasi-experimental methadone treatment program (MTP) arm

MTP patients enrolled in XOR are at the time of consent and enrollment already established on methadone maintenance, which was initiated during the same incarceration as a new treatment episode (participants already on methadone at the time of arrest who continue methadone during incarceration are ineligible for XOR). The NYC jail opioid treatment program procedures, observed daily methadone dosing and dose levels, and community methadone treatment referrals, are provided as usual care by program staff and are not study treatment. MTP participants do receive brief, 2-session ETAU counseling at the screening and final pre-release visit; this counseling reinforces the goal of methadone follow-up and

continuity after release at the assigned community MTP. Follow-up visits at Bellevue Hospital are for assessments only; community methadone treatment is provided as usual care by various opioid treatment programs throughout NYC. Community MTP attendance is tracked as self-reported outcome data. In the event of drop-out or missed visits, XOR staff attempt to confirm attendance with the community program based on the participant's prior signed consent for the release of health information.

4.4. Relapse to opioid and other drug and alcohol use

All study participants are at risk to relapse to heroin, other opioid, and other alcohol and drug use after release and throughout the trial. XR-NTX participants who miss a scheduled XR-NTX dose will reschedule the next XR-NTX injection if still in a 35-day window or if still opioid abstinent (negative self-report, negative urine sample, negative naloxone challenge). This is a standard approach to re-starting XR-NTX in similar clinical trials [1]. XR-NTX patients who are no longer opioid abstinent and intend to re-start XR-NTX will need to abstain from opioids or undergo detoxification. Any XR-NTX, ETAU, or MTP participant who has relapsed and is not interested in continuing their baseline study condition (e.g., an MTP patient refuses further program attendance, or an XR-NTX participant does not wish to continue injections) will be encouraged to pursue other appropriate community treatment, the menu of which includes the robust addiction service offerings at Bellevue Hospital Center (BHC). BHC's services are available to all persons, regardless of insurance status or an ability to pay, and include emergency detox inpatient services, methadone treatment, office-based buprenorphine, and intensive outpatient and dual diagnosis programs. These services will consist of usual care occurring outside of the study and will not be directly provided by the study.

4.5. Retention, incentives, and tracking

Attendance and participation at all planned study visits, regardless of the participant's clinical status or retention in treatment, is a priority. Participants are incentivized monetarily for their time and effort at each study visit including: \$20/visit at two jail visits, \$25 for bi-weekly brief urine and drug self-report visits, \$50–75 for monthly and long-term follow-up assessments, for a maximum total of \$610 over 16–17 total study visits (XR-NTX participants undergo an extra safety visit at week 29). Payment for the screening and randomization are provided at the first post-release visit, or may be deposited in the participant's jail commissary account.

Baseline Locator information (personal phone numbers, residential and work addresses, email addresses, Facebook accounts, and similar contact information for family and friends) is used to contact the participant following release and is updated throughout the study. Visit reminders, telephone, text messaging, mail, social media contact, and outreach to friends and family are routinely used to track participants and encourage in-person visits. We conduct periodic field visits to locate out-of-contact participants in the community. Self-report data is collected by phone if a participant is otherwise unable to be interviewed in-person. NYC incarceration databases are used to track individual re-incarceration; upon re-incarceration, every attempt is made to conduct scheduled follow-up visits in jail.

5. Assessments

The visit and assessment schedule is summarized in Table 1. The primary outcome of an opioid relapse event and time-to-relapse is a construct of urine sample and self-reported calendar Timeline Followback (TLFB) [27] data, collected at every study visit. Urine samples are tested for opiates (300 ng/ml), oxycodone, methadone, buprenorphine, cocaine, amphetamine, methamphetamine, benzodiazepines, cannabis, and barbiturate metabolites using a point-of-care dip card. Visit schedules vary between arms only at week 29, which is safety check visit one month post-treatment phase conducted with XR-NTX participants only in order to provide adequate provision of care in follow-up. Several assessments of medication-related outcomes are particular to XR-NTX or MTP arms only. All participants return for a final long-term follow-up visit at week 52 (12 months post-release), which is study close. This allows study staff to gather data on opioid use and secondary outcomes over a 6-month period following the active XR-NTX treatment phase.

5.1. Primary outcome

The primary outcome measure is post-release time-to-opioid-relapse through week 25. At randomization all randomized participants are abstinent from opioid use, as verified by urine toxicology and self-report; MTP is positive for methadone only. Beginning with the day of release, an opioid relapse event is defined as the self-report of 7 or more consecutive days of non-prescribed opioid use on the TLFB, or two consecutive bi-weekly urine samples positive for non-prescribed opioids. Missed visits and/or missing urine samples are counted as positive samples for opiates and contribute to the relapse outcome. The time of the relapse event occurs on the first day of the first week of the qualifying 1–4 week period. The relapse event is considered a onetime event per participant for the purposes of survival analysis. MTP urine samples positive for methadone while active in community MTP do not contribute to the relapse outcome; illicit methadone use does contribute to the relapse outcome across all arms.

5.2. Secondary outcomes

Secondary outcomes of interest evaluate the effectiveness of XR-NTX in reducing rates of: a) post-release opioid treatment participation, b) opioid, alcohol, and cocaine use, c) injection drug use and HIV sexual risk behaviors, d) overdose (fatal and non-fatal) and all-cause mortality, and e) re-incarceration. Economic analysis and cost effectiveness aims are core to the SOMATICS collaborative and standard economic and quality of life measures were incorporated into XOR as well.

Opioid treatment participation is defined from XR-NTX dose logs (monthly, XR-NTX arm only), ASI-Lite (monthly) [28], Methadone Treatment Exposure Form (monthly, MTP only), and Economic Form 90 (Month 3, 6, 12) [29]. Days of opioid, alcohol and cocaine use are documented in the bi-weekly TLFB and corroborated by urine samples; opioid cravings are measured using a Visual Analog Scale. Rates of injection drug use and HIV sex risk behaviors are captured using the TLFB (counts of days injecting) and the Risk Assessment Battery (RAB) [30]. Surveys of Adverse Events (AEs), Serious Adverse Events (SAEs), Opioid Overdose and XR-NTX-injection-site-specific AEs/SAEs, and in the event of drop-

out, Vital Statistics are used to track overdose-related SAEs and mortality. Re-incarceration is by self-report using a modified Addiction Severity Index Lite (ASI-Lite) and the New Arrests and Days Incarcerated Form; self-report of missing data is cross-checked using the NYC Department of Corrections Inmate Look-up database and Form, which holds public incarceration data by individual for the past 30 days.

Across the SOMATICS collaborative, the modified version of the Composite International Diagnostic Interview (CIDI-2) is used to assess relapse to opioid use disorders based on the Diagnostic Statistical Manual-V criteria (DSM-V; previously opioid dependence based on DSM-IV criteria). The Economic Form 90 and World Health Organization Quality of Life short form (WHOQOL-BREF) [31] capture individual-level costs and benefits. Finally, open-ended questions and the Client Satisfaction Questionnaire [32] assess treatment and reentry experiences and satisfaction.

6. Statistical analysis

The primary analyses will model time-to-relapse as a function of treatment assignment (XR-NTX vs. ETAU). Cox proportional hazards regression models will be used to examine whether XR-NTX prolongs time-to-relapse. Generalized and linear mixed effects models will be used to estimate differences in relapse event rates, self-reported days of opioid use, and rates of opioid positive urine samples. Cox proportional hazard models will also be used to estimate differences in time-to-relapse between the XR-NTX and MTP, a naturalistic, non-random, convenient comparison. Propensity score modeling will be used to control for baseline differences between the XR-NTX and MTP non-random cohorts.

In the event of a missed visit or dropout, missing urines are counted as positive for opiate use, therefore drop-out contributes to a relapse event. Participants dropping out are recorded as beginning the relapse event the first day of the 2-week period of the first missed visit contributing to the relapse event. Alternative imputation strategies will be compared to this missing = positive strategy, including missing-as-missing and missing-at-random. Prescribed methadone or buprenorphine opioid dependence treatments do not contribute to a relapse outcome in any participant, provided the treatment episode can be confirmed or reasonably assumed to be legitimate (vs. illicit, 'street' use). Legally prescribed or illicit opioid analgesic use (e.g., oxycodone, hydrocodone) does contribute to a relapse outcome, given the general recommendation that heroin users avoid all such medications.

Secondary analyses will compare five key outcomes at re-entry across all arms: a) post-release opioid treatment rates will be assessed based on the proportion of weeks retained on study medication (XR-NTX), engaged in appropriate community treatment (ETAU), or methadone maintenance (MTP), b) rates of alcohol and cocaine use will be examined in a similar approach to that of opioid use self-report days and urine results, c) rates of injection drug use based on count data (% days of use) from the TLFB and RAB, and HIV sexual risk scores by RAB sex risk items (score range 0–18, higher scores indicate higher risk), d) rates of opioid overdose (% of participants, rate of overdose per participant-month) from the overdose-specific surveys, and e) re-incarceration rates by count (% of participants re-incarcerated, % days re-incarcerated by participant-month). SOMATICS cost-effectiveness

analysis will estimate the downstream benefits (i.e. costs avoided) of XR-NTX vs. ETAU from societal and criminal justice system perspectives. Satisfaction ratings and qualitative interviews will summarize benefits and challenges of treatment assignment during the reentry period.

6.1. Sample size, power, and effect size

A projected randomized clinical trial sample targets 170 participants randomized 1:1 to XR-NTX vs. ETAU. Pilot study data implies roughly a 0.5 treatment effect of XR-NTX in reducing immediate post-release opioid use [6]. Our NYC jail RCT showed 50% of XR-NTX relapse-free at 8 weeks post-release vs. 6% of controls. In the Phase 3 XR-NTX efficacy study, the XR-NTX arm resulted in a 50% rate of opioid abstinence at 6 months, versus <20% in the placebo arm [3]. We therefore conservatively predict 40% of the XR-NTX arm with a time-to-event of 25 weeks (i.e., no relapse event occurs) and 20% of ETAU, with the distribution of failure (relapse) randomly distributed in both arms. A sample size of $N = 155$ accounts for possible wide variance in the hypothesized treatment effect. The quasi-experimental MTP arm ($n = 85$) is added symmetrically and naturalistically, resulting in a total randomized/initiated sample of $N = 255$.

7. Results

Recruitment began in June 2014 and is ongoing. As of January 2016 our site has obtained consent from and successfully enrolled 97 eligible participants; 30 randomized to XR-NTX and 25 ETAU; with 29 non-randomized methadone participants to date in the observational arm.

8. Discussion

This randomized effectiveness trial, XOR, assesses XR-NTX as opioid relapse prevention following release from jail among a large sample of NYC adults treated for 24 weeks and followed for a full 1 year. XOR aims to address a national and NIDA priority of building and evaluating the evidence base for interventions to improve criminal justice outcomes and diminish morbidity and mortality associated with the US opioid epidemic [33,34]. Our study in NYC and the related Injectable Pharmacotherapy for Opioid Use Disorder (IPOD) study evaluating XR-NTX with or without Patient Navigation in the Bernalillo County Metropolitan Detention Center (Albuquerque, NM), aim to provide definitive estimates of XR-NTX's effectiveness as post-jail-release relapse prevention.

As all the SOMATICS collaborative trials recognize, jails are uniquely positioned to facilitate access to medications and respond to the opioid epidemic. In the US ~740,000 persons are detained/incarcerated in jails per day, typically while serving short pre-trial detention or misdemeanor sentences, contributing to an annual affected population of over 11 million persons [35,36]. An estimated 10–25% of these individuals have an opioid use disorder. Jail incarceration is a high-risk and therefore crucial moment of intervention with medications and counseling to out-of-treatment opioid users, who will otherwise forcibly detoxify in jail, likely not access community opioid treatment at release, relapse, and too often overdose. Determining XR-NTX's impact on overdose rates is an important aspect of

this trial, given recent indications that XR-NTX does not increase and may in fact lower usual overdose rates [1].

Despite decades of evidence supporting the use of agonist therapies, methadone and buprenorphine remain mostly unused in US jails and prisons, as well as among outpatient CJS-involved adults [15,37]. As the NYC jail opioid treatment program statistics detailed in the Introduction make clear, however, even when methadone maintenance for out-of-treatment heroin users is standard of care, too few access this treatment. New and different medication treatment options, including XR-NTX and other extended-release products in development, likely offer additional benefit. Unsurprisingly, and despite limited clinical trial data [1,6], the use of XR-NTX in jails, drug courts, and reentry treatment agencies appears to be growing [38–40]. Additional larger, high-quality effectiveness trials are crucial to the field and policy makers.

This trial does not offer a placebo control or conduct blinded treatment or outcome assessments. Double-blind, placebo-controlled efficacy studies of extended-release naltrexone products have previously been conducted [3,41]. A placebo-controlled opioids and HIV prison reentry study is currently in the field, and there was little enthusiasm for duplicating these efficacy trial features in this study [7]. Like other recent NIDA XR-NTX effectiveness and comparative effectiveness trials (NCT02032433), XOR seeks to implement XR-NTX as every day treatment, open-label, and without blinding [1]. Increased attention, recall and assessment biases is certain but acceptable in an effort to mimic community treatment conditions and maximize generalizability. Nonetheless these effectiveness protocols are traditional clinical trials and include free XR-NTX treatment, visit incentives, and intensive outreach, none of which characterizes typical community opioid treatment.

In summary, prior studies including our proof-of-concept randomized trial have demonstrated the feasibility of XR-NTX prior to release. This XOR protocol aims to replicate and expand the XR-NTX pre-release model in a large effectiveness trial, estimating effects on opioid relapse and related health outcomes over 24 weeks. Data from this trial and the multi-study SOMATICS collaborative are designed to firmly establish the evidence and rationale for XR-NTX as a routine jail-to-community reentry intervention.

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References

1. Lee JD, Friedmann PD, Kinlock TW, Nunes EV, Boney TY, Hoskinson RA, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med*. 2016; 374:1232–1242. [PubMed: 27028913]
2. Sullivan MA, Vosburg SK, Comer SD. Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. *Psychopharmacology*. 2015; 189(1):37–46.
3. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend D, Silverman A. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet*. 2011; 377(9776):1506–1513. [PubMed: 21529928]

4. Binswanger IA, Stern MF, Deyo RA, Heagerty PJ, Cheadle A, Elmore JG, et al. Release from prison—a high risk of death for former inmates. *NEJM*. 2007; 356(2):9.
5. Rosen DL, Schoenbach VJ, Wohl DA. All-cause and cause-specific mortality among men released from state prison, 1980–2005. *Am J Public Health*. 2008; 98(12):2278–2284. [PubMed: 18923131]
6. Lee JD, McDonald R, Grossman E, McNeely J, Laska E, Rotrosen J, Gourevitch MN. Opioid treatment at release from jail using extended-release naltrexone: a pilot proof-of-concept randomized effectiveness trial. *Addiction*. 2015; 110(6):1008–1014. [PubMed: 25703440]
7. Di Paola A, Lincoln T, Skiest DJ, Desabrais M, Altice FL, Springer SA. 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. *Control Clin Trials*. 2014; 39(2):256–258.
8. Gordon MS, Kinlock TW, Vocci FJ, Fitzgerald TT, Memisoglu A, Silverman B. A phase 4, pilot, open-label study of VIVITROL® (extended-release naltrexone XR-NTX) for Prisoners. *J Subst Abus Treat*. 2015; 59:52–58.
9. Selling D, Lee D, Solimo A. A road not taken: substance abuse programming in the New York City jail system. *J Correct Health Care*. 2015; 21(1):7–11. [PubMed: 25403463]
10. Preliminary Mayor's Management Report, City of New York, Department of Correction. 2014. (Available from: <http://www.nyc.gov/html/doc/downloads/pdf/MMR-2014.pdf>)
11. Harris A, Selling D, Luther C, Hersherberger J, Brittain J, Dickman S, et al. Rate of community methadone treatment reporting at jail reentry following a methadone increased dose quality improvement effort. *Subst Abus*. 2012; 33(1):70–75. [PubMed: 22263715]
12. Seaman SR, Brettelle RP, Gore SM. Mortality from overdose among injecting drug users recently released from prison: database linkage study. *BMJ*. 1998; 316(7129):426–428. [PubMed: 9492665]
13. Wakeman SE, Bowman SE, McKenzie M, Jeronimo A, Rich JD. Preventing death among the recently incarcerated: an argument for naloxone prescription before release. *J Addict Dis*. 2009; 28(2):124–129. [PubMed: 19340674]
14. New York City Department of Health and Mental Hygiene. Epi Data Brief: Unintentional Drug Poisoning (Overdose) Deaths Involving Opioids in New York City. 2014. 2000–2013 (Available from: <http://www.nyc.gov/html/doh/downloads/pdf/epi/databrief50.pdf>)
15. Nunn A, Zaller N, Dickman S, Trimbur C, Nijhawan A, Rich JD. Methadone and buprenorphine prescribing and referral practices in US prison systems: results from a nationwide survey. *Drug Alcohol Depend*. 2011; 113(2–3):252. [PubMed: 21479159]
16. Rich JD, McKenzie M, Larney S, Wong JB, Tran L, Clarke J, Noska A, Reddy M, Zaller N. Methadone continuation versus forced withdrawal on incarceration in a combined US prison and jail: a randomised, open-label trial. *Lancet*. 2015; 386(9991):350–359.
17. Magura S, Rosenblum A, Lewis C, Joseph H. The effectiveness of in-jail methadone maintenance. *J Drug Issues*. 1993; 23(1):75–99.14.
18. Liebowitz N. Director of Mental Health Services, Correctional Medical Associates, personal communication. 12/1/2015.
19. Awgu E, Magura S, Rosenblum A. Heroin-dependent inmates' experiences with buprenorphine or methadone maintenance. *J Psychoactive Drugs*. 2010 Sep; 42(3):339–346. [PubMed: 21053756]
20. Fox AD, Maradiaga J, Weiss L, Sanchez J, Starrels J, Cunningham C. Release from incarceration, relapse to opioid use and the potential for buprenorphine maintenance treatment: a qualitative study of the perceptions of former inmates with opioid use disorder. *Addict. Sci Clin Pract*. 2015; 10(2)
21. Andrews G, Peters L. The psychometric properties of the composite international diagnostic interview. *Soc. Psychiatry Psychiatr Epidemiol*. 1998; 33(2):80–88.
22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. fifth2015. Available from: <http://www.psychiatry.org/practice/dsm>
23. Stazesky, R., Hughes, J., Venters, H. Implementation of an Electronic Health Record System in the New York City Jail System, 2012. Issue Paper. 2015. (Available from: <http://www.cochs.org/files/hieconf/implementation-ecw-new-york.pdf>)

24. Kiluk BD, Nich C, Carroll KM. Neurocognitive indicators predict results of an informed-consent quiz among substance-dependent treatment seekers entering a randomized clinical trial. *J Stud Alcohol Drugs*. 2010; 71(5):704–712. [PubMed: 20731975]
25. Harris PA, Taylor R, Theilke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42(2):377–381. [PubMed: 18929686]
26. Lee JD, Grossman E, DiRocco D, Truncali A, Hanley K, Stevens D, et al. Extended-release naltrexone for treatment of alcohol dependence in primary care. *J Subst Abus Treat*. 2010; 39(1): 14–21.
27. Sobell, LC., Sobell, MB. Alcohol Timeline Followback Users' Manual. Addiction Research Foundation; Toronto, Canada: 1995.
28. Cacciola JS, Alterman A, McLellan T, Lin Y, Lynch K. Initial evidence for the reliability and validity of a "Lite" version of the addiction severity index. *Drug Alcohol Depend*. 2007; 87(2–3): 297–302. [PubMed: 17045423]
29. Bray JW, Zarkin GA, Miller WR, Mitra D, Kivlahan DR, Martin DJ, et al. Measuring economic outcomes of alcohol treatment using the economic form 90. *J Stud Alcohol Drug*. 2015; 68(2)
30. Metzger, DS., Navaline, HA., Woody, GE. Assessment of Substance Abuse: HIV Risk Assessment Battery (RAB). 2001. (Available from: <http://www.encyclopedia.com/doc/1G2-3403100069.html>)
31. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychol Med*. 1998; 28:551–558. [PubMed: 9626712]
32. Attkisson, CC.Greenfield, TK., Dickey, B., editors. Outcomes Assessment in clinical practice. Williams and Wilkins; Baltimore, MD: 1996. Client satisfaction questionnaire-8 and service satisfaction scale-30; p. 120-127.
33. Chandler RK, Fletcher B, Volkow ND. Treating drug abuse in the criminal justice system: improving public health and safety. *JAMA*. 2009; 301(2):181–190.
34. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication assisted therapies – tackling the opioid overdose epidemic. *N Engl J Med*. 2014; 370:2063–2066. [PubMed: 24758595]
35. Minton, TD., Zeng, Z. Jail Inmates at Midyear 2014. US Department of Justice, Office of Justice Programs. 2015. (Available from: <http://www.bjs.gov/content/pub/pdf/jim14.pdf>)
36. Carson, EA. Prisoners in 2014. US Department of Justice, Office of Justice Programs. 2015. Available from: <http://www.bjs.gov/content/pub/pdf/p14.pdf>
37. Finlay AK, Harris AH, Rosenthal J, Blue-Howells J, Clark S, McGuire J, Timko C, Frayne SM, Smelson D, Oliva E, Binswanger I. Receipt of pharmacotherapy for opioid use disorder by justice-involved U.S. Veterans Health Administration patients. *Drug Alcohol Depend*. 2016 Mar 1;160:222–226. [PubMed: 26832998]
38. Hicks, J. Jailed Heroin Addicts in Maryland can Get Treatment under New Program. The Washington Post. 2015. Available from: https://www.washingtonpost.com/local/md-politics/jailed-heroin-addicts-in-maryland-can-get-treatment-under-new-program/2015/06/02/ceaa1bcc-0968-11e5-9e39-0db921c47b93_story.html
39. Tabachnick, C. Breaking Good: Vivitrol, a New Drug Given as a Monthly Shot, is Helping Addicts Stay Clean. The Washington Post. 2015. Available from: https://www.washingtonpost.com/lifestyle/magazine/his-last-shot-will-a-monthly-jab-of-a-new-drug-keep-this-addict-out-of-jail/2015/03/05/7f054354-7a4c-11e4-84d4-7c896b90abdc_story.html
40. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2006 Feb; 63(2):210–218. [PubMed: 16461865]

Fig. 1.

Study design. XR-NTX = extended release naltrexone; MTP = methadone treatment program; ETAU = enhanced treatment-as-usual.

Table 1

Schedule of assessments and procedures.

Assessments & interventions (weeks)	Baseline (0/1)	Week 2 (2)	Bi-weekly (3,7,11,15,19,23)	Month 1 (5)	Month 2,4,5 (9,17,21)	Month 3 (13)	Month 6 (25)	Month 7 (29) ^a	Month 12 (52)
Screening									
Informed consent	X								
Inclusion/exclusion	X								
Consent quiz	X	X							
HIV, HCV status	X								
Urine toxicology	X	X	X	X	X	X	X	X	X
Pregnancy test	X			X	X	X			
Research assessments									
Demographics	X								
Timeline Followback	X	X	X	X	X	X	X	X	X
CIDI-II DSM-5 checklist	X			X		X	X	X	X
Risk Assessment Battery	X						X	X	X
Addiction severity index-lite	X					X ^a	X	X ^a	X ^a
Motivation form	X								
Economic form 90	X					X	X	X	X
WHOQOL-BREF	X					X	X	X	X
Methadone Treatment Exposure ^b	X			X	X	X	X	X	X
Craving visual analog scale	X			X	X	X	X	X	X
Opioid quantity usage form	X								
Opioid relapse outcome form				X	X	X	X		
New arrests and days incarcerated				X	X	X	X		X
Treatment satisfaction				X	X	X			
Safety									
Adverse Events	X	X	X	X	X	X	X	X	X
Opioid-overdose AE/SAE		X	X	X	X	X	X	X	X
XR-NTX-specific AE/SAE ^a		X	X	X	X	X	X	X	
Injection-site abnormality AE/SAE ^a				X	X	X			

Assessments & interventions (weeks)	Baseline (0/1)	Week 2 (2)	Bi-weekly (3,7,11,15,19,23)	Month 1 (5)	Month 2,4,5 (9,17,21)	Month 3 (13)	Month 6 (25)	Month 7 (29) ^a	Month 12 (52)
Inmate lookup ^c				X	X	X	X		X
Vital status (NDI) ^c									X
Procedures									
Drug education, treatment referrals, counseling	X								
Naloxone challenge ^a	X								
XR-NTX injection ^a	X			X	X	X			

^aXR-NTX arm only.

^bMTP arm only.

^cIn the event of lost-to-follow-up.

[^]Drug/Alcohol-use section only.