Title: E**x**tended-Release Naltrexone **O**pioid Treatment at Jail **R**e-entry (XOR)

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PROTOCOL OUTLINE

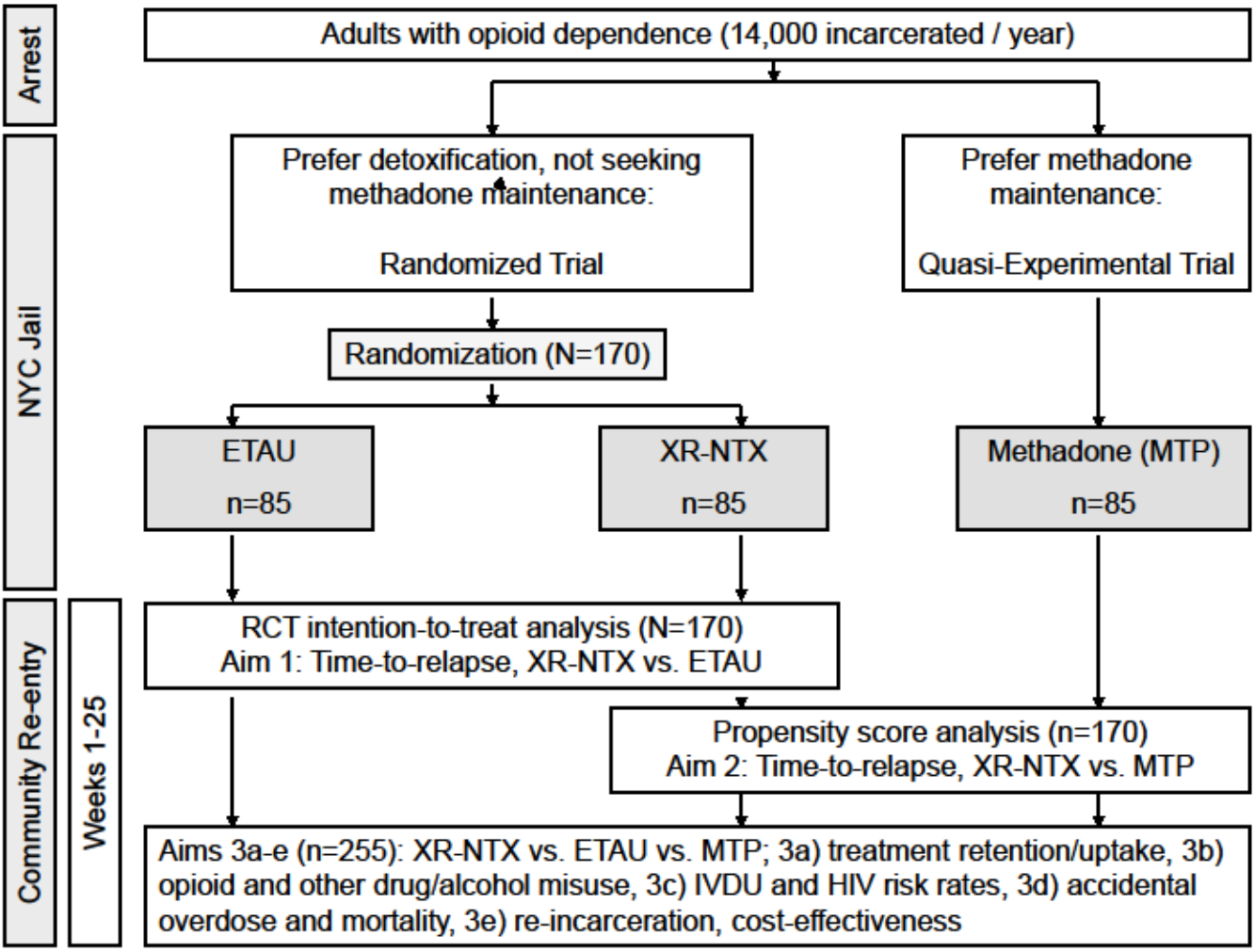
1.0 Rationale

Immediate relapse to drug, alcohol, and tobacco use is a nearly universal and an expected near-term outcome among adults with addiction disorders leaving U.S. jails. Effective jail re-entry addiction treatment strategies are a public health priority.[1,2] Among persons opioid addicted at arrest, the post-incarceration period is marked by extraordinarily high rates of accidental overdose death.[3,4,5,6] Yet while opioid agonist therapies are proven and effective re-entry interventions, many US correctional facilities, including almost all large U.S. municipal jails, do not offer these treatments.[7] However, in New York City (NYC), jail-to-community methadone treatment is, since 1986, a well-studied standard-of-care, yet many inmates eligible to initiate the methadone treatment program (MTP) while incarcerated do not, possibly due to anti-methadone patient preferences.[8,9,10,11] Rather, the vast majority of these jail detainees undergo a brief 6-day methadone taper following arrest, remain in jail for brief periods out-of-treatment while 'drug free' and undergoing a decline in physiologic opioid tolerance, nearly universally relapse to heroin or other illicit opioid use following release, and are re-arrested in the next 12 months at rates of 50-75%.[9,11] Extended-release naltrexone (XR-NTX, Vivitrol), FDA-approved for opioid dependence, produces a 30-day mu opioid receptor antagonist blockade, and offers a potentially promising modality for 'inoculating' persons leaving jails against immediate opioid relapse. Persons injected with 380mg of XR-NTX are unable to effectively experience euphoria or respiratory depression when returning to average doses of illicit opioids for the ensuing 4-5 weeks.[12] An injection prior to release would possibly give the individual a month or so to return home from jail, experience opioid abstinence, and then either continue XR-NTX, initiate agonist or behavioral treatments, or, resume a significantly postponed relapse to illicit use. Our team recently established the feasibility of administering XR-NTX to opioid dependent adults within a week of release in NYC jails.[13] We are now conducting a large randomized controlled trial estimating the effectiveness of XR-NTX as opioid treatment at release from jail with enhanced counseling and referrals vs. an enhanced treatment-as-usual (ETAU) condition receiving counseling and referrals only. We also will recruit a non-randomized, quasi-experimental methadone maintenance treatment program (MTP) cohort followed for a naturalistic comparison of XR-NTX to a jail-based methadone standard-of-care. Similar to the randomized treatment arms, the MTP cohort will also receive enhanced counseling and referrals.

Specific Aim 1: Randomized Effectiveness Trial of XR-NTX vs. ETAU for Jail-to-Community Re-Entry Opioid Relapse Prevention. Our primary aim is to compare time-to-relapse among participants treated with XR-NTX vs. randomized ETAU controls, following release from jail.
Specific Aim 2: Quasi-Experimental Comparison of XR-NTX vs. a Methadone Treatment Program (MTP) for Re-Entry Opioid Relapse Prevention. To compare time-to-relapse among the XR-NTX RCT arm vs. jail-based MTP participants using a quasi-experimental design.
Specific Aim 3a-e: Related Opioid Treatment Outcomes. To compare re-entry rates of 5 treatment outcomes across all arms: 3a) retention in any study or community opioid treatment modality, 3b) any opioid and other illicit drug or alcohol use, defined as continuous counts of both days, amount/day, and urine toxicologies, 3c) injection drug use and HIV sexual risk factors, 3d) accidental drug overdose and mortality, and, 3e) rates of re-incarceration and an exploratory analysis of cost-effectiveness.

This study is a NIH/NIDA-funded randomized trial of XR-NTX (n=85) vs. ETAU (n=85) among opioid dependent adults leaving NYC jails who explicitly reject agonist treatment. Initiating treatment the week prior to release and continuing for 24 weeks post-release, we hypothesize the XR-NTX arm will demonstrate significantly longer time-to-relapse vs. ETAU. In parallel, we will recruit a matched, quasi-experimental methadone cohort (n=85), which will result in a naturalistic comparison of XR-NTX vs. an established jail-based MTP standard-of-care.

Study Schema



1.1 The NIDA Studies of Medication for Addiction Treatment in Correctional Settings (SOMATICS) U01 Collaborative

Our distinct NIH-funded study at NYU has been aligned with two other jail-based opioid treatment studies conducted by researchers at Friends Research Institute (FRI) in Baltimore, MD, and at UCLA. Led by the NIDA Science Officer, Redonna Chandler, PhD, SOMATICS seeks to harmonize assessments and interventions across 3 research centers (RCs) and the 3 independent studies in order to leverage power, sample size, and increase the generalizability of findings. Each of the RCs in the SOMATICS cooperative will conduct their own individual trial, sharing one study arm with another RC, and several core assessments across all sites. The SOMATIC Statistical Analysis Plan and common DSMP including a single DSMB are described in the Appendix.

In brief, the individual study designs are:

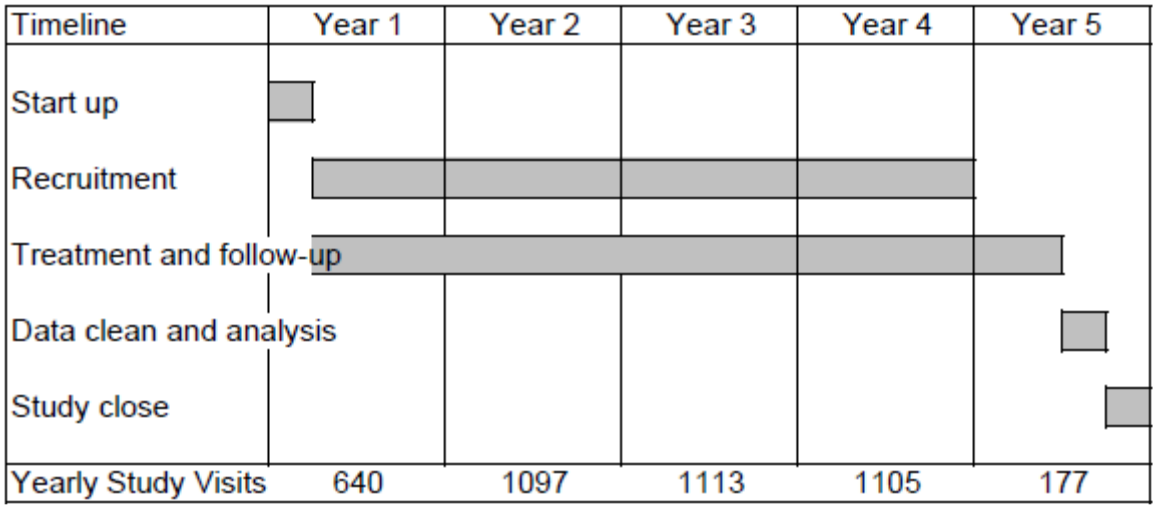
FRI: This is a 3-group randomized clinical trial in which 300 opioid-dependent adults (150 males and 150 females) being treated for opioid withdrawal in the Baltimore City jail will be randomly assigned to receive: (1) interim methadone with patient navigation (IM+PN); (2) IM without Patient Navigation (IM alone); (3) or brief methadone detoxification with drug education/overdose prevention which constitutes an enhanced treatment as usual (ETAU) condition. Participants will be assessed at baseline, and 1-, 3-, 6-, and

12-months post-release to determine: entry and retention in treatment post-release; illicit opioid and cocaine use; DSM-V criteria for opioid and cocaine dependence; criminal behavior, arrests, incarceration, and changes in HIV risk behavior. A cost-effectiveness and cost-benefits analysis will be conducted to provide policymakers with data needed for evidence-based decision making.

UCLA: Opioid dependent participants (N=150) in the Albuquerque, NM, municipal jail will be randomly assigned to a 6-month intervention condition of XR-NTX (n=50), XR-NTX + Patient Navigation (N=50), and ETAU (n=50); all participants will also be provided a toll-free number that will help them locate psychosocial treatment in the community. In addition to bi-weekly urine tests and medical management during the 6-month intervention-phase of the trial, participants will participate in extensive assessments at baseline, 1, 3, 6, and 12 months post-release. Illicit opioid and other drug-use post release will be assessed with bi-weekly urine toxicology tests and self-report use measures during the 24 week treatment phase of the trial for the purposes of assessing a time-to-relapse primary outcome for this individual study. Outcomes include opioid use (and use of other substances), meeting DSM-5 criteria for opioid use disorder at 24 weeks (the primary SOMATICS outcome), criminal activity, and economic benefits associated with the three conditions. The cost analysis will measure and value resources associated with XR-NTX, including medical personnel (physician/nurses), labs, and medications. To ascertain cost-effectiveness ratios of XR-NTX and XR-NTX + PN, cost data will be compared to changes in key clinical measures of effectiveness.

NYU: As described above, a randomized clinical trial of extended-release naltrexone (XR-NTX) (n=85) vs. a no medication, enhanced treatment-as-usual (ETAU) condition (n=85), with an additional quasi-experimental methadone maintenance treatment program (MTP) cohort (n=85), followed for a time-to-relapse primary outcome.

2.0 Study Timeline: An NIDA notice of grant award was issued on May 21, 2013, award number: U01-DA033336. We have now completed the start-up phase during which we completed protocol approval, hired study personnel, assembled study supplies including a free study drug contract with Alkermes, and completed local SOPs. Recruitment of 255 enrolled and randomized participants will take place over 3.5 years, or approximately 5-7 participants randomized (3-4 randomized to XR-NTX vs. ETAU RCT; 2-3 IM observational participants) every 4 weeks and followed for 29 weeks, for a maximum of 42 participants active in study treatment per month. The final 6 months of Year 4 will be devoted to the tail end of study visits, data cleaning and analysis, study close out, preparation of initial manuscripts, and dissemination and national presentations of results.



3.0 Introduction

3.1 Significance, Innovation, and Public Health Impact

The significance of this study derives from a national priority to evaluate and implement effective addiction treatment in U.S. jails and prisons. Clearly correctional settings cluster addicted persons, including heroin and prescription opioid dependent individuals. Historically, little to no evidence-based treatment has been offered during arrest, pre-trial detention, and incarceration, particularly in the high turnover, short stay environments of municipal jails, where most persons are awaiting trial and not convicted of a crime (detainees) or serving a brief sentence (misdemeanor conviction), as opposed to persons incarcerated for one year or longer in a state or federal prison (felony conviction). While persons can and do access illicit opioids and other drugs during incarceration, for the most part jail detainees are awaiting release while idle, opioid-free, and without plans for further community drug treatment. This is an ideal opportunity to induce opioid dependent individuals onto XR-NTX therapy, prior to release and during the initial phase of community re-entry, a strategy that has previously been applied in NIDA studies to the then well-known opioid agonists, methadone and buprenorphine.[8,37] The expected benefits are lower rates of and longer times until relapse to opioid misuse, with an attendant lower risk of post-release opioid overdose. No current or previous XR-NTX trial has implemented therapy in a jail (or prison) setting, including no actively funded NIDA studies, or compared XR-NTX to ETAU and MTP standards-of-care, as proposed in this study.

The innovation of this study necessarily overlaps with the overall significance and approach: a definitive randomized evaluation of a new extended-release mu opioid receptor antagonist during jail-to-community re-entry (Figure 2). Additionally, the above described and well-established NYC jail-based methadone treatment program (MTP), the Key Extended Entry Program (KEEP), creates a unique opportunity for a naturalistic, quasi-experimental comparison of arrestees initially selecting MTP vs. those not interested in MTP and who are later randomized to XR-NTX, a comparison not available in other XR-NTX clinical trials. Finally, XR-NTX is delivered in a simple, generalizable, primary care Medical Management (MM) model, first in the jail, then within a city public hospital and patient-centered medical home. While re-entry buprenorphine treatment has been evaluated in this same MM model by our site,[14] it has not yet been applied to XR-NTX.

Public Health Impact: while there is growing interest in the newly approved use of XR-NTX for opioid treatment, its effectiveness has not been evaluated in any correctional facilities, including large municipal jails, vs. usual care, nor in the context of standard-of-care methadone treatment. This study will allow providers, correctional and public health authorities, including our collaborators at the NYC Department of Health and Mental Hygiene, and payers and policy makers to assess the utility of XR-NTX as re-entry opioid treatment, with important implications for limiting the greater public safety and societal costs of heroin and prescription opioid addictions. Further, NYC jail inmates are predominantly African American and Hispanic, and represent communities disproportionately affected by unemployment, family poverty, HIV and hepatitis C, all downstream effects of opioid dependence. As the majority of opioid addicted persons leave jail they inevitably return to their neighborhoods untreated and prone to rapid relapse. We hypothesize adding XR-NTX to the re-entry 'toolbox' will save both money and lives in these underserved communities.

3.2 Research areas and NIDA priorities: effectiveness studies in criminal justice settings

The NYC jail population is low income, predominantly unemployed, of low educational attainment, primarily African American and Hispanic, and suffers from opioid dependence at a higher documented rate than any other chronic health condition. This study focuses on an intervention opportunity that directly relates to key NIH and NIDA priorities, described in the 2010 Strategic Plan, including treatment and "effectiveness research" which "optimize[s] strategies for disseminating and implementing research-based treatments in health care and criminal justice settings"), HIV/AIDS and communicable disease prevention, and cross-cutting priorities including limiting the depth and adverse impact of health disparities.[15]

3.3 Large urban jails: a continuous, high-volume sampling of untreated opioid dependent individuals

U.S. municipal jails have essentially no mandate and little capability to provide addiction treatment to the high turnover of short-stay detainees and inmates, as opposed to prisons (>1 year incarceration following a felony conviction), parole or probation programs (supervised community sentencing), or

alternative to incarceration programs such as drug courts explicitly designed as addiction interventions.[16] These other spheres of the 7.1 million-person (2010) criminal justice system have some explicit intention of reform and rehabilitation, whereas jails function primarily as holding facilities pending the outcome of a criminal trial, or for brief, misdemeanor incarcerations. While approximately 762,000 persons are detained overnight in U.S. jails, they are in jails such as NYC's for a mean of only 3-4 days, producing around 6 million individual jail discharges back to the community annually; of 2.1 million persons in U.S. state and federal prisons held for 2-3 years on average, approximately 800,000 return to the community annually.[17]

Recent national surveys make clear that evidence-based opioid pharmacotherapies are rarely offered to detained and incarcerated opioid dependent patients.[18,7] Many factors contribute to this, including unfavorable patient, health provider, and criminal justice system (CJS) authority attitudes towards methadone and buprenorphine treatment, and a lack of resources and poor coordination between correctional and community addiction treatment programs. XR-NTX, which is not a controlled substance, has no abuse liability and is adaptable to general medicine and general psychiatric correctional and community treatment settings, may be an acceptable alternative pharmacologic paradigm in correctional systems resistant to methadone or buprenorphine and/or concerned with diversion of these medications.[19]

3.4 Public health opportunities: opioid dependence prevalence and overdose mortality

Opioid dependence remains a leading cause of addiction-related morbidity and mortality in New York City and other large U.S. urban centers, particularly among poor and minority populations. In NYC, there are an estimated 115,459 (range, 104,236-126,681) current heroin and other opioid misusers, an estimate that likely undercounts prescription opioid misuse.[20] Opioid dependence is the most common chronic health condition diagnosed and treated across the entire male and female adult jail population in NYC, with an estimated 10-20% of the annual jail population self-reporting dependence at arrest or currently in opioid treatment.[11] Accidental opioid overdose death, HIV and hepatitis C transmission, criminal involvement, high healthcare costs, lost productivity, and the destruction of family and community health are among the harsh consequences of opioid addiction. Release from a correctional facility, when a person has usually been confined involuntarily to a drug free state and reverted to a lower physiologic tolerance to mu receptor agonists, has long been understood as an important risk factor for accidental drug overdose and drug-related mortality.[3-6] The prevention of overdose following release from NYC jails is a high priority of this study's collaborative partner, the NYC Department of Health and Mental Hygiene (DOHMH), as overdose mortality is a persistent and preventable cause of early mortality and the 3rd and 4th leading cause of death among New Yorkers aged 25-34 yrs. and 35-54 yrs., respectively.[21,22]

3.5 Evidence-based opioid treatment in jails: methadone maintenance does not seem to be enough

In NYC jails, the setting of this study, a jail-based methadone treatment program (MTP) has been the standard of care since 1986, yet the vast majority of eligible opioid dependent inmates do not elect to receive MTP during incarceration. In 2010, approximately 12,000 persons were treated for opioid dependence in NYC jails. Most (8000, 67%) were treated with a brief methadone detoxification protocol, meaning they were opioid (usually heroin) dependent but not interested in or eligible for further MTP.[23,11] The remaining 4000 persons were able to access MTP in jail through the Key Extended Entry Program (KEEP), the NYC jail MTP, either because they were community MTP patients at arrest, or newly initiated MTP during their incarceration. Based on previous analyses, the majority of jail MTP patients return to community MTP, while the bulk of the 8000 detox-only individuals quickly relapsed to heroin use,[9,10,11] a predictable post-release outcome observed elsewhere.[24,25] Why don't more jailed individuals choose methadone? Commonly cited biases against methadone include concerns about long-term side effects and the perceived restrictions of community MTPs (i.e., directly observed therapy).[26,27,28,29] Thus, even when MTP is routinely available in a large urban jail, too few inmates benefit. Research targeting alternative medications such as XR-NTX is clearly needed, particularly among persons not eligible or interested in opioid agonist treatments.

3.6 Sustained opioid antagonist blockade during jail-to-community re-entry

Extended-release naltrexone (XR-NTX) is a depot form of the mu opioid receptor antagonist that, while untested in pre-release incarcerated persons, has shown potential as community opioid treatment and among community-dwelling criminal justice populations.[30,31,32] XR-NTX vs. placebo for opioid treatment in the recent Krupitsky pivotal trial showed robust treatment effect vs. placebo in terms of percent negative urines over time and prevention of sustained opioid relapse, while noting few safety concerns and no serious adverse events or deaths. This trial follows studies of oral naltrexone, which has been shown to be efficacious in tightly controlled trials with high medication adherence, but ineffectiveness as community and CJS-focused treatment, due to low rates of daily medication adherence, relapse to opioid use, and difficulties re-starting naltrexone antagonism thereafter.[33,34,35] XR-NTX, however, neatly solves the oral naltrexone adherence issues with, in the case of Vivitrol (Alkermes, Inc., Cambridge, MA), a depot, long-acting polylactide-co-glycolide microcapsule formulation.[36] Following an XR-NTX injection, a patient has a 4-week period when the use of heroin or other opioids at normal illicit levels is unable to produce the expected euphoria or re-establish opioid tolerance.[12] This sustained naltrexone blockade would potentially give persons leaving jail, who usually lack significant social support, stable housing, or employment, the time to make constructive decisions regarding further community treatment, including continuing XR-NTX treatment, initiating methadone or buprenorphine therapy as the naltrexone e blockade wears off, or becoming involved in an intensive outpatient or residential program.

In this current study, the jail-based population is often released to the community with little to no supervision, unlike parolees being released from prison. Parolees would be particularly invested in avoiding opioid relapse due to legal supervision and the threat of drug-related parole violations. Further, parolees are typically mandated to on-going drug treatment as a condition of their parole. In this current study, potential participants are not necessarily parole-involved (some may be), have essentially been involuntarily detoxed as a consequence of incarceration, likely have not experienced any recent abstinence prior to incarceration, and, if not parole-involved, typically have no external CJS pressure to pursue drug treatment and opioid-free or medication-assisted recovery. The average opioid user leaving jail is therefore much more at risk for opioid relapse than the average opioid user leaving prison, and the potential benefit of XR-NTX is therefore that much greater in the current study. Further, the Rikers Island (NYC jails) setting allows a naturalistic comparison to jail-based MTP that is not found in any other published or on-going evaluation of XR-NTX, providing a unique and innovative setting to this study.

3.7 Preliminary NYUMC studies of opioid treatment and XR-NTX in jail and CJS populations

We have extensive experience conducting opioid pharmacotherapy trials in the NYC jails and among re-entry populations at NYU/Bellevue, as well as XR-NTX delivered in a Medical Management model:

1. Buprenorphine vs. Methadone at Jail Re-entry in NYC, 2006-2008 (R21-DA020583, MaguraS)
2. XR-NTX Among Parolees and Probationers, 2007-2014 (Dana Foundation, DA024555, LeeJD)
3. XR-NTX NYC Jail Pre-release Pilot Study, 2010-2012 (NYUMC Seed Grant, LeeJD)
4. XR-NTX and Primary Care Medical Management (NYUMC, GourevitchM, LeeJD)

1. Buprenorphine vs. Methadone at Jail Re-entry in NYC (R21-DA020583, MaguraS). Collaborating with the lead investigators, Drs. Steven Magura and Andrew Rosenblum at the National Development and Research Institute, we evaluated buprenorphine vs. standard-of-care methadone maintenance within a recently conducted, NIDA-funded RCT design. Dr. Lee was a co-investigator on this trial, and our NYU/Bellevue team and primary care buprenorphine clinic provided the bulk of the re-entry buprenorphine treatment in this N=133, 2-year study, which found higher re-entry treatment retention in the buprenorphine arm, as well as longitudinal treatment outcomes similar to those of community-referred buprenorphine patients.[37] Overall, 48 of 181 eligible persons refused participation, with few individuals (n=23) stating no interest in a clinical trial, thus demonstrating on a scale similar to the proposed study the feasibility of recruiting and enrolling 300 opioid dependent persons detained in the NYC jails over 3.5 years. Subjects were primarily African American (25%) or Hispanic (64%); all were heroin users. Following release of 126 of the 133 randomized participants, 35 persons were lost-to-follow-up, yielding a 72% retention rate through 3 months post-release in a modestly budgeted R21 study. Of note, incentives for monthly post-release

follow-up were more limited than proposed herein, and we therefore anticipate higher post-release follow-up rates among participants in the current study. Further, this study helped solidify our on-going collaboration with NYC DOHMH and KEEP staff, and also modeled recruitment of a methadone cohort.

2. XR-NTX among Parolees (Dana Foundation and DA024555, LeeJD). A completed N=9 observational, single-arm pilot of community-dwelling parolees and probationers treated with 3 months of XR-NTX followed by 3 months of drug-free follow-up was conducted to establish feasibility of XR-NTX opioid treatment among community-dwelling, CJS-involved persons. This pilot was conducted in parallel at 5 other sites, and demonstrated significantly less opioid use among participants retained on XR-NTX vs. treatment drop-outs.[32] These same sites then initiated the current NIDA RCT of XR-NTX vs. TAU in parolees/probationers, DA024555 (lead site, Univ. Pennsylvania, O'Brien C; NCT00781898). This 2009-2014 N=400 study is on-going, and the NYU/Bellevue site has been able to recruit and retain participants at a robust pace, in step with our completed recruitment rate (80 of 80 participants randomized) and slightly faster than the 4 other sites. These and other studies have established the core mechanics of XR-NTX clinical trials at NYU/Bellevue, and have documented the feasibility of XR-NTX among populations similar to that targeted by the current study.

3. XR-NTX NYC Jail Pilot Study, 2010-2012 (NYU School of Medicine, LeeJD). This completed pilot, funded by a small NYU School of Medicine seed grant, additional Department of Medicine support, and free study drug donated by Alkermes, closely collaborated with co-investigators at NYC DOHMH, and recruited persons to an 8-week pilot RCT of XR-NTX vs. Treatment As Usual (TAU) among opioid dependent adults leaving jail and explicitly not interested in agonist treatment.[13] Active recruitment began in January 2010 with the final study visits ending in July 2013. Overall, 142 persons were pre-screened, 48 consented participants, and 34 (17 to XR-NTX; 17 to TAU) were randomized. Results showed that acceptability of XR-NTX injections was high (15 of 17 participants received a first injection). 4-week post-release opioid relapse rates were lower among XR-NTX participants: 38% vs. 88% ($p<0.004$). Over 8 weeks, a greater proportion of urines were negative for opioids in the XR-NTX arm, 59% vs. 24% ($p<0.0001$). There were no overdose events or deaths.

The inclusion and randomization procedures in this pilot were essentially the same as that of the current study's RCT; all participants were out-of-treatment at arrest, not interested in methadone or buprenorphine treatment at release, and using 5-15 bags/day heroin, illicit daily 'street' methadone plus heroin, or heroin plus oxycodone/hydrocodone at arrest. All participants had opioid positive urine at admission to jail and requested a brief, 6-day methadone detox (10mg by mouth daily x 3 days, 5mg x 3 days). All were subsequently opioid negative when randomized. This study has allowed our team to explore and resolve a number of key feasibility issues: IRB and FDA IND approval for a study of XR-NTX (initially pre-FDA approval) among prisoners, identification and recruitment of potentially eligible participants, acceptability of study procedures, including naloxone challenges and XR-NTX injections in the jail medical clinics, and a high likelihood of post-release follow-up at NYU/Bellevue. Thus, as a proof-of-concept effort, this trial established the feasibility of XR-NTX treatment in a jail setting with a high prevalence of opioid dependence.

4. XR-NTX and Primary Care Medical Management. The psychosocial components of XR-NTX treatment proposed in this trial are those of Medical Management (MM), a simple, office-based approach to addiction pharmacotherapy designed for use in general care settings. MM, commonly included in clinical trials of addiction medications, including the COMBINE and Garbutt XR-NTX alcohol efficacy trials, focuses on patient education regarding the participant's addiction diagnosis, medication adherence, medication side effects and barriers to adherence, and psychosocial support for recovery and the uptake of related resources (i.e., intensive outpatient treatment or 12-step involvement).[38,39] We have studied MM as a feasible and likely effective approach to XR-NTX alcohol treatment, in a novel observational trial of 3 months of XR-NTX primary care MM among 72 adult alcohol dependent patients,[40] and in the above community and CJS-focused trials of XR-NTX and buprenorphine opioid treatment.[32,37,41,42] Over the last 5 years we have administered approximately 300 XR-NTX injections within an MM model and are confident of its safety, ease-of-use, and potential for dissemination.

3.8 Investigative Team Roles and Study Management

Dr. Lee will oversee all aspects of the study. Drs. Lee and Laska will conduct the analyses of the primary and secondary effectiveness outcomes, based on the dataset collected and managed by James Robinson and Chris Torgersen. Dr. Rotrosen, also a senior mentor to Dr. Lee and Director of the former Addiction Center of Excellence (COE) and NIDA CTN NY Node will assist in all aspects of the design and conduct of the study.

Dr. Lee will be in daily contact with the Project Manager, Research Coordinators, and study clinicians. Weekly meetings will bring together core staff to trouble-shoot study implementation and daily management. Monthly conference calls will bring together all of the key personnel to discuss study conduct and eventual analysis and manuscript preparation. Separately, Dr. Lee will meet monthly or more frequently, depending on the study phase, with Dr. Laska, James Robinson and Chris Torgersen regarding data management and analysis. Laska and Robinson, while at the Nathan Kline Institute in Rockland County, NY, are busy collaborators with on-going NYU CTSI and CTN studies and are available for regular in-person meetings on the NYUMC campus, while Mr. Torgersen is easily accessible working on the NYULMC campus.

4.0 Study Aims

4.1 Primary Aim 1: Our primary aim is to compare time-to-relapse among participants treated with XR-NTX vs. randomized ETAU, following release from jail.
Hypothesis: We hypothesize XR-NTX will be associated with a significantly longer time-to-relapse vs. ETAU controls.

4.2 Secondary Aim 2: Time-to-relapse between XR-NTX vs. methadone (MTP).
Hypothesis: We hypothesize XR-NTX will be associated with an equivalent time-to-relapse curve compared to the MTP observational cohort.

4.3 Secondary Aims 3a-e: Specific Aim 3a-e: Related Opioid Treatment Outcomes. To compare re-entry rates of 5 key outcomes across all arms (XR-NTX, ETAU, MTP): 3a) community treatment retention/initiation, 3b) any opioid, alcohol, or other illicit drug misuse, defined as continuous counts of both days, amount/day, and urine toxicologies for heroin or other illicit opioid and other drug use, 3c) injection drug use and HIV sexual risk factors, 3d) accidental drug overdose and mortality, and, 3e) re-incarceration and exploratory cost-effectiveness.
Hypothesis: We hypothesize the XR-NTX participants will report less continuous opioid, alcohol, and other illicit drug misuse, injection drug use and HIV risk, and accidental drug overdose events compared to ETAU participants, and similar rates to those of MTP participants. We do not hypothesize a difference in re-incarceration rates over the 24-week treatment phase.

4.4 Secondary Aims 4a-e: Qualitative interview aims: a) Themes on social barriers to "successful" jail-to-community re-entry; b) Themes on social facilitators of "successful" jail-to-community re-entry; c) Themes on treatment barriers to "successful" jail-to-community re-entry; d) Themes on community treatment facilitators of "successful" jail-to-community re-entry; e) Other factors surrounding relapse or abstinence since release.

5.0 Study Design: A randomized trial of XR-NTX vs. ETAU as jail-to-community re-entry opioid treatment and a quasi-experimental comparison of XR-NTX vs. MTP

The core of this study is a randomized controlled trial of XR-NTX vs. ETAU for prevention of post-release opioid relapse among opioid dependent adults not seeking agonist treatment who are leaving NYC jails, N=170 participants followed for 25 weeks in order to provide robust, long-term effectiveness data. ETAU participants will receive 'enhanced counseling' and community treatment referrals in order to provide study benefit beyond usual care, and will consist of psychosocial support, referrals to community treatment, and encouragement to pursue methadone, buprenorphine, or any other appropriate addiction treatment at

release. A cohort of MTP participants will form a quasi-experimental comparison between XR-NTX and MTP, with prospective and propensity score matching used to account for baseline non-equivalence between the two arms

5.1 Qualitative Interviews: In addition to the primary study design above, the research team will conduct semi-structured qualitative interviews with a sub-set of participants randomized into the study. Participants who are successfully randomized into the study and who specifically agree to participate in a qualitative interview by indicating as such on the primary consent form may be asked to participate in one or more audio-recorded interview(s) conducted 2 weeks (or at later time points) after release from jail. Interviews will last about 10-15 minutes. We are interested in the personal accounts of individuals who have experienced community re-entry, to shed light on barriers and facilitators of successful community reintegration. We will also describe these obstacles and promoters of success in terms of substance use and incarceration history.

6.0 Study Population

6.1 Inclusion/Exclusion Criteria for Randomized groups only (XR-NTX, ETAU):

Inclusion criteria

1) Adults ≥18yo incarcerated in NYC jails with known release dates.
2) DSM-V criteria for current opioid use disorder (DSM-IV opioid dependence).
3) Not currently in or planning to pursue agonist (methadone, buprenorphine) treatment at release.
4) Currently opioid free by history ('detoxed') and with a negative urine for all opioids.
5) General good health as determined by medical evaluation.

Exclusion criteria:

1) Pregnancy, lactation, or planning conception.
2) Active medical illness (i.e., severe liver disease, congestive heart failure) precluding safe participation.
3) Untreated or poorly controlled psychiatric disorder precluding safe participation.
4) History of allergic reaction to naltrexone.
5) Current chronic pain condition treated with opioids.

For an observational comparison of XR-NTX vs. MTP, a third arm of pre-release MTP patients who are not otherwise eligible for XR-NTX treatment will be recruited and be prospectively matched to XR-NTX subjects in an effort to increase the baseline similarity of the two cohorts (below). These persons will be eligible based on a separate set of inclusion/exclusion criteria listed below.

6.2 **Inclusion/Exclusion Criteria for Non-randomized Methadone group only (MTP)**:

Inclusion criteria:

1) Adults ≥18yo incarcerated in NYC jails with known release dates.
2) DSM-V criteria for current opioid use disorder (DSM-IV opioid dependence).
3) Currently receiving regular methadone maintenance treatment through KEEP.
4) General good health as determined by medical evaluation.

6.2 Exclusion criteria:

1) Pregnancy, lactation, or planning conception.
2) Active medical illness (i.e., severe liver disease, congestive heart failure) precluding safe participation.
3) Untreated or poorly controlled psychiatric disorder precluding safe participation.
4) In community methadone treatment program at the time of most recent arrest.

7.0 Study Procedures

7.1 Recruitment and Pre-screening

Persons with known Department of Corrections release dates and recent or on-going opioid treatment are clustered into two NYC jail facilities, both on Rikers Island; one male (Eric M. Taylor Center), one female

(Rose M. Singer Center). NYULMC study staff with Department of Health and Mental Hygiene (DOHMH) clinical credentials and DOHMH-approved access to Rikers electronic medical record database (EMR) will search for opioid dependent diagnoses and pending release dates of potential participants located in these housing units. They will then approach the potentially eligible persons through a scheduled meeting in the jail's clinic. It is here that study staff will first introduce the study and assess each person's eligibility and interest in participation. A one-page handout explaining detailed information about the study medication (XR-NTX) will be handed out by research staff to all potential randomized arm participants who appear eligible and express interest after the initial scheduled meeting with research staff. The study team will receive IRB-approval for this informational handout prior to distributing. In order to receive EMR access research coordinators will complete all DOHMH Volunteer Staff Application Forms. This includes a signed agreement between the research coordinator and DOHMH regarding the protection of patient privacy and any medical information obtained from EMR's or in any other form while at a DOHMH facility. The primary investigator of the study, Dr. Lee, is a credentialed Rikers physician and provider in the system with full EMR access. Potentially eligible patients will then be informed of study purposes and procedures and invited to participate in screening assessments. In addition, outreach and education efforts adapted from previous NYC jail opioid treatment trials, including flyers, pamphlets, and announcements within specific housing areas and detailing of opioid treatment program staff will be used to interest potential participants.

Oversampling of women and children. Women and children age 18-21 years are a small sub-sample of the overall populations of opioid dependent persons in NYC jails general adult population (age 18+). For example the youngest participant in our current jail pilot is 28 y.o., while our jail buprenorphine RCT's youngest participant was 31 y.o. Women constitute only 10-15% of the general jail population. We are planning on oversampling both groups, women and persons age 18-21 y.o., through the above prescreening process, with an overall goal of 20% women and 10% persons age 18-21 y.o., equally distributed across all arms.

7.2 Screening and Randomization

Potential participants will meet with study staff to learn about study procedures, XR-NTX treatment, and follow-up protocols. A pre-screen checklist will evaluate eligibility. Written informed consent including a consent quiz adapted from the parent grant protocol will be used to document informed consent. A screening/baseline visit will be conducted by research staff and a study clinician to determine eligibility. Eligible persons will then be randomized using consecutive pre-numbered envelopes containing treatment assignments based on a random number generator.

Illiterate participants

In accordance with NYU policy and procedures for research that involves greater than minimal risk, study staff will take great care ensuring participants that are unable to read a written consent form (i.e. blind or illiterate participants) are able to provide full consent from an oral consent process. In such cases, study staff will read the consent form out loud to the participant and the participant will be given adequate opportunity to ask questions. Participant consent will be acknowledged, provided the participant (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally and (2) is able to indicate approval or disapproval to study entry. If capable of doing so, the participant will sign, or marks an "X" to signify consent. If that is not possible, the participant will provide verbal consent. The study staff obtaining consent and a witness will sign the written study consent form to acknowledge that an oral process was used and, if necessary, that the participant gave oral consent. In addition, the consent process will be documented in the participant's medical record and signed copies of the consent form will be given to the participant. Although, audio and/or video tape of this oral consent process would be ideal, neither will be possible in this type of recruitment setting as electronic equipment are not allowed in DOC jail facilities. Similarly, the consent quiz will be read aloud to the participant. If possible, the participant will make a mark ("X") to signify "True" or "False" as their answer to each consent quiz question. If that is not possible, the participant will provide a verbal answer to each question. The study staff obtaining consent and a witness will sign the written consent quiz to acknowledge that an oral process was used to obtain the participant's consent quiz answers. For subjects that

understand English, but do not read or write English well, or at all, again the study staff obtaining consent and an impartial witness will document that the participant understands the research and the consent process and consented to participate.

7.3 Study Interventions: RCT XR-NTX and ETAU Arms

Extended-Release Naltrexone (XR-NTX) Medical Management Treatment. Participants randomized to XR-NTX treatment will be scheduled for an injection visit within the week of their scheduled release, so as to maximize the time post-release that the naltrexone dose is active. Using an identical treatment protocol to that currently employed by the pilot jail study and DA024555, the participant must report no recent opioid use, provide a second opioid negative urine, undergo a 'naloxone challenge' consisting of a 0.8mg SC or intramuscular naloxone challenge, only after which, if no opioid withdrawal symptoms are present, a single 380mg XR-NTX dose will be administered intramuscularly to the right upper outer gluteus by the a trained study physician, physician assistant, or registered nurse.

The injection site and any side effects will be assessed during the final week of incarceration as needed and at the initial post-release follow-up visit. Five subsequent XR-NTX injections will be provided in 4-week intervals at Bellevue Hospital Center in Manhattan. In the event of a participant missing a scheduled dose by more than one week, study staff will attempt to reschedule the injection provided the participant remains opioid free by self-report and urine toxicology and has a negative naloxone re-challenge, as per standard protocols.[32] Participants relapsing to opioid use will be offered rescue treatments (below). In addition to physician MM, XR-NTX participants will receive brief, 2-session enhancement counseling and a patient-drug educational handout with referrals to re-entry community treatment delivered by a trained Research Coordinator. This counseling intervention will exceed standard of care jail services and will be common across all study arms.

The 25-week XR-NTX treatment phase (24-weeks post-release) will constitute the active phase of the trial, and mark the end-point for the primary outcome, time-to-relapse. Thereafter, all participants, including XR-NTX participants, will be followed for an additional 4 week post-treatment follow-up period, which will allow us to gather data on immediate post-XR-NTX safety and treatment outcomes (opioid relapse, AEs, and other treatment uptake). XR-NTX participants will be prompted by the study clinician prior to and at the final injection visit to plan for the discontinuation of the medication and to consider appropriate aftercare. Lastly, all participants will return for follow-up study visits at week 52 (12 months post-release), and 104 (24 months post-release) in conjunction with the NIDA SOMATICS U01 collaborative. This will allow study staff to gather data on opioid use and relapse over a 6-month period following the active XR-NTX treatment phase.

Enhanced Treatment-As-Usual (ETAU). The ETAU assignment will include brief, 2-session enhancement counseling centered on post-release treatment involvement and a patient-drug educational handout with direct referrals to re-entry community treatment, including agonist maintenance (methadone and buprenorphine programs), drug-free outpatient and 12-step resources, and residential treatment including supportive housing programs. These counseling and referral efforts are designed to exceed standard, out-of-treatment experiences, and will ensure both randomized arms of the trial are offered tangible health benefits above and beyond that of the usual jail incarceration period in accordance with DHS prisoner research standards. Behavioral counseling by the same study clinicians will be primary care psychosocial counseling, essentially a SBIRT-like primary care counseling session focused on behavior change and treatment engagement. Referrals will be coordinated by the study clinician, research coordinator, and existing re-entry treatment and counseling services available to all soon-to-be-released inmates. Counseling and aftercare referral resources will continue at the initial and monthly post-release treatment visits.

7.4 *Quasi-experimental methadone cohort (MTP).*

In an effort to recruit comparable MTP and XR-NTX cohorts, we plan on a prospective matching strategy, in addition to post-hoc propensity score matching, to interpret outcomes in both arms. Each potential participant will be characterized by baseline characteristics likely to confound the primary outcome of time-to-relapse: 1) gender, 2) age (within +/- 5 years), 3) homelessness (yes/no), 4) level of opioid use

prior to arrest (</≥10 bags/day), 5) current IV use (yes/no), 6) pre-arrest cocaine misuse (yes/no), and 7) pre-arrest alcohol and/or benzodiazepine misuse (yes/no). These variables are routinely available for all arrestees identified at intake as opioid dependent within the jail's EMR system. Following the randomization of an XR-NTX participant, a 1:1 XR-NTX:MTP matching algorithm will attempt to recruit the most similar potentially eligible methadone participant (up to 7 of 7 baseline criteria matching, with a minimum of both age and gender matching) in real-time. Prospective matching in addition to post-hoc propensity score matching (PSM, below) is possibly superior to PSM alone within quasi-experimental designs.[43,44]

The jail-based methadone treatment program procedures, daily dose levels and community methadone treatment referrals will be per standard KEEP protocols and not proscribed or directly provided by the study. Similar to XR-NTX and ETAU, MTP participants will also receive brief, 2-session enhancement counseling centered on MTP treatment goals at release and a patient-drug educational handout with direct referrals to re-entry community treatment. Follow-up visits at NYU/Bellevue will be for assessment and counseling only and will be independent of community methadone treatment participation. MTP participants discontinuing treatment and relapsing to illicit opioid misuse will be offered the same rescue protocols as ETAU and XR-NTX participants.

7.5 Rescue strategies for persons relapsing to opioid and other drug misuse

Any person regardless of study group stands a risk of relapsing to illicit opioid or other drug/alcohol misuse. Participants in the XR-NTX arm who miss a scheduled monthly dose will continue XR-NTX only if opioid abstinent (above). This is a standard approach to re-starting XR-NTX in our recent clinical trials.[32] XR-NTX patients relapsing to opioid use and wishing to re-start XR-NTX will have to re-detox in order to resume XR-NTX. The study will assist with treatment referrals for detox services at Bellevue Hospital Center, but will not otherwise directly provide such services or medications. Otherwise any XR-NTX, ETAU, or MTP patient who has relapsed and is not interested in continuing their baseline study condition (i.e., an MTP patient refuses further program attendance, or an XR-NTX participant does not wish to continue injections due to side effects or for any other reason) 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 or paid for by the study.

8.0 Assessments and Outcome Measures (Table 1)

TABLE 1	**Jail, Pre-Release**			**Bellevue Hospital Center, Post-Release**														
	Screen	Randomize	FU	FU	Rx#2	FU	Rx#3	FU	Rx#4	FU	Rx#5	FU	Rx#6	FU	FU	FU	FU	FU
	v0	v1	v2	v3	v4	v5	v6	v7	v8	v9	v10	v11	v12	v13	v14	v15	v16	v17
Assessments & Interventions *(CRFs = italics)*	wk 0	wk 1	wk 2	wk 3	wk 5	wk 7	Wk 9	wk 11	wk 13	wk 15	wk 17	wk 19	wk 21	wk 23	wk 25	*wk 29**	wk 52	Wk 104
Clinical Safety																		
Inclusion/Exclusion	x																	
Study consent	x																	
Consent Quiz	x		x															
RC Visit Checklist & RC Progress Note	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medical Management Progress Note*		x			x		x		x		x		x					
XR-NTX-specific AE/SAE*			x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Opioid OD-specific AE/SAE			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AEs/SAEs		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
biometrics																		
Pregnancy	x	x			x		x		x		x		x		x			
Urine toxicology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Surveys and Clinical Research Forms																		
DSM-5 Opioid Use Dx CIDI-2)	x				x				x						x		x	x
Demographics (PhenX)	x																	
SOMATICS Motivation (2)	x																	
ASI-Lite		x			x^				x^						x		x^	x^
Risk Assessment Battery (RAB)		x			x				x						x		x	x
EF90, baseline		x																
EF90, follow-up									x						x		x	x
WHO-BREF		x							x						x		x	x
Treatment satisfaction					x		x		x		x		x		x			
TLFB	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Craving Visual Analog Scales		x			x		x		x		x		x		x	x	x	x
Days Incarcerated					x		x		x		x		x		x		x	x
New Arrests					x		x		x		x		x		x		x	x
Inmate Look-up#					x		x		x		x		x		x		x	x
Methadone Tx Exposure&	x	x			x		x		x		x		x		x		x	x
XR-NTX inj Log*		x			x		x		x		x		x					
Vital Status (NDI)#																	x	x
Opioid Quantity Usage	x																	
Opioid Relapse Outcome					x		x		x		x		x		x			
Treatment Events	**treatment phase**															**fu**		
Counseling & Referrals		x			x		x		x		x		x		x		x	x
Naloxone challenge*		x																
XR-NTX injection*		x			x		x		x		x		x					
Qualitative Interviews				X+														

***XR-NTX arm only; &Methadone arm only; #among those lost to f/u only; ^ASI-Lite Drug-Section Only +Qualitative interviews completed w/subset of participants at Week 3 and later time points, as needed.**

A comprehensive panel of measures is planned including standard measures of drug and alcohol use, medical status, and on-going treatment services utilization (Table 1). Drug use and treatment history questions will be adapted from the Addiction Severity Index Lite (ASI-Lite).[45] The Time Line Follow Back (TLFB) is a validated, best practice method of assessing recent drug and alcohol use using a daily calendar count methodology,[46] and will combined with urine toxicology results to define the primary relapse and related outcomes (Aim 1, 2, and 3b). Assessment forms including the Economic Form 90, ASI-Lite, Methadone Treatment Exposure, World Health Organization Quality of Life BREF (WHO-BREF), and the NYC Department of Corrections Inmate Look-up form will be used to track non-study addiction treatment (Aim 3a), medical and other costs, employment and benefits, and re-incarceration, which will capture the basic data for exploratory cost-effectiveness analysis (and later for formal economic modeling through a linked economic study, if funded) (Aim 3e). The Risk Assessment Battery (RAB) will be used to compare baseline to post-release injection drug use and HIV risk factors (Aim 3c).[47] Surveys of Adverse Events (AEs), Serious Adverse Events (SAEs), Opioid Overdose-and XR-NTX-injection-site-specific AE/SAE, and in the event of a drop-out, Vital Statistics, will be used to track overdose-related AEs and mortality (Aim 3d). Open-ended questions and the Client Satisfaction Questionnaire[48] will assess attitudes regarding treatment preferences in the three study arms.

8.1 Primary outcome: time-to-relapse.

The primary outcome measure will be the time-to-relapse (or loss of persistent abstinence). All individuals are abstinent from illicit opioid use at randomization, as evidenced by urine toxicology and self-report. Beginning at release from jail and study visit 2 (week 2), opioid relapse is defined as a) self-report of ≥7 consecutive days of non-prescribed, illicit opioid use, or, b) two consecutive urine toxicology tests positive for illicit, non-prescribed opioids (opiates, oxycodone, methadone, or buprenorphine).

This definition of relapse is chosen to concur with the on-going XR-NTX RCT DA024555, which uses the same criteria for relapse, as well as the planned NIDA CTN-0051, X:BOT, XR-NTX vs. Buprenorphine Opioid Treatment comparative effectiveness trial, which proposes a similar primary outcome and relapse event definition. Self-reports (Timeline Follow Back) and urine results are the on-going measures of illicit opiate use. If the urine tests are consistent with self-report, self-report will be used as the primary measure of use. In the event that a participant reports no use, but their urine tests indicate use, we will regard the 5 days prior to and including the day of testing to be positive for opioid use. A person with two positive urine tests but no self-reported use would be designated as positive for sustained relapse (≥7 days of use). The time of the event occurs at the start of the qualifying clinical event period (first of the 7 consecutive use days). In the event of a missed visit or drop-out, missing urines will be counted as positive results. Thus, persons dropping out will be recorded as reaching the relapse event beginning 5 days prior to the first missed visit. Alternative imputation strategies will be compared to this missed=positive strategy for missing urine data.

9.0 Power and Sample Size

A projected RCT sample of 170 persons is based on Specific Aim 1, the RCT comparison of XR-NTX vs. ETAU for time-to-relapse following release. Our current pilot study implies roughly a 0.5 treatment effect of XR-NTX in reducing post-release opioid use, in other words, it is to date roughly twice as effective at preventing any opioid use, relapse immediately post-release, or days of use following release from jail during the current 8-week trial. In the pivotal Krupitsky trial, the XR-NTX arm resulted in 50% success at avoiding relapse at 6 months, versus less than 20% in the placebo arm. We therefore predict 50% of the XR-NTX arm to produce a time-to-event of 25 weeks (no relapse event occurs), versus 20% of the ETAU arm, with the distribution of failure (relapse) randomly distributed in both arms across the trial.

Although we will use a proportional hazards model for comparing two groups, as described below, we use a logrank test to estimate the required sample size for the core RCT of XR-NTX vs. ETAU. The estimate of power is conservative because the logrank statistic, which essentially ignores covariates, is the score test for the Cox proportional hazards model, which accommodates use of prognostic mediators. Given the projected 25-week 50% success (no relapse event) rate in the XR-NTX arm, a two-sided

alpha=0.05, N=96 provides 90% power to detect a hazard ratio of 0.50 for the second (ETAU) treatment. (Stata SE 10) Given possible attrition following enrollment and post-release conservatively estimated to be around 50-75% by week 25, we have increased the target sample for randomization to N=170 persons total, or n=85 per arm. The quasi-experimental observational MTP arm (n=85) is added symmetrically (equal size) and naturalistically to compare abstinence and treatment retention rates between XR-NTX and MTP standard-of-care, and results in a total enrolled sample of N=255. If post-release opioid relapse rates are also low in this group, as we would predict, there may be in fact no significant differences between XR-NTX vs. MTP, which would enable an estimate of the relative effectiveness of a newer opioid antagonist treatment strategy with respect to an established opioid agonist maintenance approach.

10.0 Statistical Analysis Plan

In addition to this study's original and distinct analysis plan, described here, the NIDA SOMATICS U01 cooperative, which includes Friends Research Institute Inc. (FRI), New York University (NYU), and the University of California, Los Angeles (UCLA), will share several core assessments and similar study-arms, allowing for naturalistic comparisons across the 3 distinct studies. A SOMATICS Statistical Analysis Plan is described in the Appendix.

Eugene Laska PhD will be responsible for the overall statistical analysis plan and will co-author all relevant manuscripts with Dr. Lee. Dr. Laska is a senior biostatistician, a Professor in the NYU Department of Psychiatry, and the Director of the Statistical Sciences Laboratory of the Nathan Kline Institute (NKI) for Psychiatric Research in Orangeburg, NY. His theoretical work has focused on design and statistical analysis of clinical trials, and he was a recently consultant to Alkermes, Inc., on the FDA approval of XR-NTX (Vivitrol) for the treatment of opioid dependence.

Preliminary analyses to check for unbalanced baseline characteristics among the randomized arms: as a first step, several analyses will be performed to assess the balance achieved by the randomization on all baseline variables that may be prognostic of outcomes. These comparisons will use analyses of variance for continuous variables and chi square models for discrete or ordinal responses. Variables for which there is evidence of non-equivalence will be included as covariates in treatment comparisons.

Specific Aim 1: Time-to-relapse between XR-NTX vs. ETAU. We hypothesize XR-NTX will be associated with a significantly longer time-to-relapse vs. ETAU controls. The analyses will model time-to-relapse as a function of treatment assignment (XR-NTX vs. ETAU), including possible mediating factors, including opioid dependence severity at baseline, concurrent cocaine or alcohol and/or benzodiazepine misuse, and homelessness as covariates, in a Cox proportional hazards regression model. The proportionality of the relative hazard assumption will be examined via the treatment by a time interaction term. An asymptotic 95% CI for the hazard ratio of the difference between the treatment arms in time-to-relapse will be constructed. The study arm success rates with 95% CIs at week 25 (end of active treatment) and the difference in success rate at that time point will be constructed. As drop-outs are counted as reaching the relapse event beginning with the first missed visit, intention-to-treat analysis will include all randomized participants. Alternative missing data imputation strategies will be compared to this missed=positive approach.

A further analysis of time-to-relapse differences between groups will be a "cure model." This is a strategy to disentangle the issue of participants who never respond (immediate relapse) and subjects who had an overall positive treatment effect (indefinite time-to-relapse). A cure model will be used in the form $H(t) = 1 - p + pS(t)$; where $H(t)$ is the survival distribution, p represents the probability of relapse, and $S(t)$ the survival distribution of time-to-relapse, *conditional* on relapse occurring. The parameters will be estimated based both on Kaplan Meier methods and parametrically. The equality of the values of p for the two treatment arms will be tested using a nonparametric likelihood ratio test. For the parametric test, a logistic will be used to model p and a Weibull survival distribution will be used to model time-to-relapse, S(t). Both allow the use of covariates. In all analyses, the assumptions underlying the application of all the statistical methods that are used will be examined, principally through examination of standardized residuals, influence diagnostics, and graphical displays.

Specific Aim 2: Time-to-relapse between XR-NTX vs. methadone. We hypothesize XR-NTX will be associated with an equivalent time-to-relapse curve compared to the MTP observational cohort. The same

Cox proportional hazard and cure model approaches using an indicator variable for treatment condition and the same covariate terms for baseline potential prognostic indicators will be used to compare time-to-relapse rates between XR-NTX and MTP, which are hypothesized as similar (overlapping 95% CIs).

Further, and within this quasi-experimental comparison of the XR-NTX (and ETAU) RCT participants and those choosing MTP, our interest is in comparing outcomes in the counterfactual sense: what would have happened to those who did not receive XR-NTX treatment, either MTP or ETAU, had they received it? If we were able to estimate the "potential outcome," it could be compared to the outcome that resulted from the treatment they actually received. Propensity score matching (PSM) will be used to control for treatment selection bias.[49] The clinical and demographic factors that may have been implicit in the physician's treatment choice presumably follow some rational clinical logic that can be mirrored on average by statistical modeling. However, the treatment assignment mechanism, detox and subsequent randomization in the RCT portion of this study, or initial methadone treatment selection in the MTP arm, is for the most part through subject preference. Hence, while the hoped for explanation of treatment choice is not likely to be robust, the PSM approach at the very least is a method for matching subjects on baseline characteristics, so as to compare "like with like," which should be greatly strengthened by our prospective matching strategy. The crucial difference between PSM and traditional matching approaches is that the former matches on multiple variables simultaneously while the latter matches on one variable at a time. We will use Mahalanobis Metric Matching or Caliper to find the closest subjects in the XR-NTX group and independently the closest subject in the ETAU and MTP groups, using the SAS SUGI 214-26 "GREEDY" Macro. In this approach, both the baseline covariates and the propensity score are utilized. The subjects will be divided into 5 groups (quintiles) based on the propensity score distribution. A fully nonparametric randomization test will be utilized to test for treatment differences in time-to-relapse where the reassignment is within quintiles but the randomization probability distribution is across the 5 groups. PSM also allows us to assess the trial design validity: if treatment effects of either XR-NTX or MTP washout vs. ETAU, this would suggest either the experimental or observed interventions, respectively, were less effective than proposed, and observed 'head-to-head' differences between arms may stem from unplanned biases.

Specific Aim 3a-e: Related Opioid Treatment Outcomes. To compare re-entry rates of 5 key outcomes across all arms (XR-NTX, ETAU, MTP): 3a) community treatment retention/initiation, 3b) any opioid, alcohol, or other illicit drug misuse, defined as continuous counts of both days, amount/day, and urine toxicologies for heroin or other illicit opioid and other drug use, 3c) injection drug use and HIV sexual risk factors, 3d) accidental drug overdose and mortality, and, 3e) re-incarceration and exploratory cost-effectiveness.

We hypothesize the XR-NTX participants will report less continuous opioid, alcohol, and other illicit drug misuse, injection drug use and HIV risk, and accidental drug overdose events compared to ETAU participants, and similar rates to those of MTP participants. We do not hypothesize a difference in re-incarceration rates over the 24-week post-release treatment phase. These secondary outcomes will be evaluated using the appropriate between-group analysis, though low frequency events such as death or accidental overdose are expected to allow only exploratory analysis. Aim 3e, cost-effectiveness, is now performed in concert with the SOMATICS U01 Statistical Analysis Plan, which will examine cost-effectiveness of the active interventions in each of the 3 studies.

Specific Aims 4a-e: Qualitative interview aims: a) Themes on social barriers to "successful" jail-to-community re-entry; b) Themes on social facilitators of "successful" jail-to-community re-entry; c) Themes on treatment barriers to "successful" jail-to-community re-entry; d) Themes on community treatment facilitators of "successful" jail-to-community re-entry; e) Other factors surrounding relapse or abstinence since release.

We plan to conduct qualitative interviews with randomized participants who agree to participate in them by indicating as such on the main consent form. These interviews will be conducted with participants in all three arms at 2 weeks after release from jail and later time points, as needed. We will be using a grounded-theory approach to identify themes that emerge among opioid-dependent persons transitioning from jail to the community.

We will use ATLAS.ti, a software package used primarily for qualitative, unstructured data analysis, to transcribe and analyze our qualitative data, including the coding of text or text passages and data

visualization and interpretation. Further analysis may be conducted in other software packages after transcription is completed.

11.0 Data Collection and Management

The NYU/HHC CTSI and NYULMC Clinical Research Informatics and Data Management Unit (CRIDM), led by James Robinson, M.Ed., will provide clinical research informatics and data management support for the study. CRIDM has developed a comprehensive data acquisition and management system for use across the NYULMC campus, which we will customize for this study. CRIDM personnel will develop the additional electronic case report forms (CRFs) required to manage the data for this study, and work with study personnel to ensure the completeness and integrity of all study data. All data will be checked in real time, stored in a centralized database, reviewed and monitored for completeness and accuracy, and undergo a final cleaning following the last subject visit, following which the study database will be locked.

Protected Health Information (PHI) will be collected and stored in the form of each participant's original signed informed consent and locator form. These written documents will be filed as individual charts and locked securely in a private Department of Population Health office cabinet. These charts will be accessed to call and follow-up with patients post-release and to maintain the ICF on file. Participants will be assigned sequentially numbered unique study ID numbers at the time of consent (e.g. #001-510). These ID numbers will be the only identifier entered on Case Report Forms (CRF) and research assessments to distinguish one participant from another. Secure laptops will be used for web-based data entry, CRF variables will be input into a secure central database on an NYULMC server. The laptops themselves will be password-protected, but will not store PHI, study ID number information or any research assessment data and will be used for web-based data entry only. To maintain a link between the study ID and PHI for purposes of follow-up and record-keeping, individual participant charts and research assessment/CRF data there will be a master participant ID key that will contain each participant's PHI (name, DOB) and their corresponding unique study ID number. This master key identifier file (.xls) will be maintained by the PI and Project Manager on a secure NYULMC desktop file and accessible only to study staff. Similarly, audio recorded tapes for qualitative interviews will be maintained by the PI and Project Manager and locked in secure NYUMC file cabinets that only study staff have access to. Any notes taken during qualitative interviews will also be locked in secure NYUMC file cabinets and will not contain linkage to the participant's study ID#, instead each interview will be numbered consecutively (e.g. Qualitative Interview, QI #001, QI #002. etc.). Audio-recordings will be transcribed by the study team and then destroyed within 2 weeks of the interview.

At the end of a three-year period following study closure, written identifiable data will be destroyed. De-identified study data will remain in digital and written file storage for a period of 6 years following study conclusion and protocol close per standard NYU IRB guidelines. The final de-identifiable digital dataset may be used by the Principal Investigator or Co-Investigator for secondary analysis, in which case future IRB-approval would be sought. In addition, considering NIDA has combined this proposal, which was originally an independent R01 submission, as 'U01' center grant with two other contemporaneous but different study sites (Friend Institute: Baltimore, MD and UCLA: Los Angeles, CA), we anticipate all three 'U01' study sites will combine harmonized data for additional analyses after all study sites have closed.

12.0 Protection of Human Subjects

12.1 Study participants

Up to 510 participants will be enrolled after baseline evaluation as detailed in the Research Plan. Eligible patients will be 18 years of age or older, have a current DSM-V diagnosis of opioid dependence, and be without disqualifying criteria such as uncontrolled medical or mental illness. Chronic medical and psychiatric conditions that are reasonably controlled and not majorly disabling in the view of the study clinician will be otherwise eligible for inclusion. The anticipated distribution of participants by demographic characteristics and based on our recent buprenorphine and XR-NTX studies in NYC jails is a mean age 40 years (range, 31-61), 45% Hispanic Caucasian, 10% non-Hispanic Caucasian, 45% African American, and 10-20% female.

Federal Research among Prisoners. Study participants are clearly considered prisoners at the time of enrollment. The NYU SOM IRB will contact DHS/OHRP to address this topic and for permission to enroll prisoners in a federally funded research trial. However, we believe this study carefully conforms to the Federal guidelines for research among prisoners (CFR 46.306) in the following manner:

1.) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the Federal Register, of his intent to approve such research.

2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired. Incentives and benefits from participation are not coercive and are fair value of participant's time and, following release, travel.

(3) The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers. This study's methods and interventions are consistent with good clinical practices in community settings.

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project. Jail authorities have no role in this study or in treatment assignment, which is random.

(5) The information is presented in language which is understandable to the subject population. The informed consent and consent quiz are intended to be understandable to adults in jail.

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole;
There is no role for, relationship, or other interaction with parole or probation authorities and this study.

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact. The study primarily consists of community follow-up of adults released from NYC jails. Follow-up is extensive (every 2 week assessments), with follow-up visits extending 4 weeks beyond the end of study treatment phase (at Week 29) and two long-term follow-up visits at 6 months and 18 months post-treatment phase (at Week 52 and Week 104).

12.2 Research Information

The assessments and instruments that will be used to obtain information from participants consenting to enroll in this study are as above (8.0, Table 1). Participants will be recruited by direct invitation, advertisements and broadcasts within the appropriate jail facilities and housing areas, word of mouth, and by working with the jail opioid treatment program staff. Pre-screening for persons who are opioid dependent, have completed a methadone detox or are actively receiving methadone maintenance, and have a known pending release date can be generated by cross-referencing existing electronic health,

pharmacy, and correctional databases. Informed consent will be obtained only after the prospective participant demonstrates comprehension of the study by reading the consent form and scoring 100% on the consent quiz. Due to differing inclusion/exclusion criteria sets between the randomized treatment arms (XR-NTX and ETAU) and the non-randomized observational methadone cohort (MTP), separate consent questionnaires will be used depending on whether participants are enrolled to be randomized to XR-NTX or ETAU vs. those enrolled into the MTP group.

12.3 Potential Risks

General Risks Associated with Treatment of Opioid Dependence and Study Participation. This study randomizes 170 opioid dependent participants to extended-release naltrexone (XR-NTX, n=85) treatment or no medication, enhanced treatment-as-usual conditions (ETAU, n=85), and also recruits 85 persons active in jail-based methadone maintenance treatment program (MTP). All participants will be followed in-jail and for 24 months, with three post-treatment phase follow-up visits at weeks 29, 52, and 104. Any relapse to illicit opioid and other drug and alcohol use among any of the two treatment or the methadone observational arms after release from jail (or while incarcerated) implies a risk of death and disability, and some proportion of participants in all three arms can be expected not to respond to treatment and resume opioid and/or other drug and alcohol use. All participants relapsing post-release and struggling with on-going drug and alcohol use will be counseled and referred by staff to any appropriate treatment modalities, including the immediately available addiction services available at Bellevue Hospital (emergency detoxification with referral to residential treatment or supportive housing, methadone treatment, buprenorphine, intensive outpatient, dual diagnosis).

The Informed Consent Form (ICF) will cover this reality of opioid and other drug addiction, the referrals and rescue options, and study staff will clearly discuss this risk at baseline and at each follow-up visit. The ICF and consent quiz will also clearly detail in plain language the below-described treatment and medication side effects. We feel strongly that none of the study procedures or treatments heightens the risk of relapse or overdose beyond the daily, baseline risks of on-going opioid addiction. The study visit schedule may be altered to accommodate and evaluate adverse events or relapse-related concerns, and study staff will be available by phone for emergency consultation at any time (all patients will be given the PI's direct mobile number).

Enhanced Treatment-As-Usual Arm. All study participants will receive psychosocial support and assistance with and referrals to other addiction treatment services and supportive housing resources, as well as monetary compensation for visit time and travel. These benefits may be particularly helpful to this study's group, which represents 'enhanced' counseling and involves more therapeutic attention, more referrals to treatment, and much greater support in the event of post-release relapse, than actual 'treatment' in NYC jails for persons not interested in methadone, which in reality amounts to no treatment after a brief methadone detox, no on-going interaction with counseling staff, and no formal discharge planning pending release. Provision of concrete benefit to the ETAU arm is in keeping with ethical standards for clinical trials among prisoners, in which all experimental arms must receive some tangible yet non-coercive benefit beyond usual care. With that said, the analytic plan and rationale of this study is based on the fact that a greater proportion of ETAU participants will relapse following release. As above, on-going study follow-up and an abundant local treatment referral base is intended to minimize the harm associated with these higher rates of relapse.

Methadone Treatment Program Arm. The ETAU and MTP groups will otherwise not be exposed to risks beyond those of usual care, which will be provided by existing jail and community providers. Methadone maintenance can of course be associated with bodily symptoms including fatigue and constipation, and over-sedation and a risk of overdose when combined with sedative-hypnotics or alcohol. High-dose methadone is likely associated with prolonged QT syndrome and implies a higher risk of unstable and fatal arrhythmias.[50] However, methadone maintenance provides a much lower risk of disability and death than untreated illicit opioid use, and stands as the best evidence-based standard of care for re-entry treatment of opioid dependence, thus our interest in recruiting this quasi-experimental cohort.[51] Further, participants in the methadone arm will have already agreed to these risks and benefits of a methadone treatment program (MTP) prior to recruitment and enrollment, as their choice to engage in jail MTP will have

been established well before enrollment, which will occur at the end of the incarceration period. The study will not otherwise recommend, influence, or involve itself in the daily aspects of MTP, such as dose level, attendance and take-home schedules, or ancillary counseling. The MTP arm will receive additional brief 2-session enhanced counseling intended to provide all participants with a higher than usual level of care and additional community treatment referrals.

Extended-Release Naltrexone Arm, Expected Adverse Events. Persons receiving XR-NTX may experience several common side effects of naltrexone therapy, whether injectable or oral, including nausea, headache, and fatigue ('naltrexone flu'), particularly during the initial first few days of dosing. Nausea may be more likely with oral vs. injectable naltrexone (only injectable XR-NTX is used in this study). In most published naltrexone clinical trials, these side effects are well-tolerated by patients, though it is certainly possible some patients will discontinue XR-NTX based on these common and expected naltrexone side effects, as a small percentage of patients did in our team's recent alcohol treatment study, the COMBINE study which used oral naltrexone, the Garbutt XR-NTX alcohol efficacy study, and the Krupitsky XR-NTX opioid pivotal trial.[38,39] Theoretically, XR-NTX can cause transient liver inflammation, and liver function will be monitored throughout the trial. In reality, few patients in recent clinical trials or usual care experience any XR-NTX-related liver toxicity.

XR-NTX as an injectable medication involves possible injection site soreness, usually well tolerated, and more severe injection site reactions, which may be prolonged and resemble a sterile abscess. Nationally, a small number of injection site reactions have been recorded, with a very low percentage progressing to necrosis and requiring surgical debridement, according to a 2008 FDA Alert, *Naltrexone Injection Site Reactions*.[52] Our own XR-NTX alcohol study recorded one such severe injection site reaction (1 of 154 injections), in this case experienced by a 54yo female participant with substantial hip adipose tissue.[40] It is thought that mis-injection of the XR-NTX bolus into subcutaneous adipose tissue is the cause of injection site reactions, as opposed to proper intramuscular placement. Study clinicians will be carefully trained on this issue and take extra caution among participants with increased hip and buttocks adipose tissue. We will not, however, exclude patients based on body habitus or BMI, as this is not a national recommendation and therefore not part of usual XR-NTX care.

XR-NTX introduces a prolonged mu opioid antagonist blockade, which complicates the treatment of acute or chronic pain with opioid medications. While this is the very reason naltrexone is used to treat opioid disorders, treatment of an unanticipated painful event or an unexpected need for prolonged opioid pain control is compromised in an XR-NTX participant during the 4-5 weeks of clinical mu opioid antagonism following the last injection. Persons randomized to XR-NTX will be provided a wallet card identifying them as an XR-NTX patient and containing the PI's and study mobile numbers. XR-NTX blockade can be 'overridden' due to competitive mu receptor pharmacodynamics with increasing doses of full mu agonists, which should be provided only in a monitored medical setting such as an Emergency or Recovery Room. There have been no such unanticipated painful events to date in our on-going jail XR-NTX pilot study, and nationally within the Vivitrol alcohol treatment market these events have been uncommon. Persons with chronic pain conditions requiring opioid medications are excluded from enrollment.

XR-NTX Arm, Unexpected Adverse Events. XR-NTX as opioid treatment is not thought to be associated with higher risks of relapse, disability or death vs. placebo or treatment-as-usual controls.[30] That said, it is quite early for this product as opioid treatment following the Oct., 2010, FDA approval, and the probabilities that XR-NTX participants attempt to 'overide' the mu opioid blockade with relatively massive doses of illicit opioids,[53] or that participants discontinuing or dropping out of XR-NTX return to illicit use with a lower tolerance, and therefore expose themselves to very high risks of hypoventilation and overdose, are to date not well characterized. It is reassuring that no such events have been noted in the Comer and Krupitsky XR-NTX clinical trials, nor were these events noted in 1-3 years of long-term opioid treatment reported by the manufacturer. Nonetheless, we will rely on close monitoring of AEs/SAEs, regular communication with and oversight by our DSMB, and close follow-up and prompt rescue referrals among persons relapsing to opioid use in order to minimize any such possible risks and harms. We note again that it is unlikely the XR-NTX arm is at greater risk for relapse and overdose than the ETAU participants and that it is unknown to what extent XR-NTX re-entry participants are at greater or lower risk than methadone

patients; these are the primary and secondary aims of this study. No interim analysis of the primary outcome will be conducted.

12.4 Confidentiality

Participants will be asked to provide information regarding a number of sensitive behaviors (e.g., alcohol and drug use, sexual history, criminal history and on-going illicit activities). This type of personal information divulged by participants at study visits may have adverse social and other unknown consequences for participants if released. Therefore, in addition to the safeguards put in place for the collection and storage of all data as described above (section 11.0 Data Collection and Management), the study team has obtained a Federal Certificate of Confidentiality to encompass protocol activity and further safeguard the possible risk of released confidential information (COC #DA-13-154, 1/10/14). We will provide all staff with training in their responsibilities for maintaining subject confidentiality; we will use unique identifiers to identify subjects in the database; all data will be kept in locked filing cabinets or on our secure server to which only the investigators and project manager will have access to. Study findings will utilize only aggregate data and no publication or presentation will involve any use of individual information.

12.5 Emotional Discomfort

There is a small chance that participants may become upset when discussing their history of addiction problems, criminal justice involvement, family conflict, prior trauma, or role failure, etc. We will discontinue administration of research instruments if a subject shows great discomfort or asks to terminate an interview. Such events have not been observed in our preliminary studies.

12.6 Risk/Benefit Ratio

Most of the risks described are expected adverse events associated with XR-NTX, or those of baseline opioid dependence and jail-to-community ETAU or MTP. The additional risks of the active treatment arm (XR-NTX) or observational methadone arm are likely small compared to the expected benefit of discontinuing alcohol use.

12.7 Data Safety & Monitoring Board (DSMB)

Due to the uniqueness of this NIDA U01 protocol a common DSMB coordinated by NIH/NIDA will be shared across all three collaborative sites (Friend Institute: Baltimore, MD and UCLA: Los Angeles, CA) to monitor the study according to a bi-annual schedule of clinical trial monitoring. The University of California Los Angeles' Integrated Substance Abuse Programs (UCLA ISAP) DSMB will monitor each collaborative site.. UCLA ISAP's Data Safety and Monitoring Board consists of a standing chair and 5 committee members, who are drawn from the ranks of Principal Investigators, and includes at least one medical doctor and a biostatistician. William Burdon, PhD., serves as DSMB Chairperson. DSMB members include: Mary-Lynn Brecht, PhD., Mitchell Karno, PhD., Nena Messina, PhD., Ardis Moe, M.D., and Peter Friedmann, M.D., M.P.H. (Brown University).

The DSMB will conduct a review of the initial study protocol to ensure that certain elements are in place and then meet twice a year or more frequently as needed in order to review and monitor this protocol. The DSMB may provide recommendations to improve upon the protocol. Each protocol includes a detailed Data Safety and Monitoring Plan (DSMP). DSMPs typically include stopping rules that specify the outcome differences detected between groups during an interim analysis that can result in stopping the clinical trial. In general, stopping rules will reflect one of the following conditions: 1) there is clear evidence of harm or harmful side-effects of the treatment; 2) there is not likelihood of demonstrating treatment benefit; 3) there is overwhelming evidence of the benefit of the treatment. Following review, the DSMB Chair issues a written letter to the study PI summarizing the results of the DSMB review and recommending continuation of the current study protocol, modifications based on specific committee concerns, or termination of the study in the event of overwhelmingly significant efficacy differences between groups or unacceptable adverse events. PIs are advised to include these letters with their IRB continuing applications and their annual funding agency progress reports.

The current trial is not blinded, so the DSMB would be able to compare the outcome of the two groups during each review without decoding the patient's group and determine whether the study should have an early termination. However because we are comparing alternative paradigms involving a study medication (XR-NTX) or community treatment (ETAU, MTP) that are already FDA-approved as opioid treatment, and regarding which our own preliminary data do not suggest significant safety considerations, early stopping on the basis of clear benefit (yes/no) is not anticipated in this trial.

Detailed Data and Safety Monitoring Plan (DSMP)
A full DSMP for the NIDA SOMATICS U01 Collaborative (Friends Research Institute, NYU, UCLA) is included in Appendix A.

I. Protocol Description

As described, see Research Plan

II. Data Management and Analysis

A. Data Acquisition and Transmission and Data Entry Methods

As described, see **Data Collection and Management**

B. Data Analysis Plan

As described, see Statistical Analysis Plan for planned data analysis specific to our individual NYU trial. In addition to our sites original and distinct analysis plan, the Studies of Medication for Addiction Treatment in Correctional Settings (SOMATICS) NIDA U01 cooperative, which includes Friends Research Institute Inc. (FRI), New York University (NYU), and the University of California, Los Angeles (UCLA), will share several core assessments and study-arms. These shared core measures across the three sites will have a shared SOMATICS Statistical Analysis Plan including primary/secondary outcome measures and its statistical methodology that is separate from our individual sites plan and described in the DSMP below.

III. Quality Assurance

A. Procedures in Place to Ensure the Validity and Integrity of the Data

Study clinicians and research staff will undergo the same baseline training at the inception of the study. The Program/Project Manager and Data Management staff will ensure the quality of the clinicians' and the research assistants' administration of study assessments and instruments and of integrity of the data recorded through regular reviews and on-going data monitoring. *Integrity of collected data (Reviewer 1):* The identification key linking the separate charts containing the Informed Consent document and patient identifiers (name, signature, DOB, address, phone numbers) and the assessment instruments and study dataset will be stored in a locked cabinet (paper copy) as well as on a password-protected file stored on a secure NYUMC server, accessible only to the study staff. The study dataset will be otherwise de-identified and securely stored as described below. Only authorized study staff will have access to the dataset. All reasonable requests for data-sharing will be accommodated after study close (see Resource and Data Sharing Plan).

B. Procedures to Guarantee the Accuracy, Completeness, and Confidentiality of the Data during Data Collection,
Entry, Transmission, and Analysis

Accuracy and completeness of the data will be ensured by the NYU/HHC CTSI and NYULMC Clinical Research Informatics and Data Management Unit (CRIDM), led by James Robinson, M.Ed., and as described in the Research Plan. Study data will be managed by the Data Management staff using a customized web-based e-research platform. Data will be entered using laptops with secure wireless broadband internet cards or access points connected to the NYUMC network, encrypted, and transmitted to CRIDM servers at NYUMC. All data analyses for the study will be performed by the biostatistician, Eugene Laska PhD, and the PI, Joshua D. Lee MD MSc. Quality control is performed as the data are being entered, and then at further stages of the storage and management process.

IV. Regulatory Issues

A. Reporting of Serious Adverse Events

Death, disability, hospitalization (or prolongation hospitalization), congenital defects, and life threatening events including drug overdose will be deemed serious adverse events (SAEs) and immediately reported (orally and by fax) to the NYU School of Medicine Institutional Review Board (IRB), at the time they are identified by the investigators or research staff. In addition, a written report will be filed within 72 hours to the IRB and to the NIDA program office (and FDA as indicated by applicable regulations) and medical review officer. When additional clinical information becomes available, a follow-up and/or final SAE report will be filed with the IRB, NIH, and the FDA (if indicated).

B. Reporting of IRB Actions to NIH/NIDA

The initial IRB approval will be forwarded to NIH for review, as will all subsequent approvals and any amendments to the protocol, as appropriate and/or requested. All proposed protocol amendments will be presented to the IRB and communicated to the NIH project officer if approved, as appropriate and/or requested. Original amendment approvals will be maintained in the regulatory file. Major protocol changes such as the NIDA SOMATICS U01 collaborative will be undertaken in close communication with the NIH program officer.

C. Report of Changes or Amendments to the Protocol

All proposed changes/amendments to the protocol will be filed with the IRB, and major protocol changes will be forwarded to the NIH project officer, and the original amendment approvals will be filed in the primary document manual.

D. Interim Analysis and Trial Stopping Rules

The PI, DSMB, and NYUMC IRB will examine any study-related SAEs on an urgent basis. Other safety data will be monitored on an on-going basis by the PI and semi-annually by the DSMB. Regarding relapse rates and the time-to-relapse primary outcome, these rates will be examined semi-annually in this non-blinded study. It is expected ETAU participants will experience shorter time-to-event and higher relapse rates, which would not prompt consideration of trial stopping.

E. Disclosure of Any Conflict of Interest in the DSMB

The investigator, co-investigators, and members of the DSMB will report on an annual basis or more frequently if indicated any conflicts of interest or apparent conflicts of interest to the NIH project officer. On an annual basis, the above individuals will sign a disclosure statement. There are currently no declared conflicts of interest with the proposed study among all Key Personnel.

V. Trial Safety

A. Potential Risks and Benefits for Participants

Potential risks See above for risks in all arms. Risks are primarily well-defined risks of XR-NTX and those of continued drug use despite the interventions within the three arms. Participants will be educated regarding these risks during the informed consent process.

Potential benefits (each arm)

XR-NTX: Participants will possibly benefit by receiving a medication that is FDA-approved for opiate-addiction and has shown good efficacy for preventing relapse to opioid (heroin) use. In addition, participants in this arm will receive enhanced counseling and referrals to treatment programs that they would not otherwise receive prior to release. They will receive a reasonable yet non-coercive sum of money for their time at each study visit ($20/visit at two jail visits, $25-75/visit at follow-up visits. Lastly, participants will be seen for all study visits at a large tertiary academic center (NYU/Bellevue), with a wide menu of medical, mental health, and addiction treatment programs available regardless of an individual's ability to pay.

ETAU: Participants in this arm will receive enhanced counseling and referrals to treatment programs that they would not otherwise receive prior to release, though will not receive a study medication. Like the XR-NTX treatment arm, they will receive compensation for time and travel and follow-up visits at Bellevue.

Methadone Treatment Program: Participants in this arm will also receive enhanced counseling and referrals that they would not otherwise receive prior to release, in addition to usual care methadone treatment and referrals. They will receive the same compensation for time and travel and follow-up visits at Bellevue.

B. Collection and Reporting of AEs and SAEs

All adverse events (AEs) and serious adverse events (SAEs) will be captured on the appropriate adverse event source documents and entered into the database. All SAEs will be reported to DSMB

members within 72 hours after they occur as well as to the IRB (and if indicated to the FDA) as described above. Collection and reporting of AEs and SAEs will be reviewed on a semi-annual basis, and a report will be prepared for the study record and DSMB. After the proper authorities (IRBs, NIH, FDA when appropriate, DSMB members) are notified of any SAE, the PI and co-investigators will convene a meeting to examine clinical events leading up to the SAE to determine what, if any, immediate procedures should be put in place to ensure that a repeat of this SAE does not occur. Guidance will be sought from the NIH project office and DSMB members, and guidance may well be issued from the IRB as well. Any changes in procedures could involve protocol amendments, and such amendments would subject to the procedures as noted above.

C. Confidentiality

Participants' paper records at NYU/Bellevue are in locked files in locked rooms in areas that are locked during holidays, weekends, and non-working hours. Study material at Rikers Islands are of course even more secure, as only authorized clinical and administrative personnel are allowed access to the jail medical clinic areas, which are monitored 24/7 by corrections officers. At NYU/Bellevue, security personnel are on-duty in our building 24 hours a day and make routine observations in research areas multiple times during work/non-work hours. De-identified (no personal identifying information) databases are stored on secure servers and password-protected laptops. No specific or general subject information will be left in public access areas, and no oral communication regarding subjects with identifiers will be made in any public areas. Research staff have been given extensive training in new, required HIPAA regulations.

Participant's study status will not be shared, communicated, or otherwise available to correctional, parole, probation, or judicial authorities without the expressed written consent of the individual participant. Every measure will be taken to make study participation voluntary, anonymous, and non-coercive, in keeping with good clinical practice and ethical standards governing research among prisoners.

VI. Trial Effectiveness

The primary outcome is based on longitudinal treatment retention and self-reported drinking calendar measures (Timeline Follow Back). This is not an efficacy study but rather a pragmatic comparative effectiveness study designed to compare alternate forms of approved naltrexone medication as part of primary care-based Medical Management.

VII. DSM Plan Administration

The principal investigator, Dr. Lee, will have overall responsibility for data analysis and management. Dr. Lee will have overall responsibility for safety and data monitoring on a day-to-day basis at the two clinical sites. The DSMB, as noted below, will provide guidance and input on a semi-annual or as-needed basis. The members of the DSMB will be responsible for monitoring the trial.

VIII. Frequency of DSM Report

Safety data will be review by the Data Safety Monitoring Board every six months. There will be an annual analysis of efficacy data by the Date Safety Monitoring Board and the necessity of and potential criteria for trial stopping rules will be evaluated as previously described. A Data Safety Monitoring Board report will be issued to the NIDA project officer every six months.

IX. Content of the DSM Report

An annual data safety monitoring report will be submitted to the NIH project officer and will include, but may not be limited to, a synopsis of the trial, socio-demographic characteristics of subjects accrued, retention and disposition of subjects, quality assurance issues regulatory issues, and reports of AEs/SAEs.

X. DSMB Plan

The ISAP DSMB at UCLA will oversee all ongoing protocol review, including data, protocol compliance, safety and efficacy data, in compliance with NIH and NYU guidelines. All board members will meet NIH requirements regarding background and experience, and none will have ethical conflicts, including financial interest related to study outcome. Individuals invited to serve on the board will disclose any potential conflicts in writing. The board will meet every six months (unless more frequent meetings are deemed necessary). Dr. Lee and other research personnel report on the trial status, followed by a closed session under the direction of the DSMB chairperson, during which time the investigators and research team may be present. This will be followed by an executive session restricted to DSMB members. Issues discussed may include those related to subject safety and benefit, whether the primary study question is

being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues). Following each DSMB meeting, recommendations will be made by the chairperson to Dr. Lee and a final report (edited by all DSMB members) will be prepared and submitted to NIH, the NYUMC IRB, and (if required) the FDA.

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