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Protocol Cover Page

Protocol Title: *Long-acting naltrexone for pre-release prisoners: A randomized trial of mobile treatment*

Sponsor: National Institute on Drug Abuse (Grant # R01DA040636-01)

Study Drug: VIVITROL® (naltrexone for extended-release injectable suspension, Alkermes)

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FRI Protocol Number: 16-05-237

Initial Version/Number Date:	v. 0.1	2 June 2016
Revised Version/Number Date:	v. 1.0	28 June 2016
	v. 2.0	18 August 2016 (#1 Amendment)
	v. 3.0	26 January 2017 (#2 Amendment)
	v. 4.0	2 February (#3 Amendment)
	v. 5.0	22 February 2017 (#4 Amendment)
	v. 6.0	19 May 2017 (#5 Amendment)
	v. 7.0	23 May 2017 (#6 Amendment)
	v. 8.0	29 June 2017 (#7 Amendment)
	v. 9.0	1 Nov 2017 (#8, #9 Amendment)
	v. 10.0	4 Dec 2017 (#10 Amendment)
	v.11.0	29 Mar 2018 (#11 Amendment)
	v. 12.0	2 Nov 18 (#12 Amendment)

TABLE OF CONTENTS

LIST of FIGURES

Study Contact List

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Protocol Synopsis

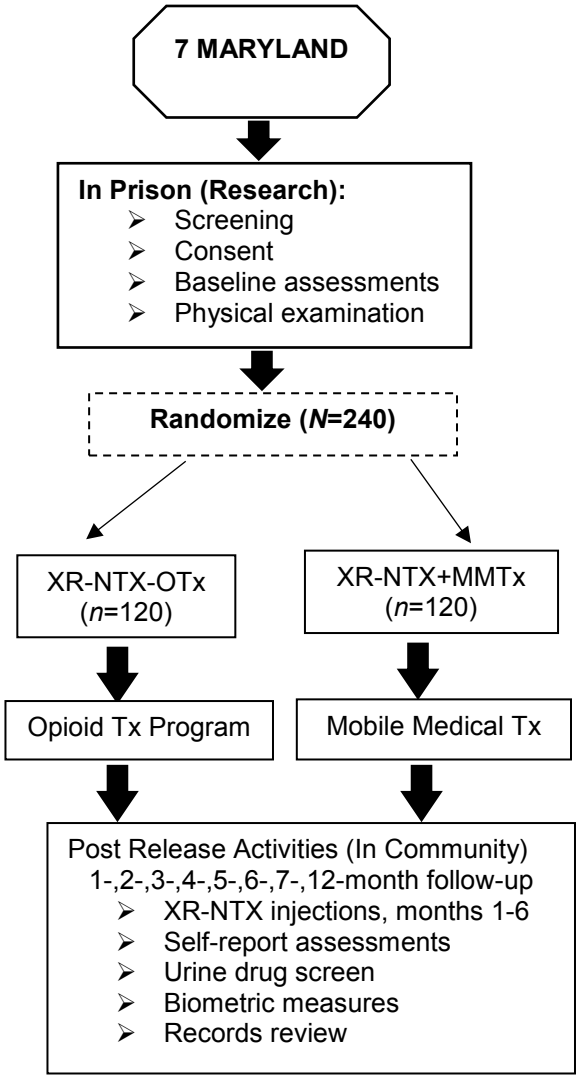
TITLE	*Long-acting naltrexone for pre-release prisoners: A randomized trial of mobile treatment*
Investigational site:	Project implementation will occur at seven pre-release prisons: 1) Brockbridge Correctional Facility (BCF); 2) Dorsey Run Correctional Facility (DRCF); 3) Baltimore City Correctional Center (BCCC); 4) Maryland Correctional Institution (MCIW) for Women; 5) Central Maryland Correctional Facility (CMCF), 6) Maryland Correctional Training Center (MCTC); and 7) Roxbury Correctional Institution (RCI)
Investigators:	Michael S. Gordon, DPA, Frank J. Vocci, PHD, Terrence T. Fitzgerald, MD
Sponsor:	National Institute on Drug Abuse (NIDA); Grant # R01DA040636-01
Protocol number:	16-05-237
Objectives/Outcomes:	**Aim1.** To compare the two study conditions in terms of: a) XR-NTX treatment adherence; b) opioid use; c) criminal activity; d) re-arrest; e) re-incarceration; and f) HIV risk-behaviors (i. needle use; and ii. risky sexual behaviors). **Aim 2.** To determine if the number of months of post-release XR-NTX treatment is related to outcomes (a-f above), and if so, is there a point at which XR-NTX v. Non-XR-NTX equilibrates. Such a finding could be potentially important because it would be informative about the needed length of XR-NTX treatment
Study Design:	The study is a parallel two-group randomized controlled trial in which 240 (120 per condition) incarcerated men and women will be randomly assigned within gender to one of two conditions: Condition 1. XR-NTX-OTx. One injection of XR-NTX in prison, followed by 6 monthly injections post-release at a community opioid treatment program. Condition 2. XR-NTX+ MMTx. One injection of XR-NTX in prison followed by 6 monthly injections post-release at the participant's place of residence utilizing mobile medical treatment. All participants will be evaluated at 1-, 2-, 3-, 4-, 5-, 6-, 7- (safety visit) and 12-months after release from prison.
Subjects:	**Inclusion Criteria:** (1) adult male or female inmate at BCF, DRCF, BCCC, MCIW CMCF, MCTC, or RCI and be eligible for release within 30 days; (2) history of opiate disorder [meeting DSM-5 criteria of dependence at the time of incarceration; individuals who do not meet criteria at time of incarceration and become addicted during incarceration will be eligible]. Inmates not meeting the opioid-dependence criterion will be eligible if they were treated in an opioid agonist treatment program during the year before incarceration (3) suitability for XR-NTX treatment as determined by medical evaluation; (4) currently opioid-free by history, with negative urine for all opioids and no signs of opiate withdrawal; (5) willingness to enroll in XR-NTX treatment in prison [not currently in or planning to pursue agonist (methadone, buprenorphine) treatment at release]; and (6) planning to live in Baltimore City or County (individuals planning to live outside of Baltimore City/county will be allowed to participate as long as they agree to travel to the treatment clinic if randomized to OTX. **Exclusion Criteria:** (1) Liver function test levels greater than three times normal (if a blood sample is not obtained at baseline participants will still be eligible for participation); (2) Active medical illness that may make participation hazardous (e.g., unstable diabetes, heart disease). Adequately treated medical conditions are acceptable; (3) Untreated psychiatric disorder that may make participation hazardous (e.g., untreated psychosis, bipolar disorder with mania). Adequately treated psychiatric disorders and appropriate psychotropic medications will be allowed; (4) History of allergic reaction to XR-NTX; (5) Current chronic pain diagnosis for which opioids are prescribed; (6) creatinine above normal limits; (7) pregnancy (for women); (8) Breast-feeding (for women); (9) suicidal ideation (within the past 6-months); and (10) Body Mass Index (BMI) > 40
Study Product:	Vivitrol ® (naltrexone for extended release injectable suspension) 380 mg per month delivered in monthly intramuscular injections
Duration:	7 months (1 injection in prison and 6 in the community.
Sample Size:	240 subjects
Statistical Methodology:	A Generalized Linear Mixed Model (GLiMM) will be used to conduct all analyses.

List of Abbreviations

Abbreviation/specialist term	Explanation
XR-NTx	Long acting naltrexone
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
MTC	Metropolitan Transition Center
BPRU	Baltimore Pre-Release Unit
JPRU	Jessup Pre-Release Unit
BCCC	Baltimore City Correctional Center
MCIW	Maryland Correctional Institute
CMCF	Central Maryland Correctional Facility
MCTC	Maryland Correctional Training Center
RCI	Roxbury Correctional Institution
GLiMM	Generalized Linear Mixed Model
MMTx	Medical Mobile Treatment
OTx	Opioid Treatment Program
CJ	Criminal Justice
PI	Principal Investigator
Co-I	Co-Investigator
AE	Adverse Event
SAE	Serious Adverse Event
FRI	Friends Research Institute
GLCC	Glenwood Life Counseling Center
ASI	Addiction Severity Index
TLFB	Time Line Follow Back
UDS	Urine Drug Screen
OOS	Opioid Overdose Scale
VAS	Visual Analog Scale (Craving)
RAB	Risk Assessment Battery

Schematic of Study Design

Figure 1. Study Flow



Statement of Compliance

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the <NIH IC> Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Michael S. Gordon, DPA Michael S. Gordon
Print/Type Name

Signed:
_____ Date: _____

1.0 SPECIFIC AIMS

Heroin use has risen significantly over the past 11 years[1] with heroin overdoses increasing by 23%.[2] Opioid use disorders are a severe problem among jail and prison inmates throughout the world.[3-7] In the United States, there are over 1.5 million state and federal prisoners,[8] of whom an estimated 12-15% have histories of OUDs.[9] Moreover, scarce resources are provided for corrections-based substance use treatment in many nations, and many inmates with OUDs remain untreated;[7,10] and less than .1% receive agonist treatment.[11] Correctional health officials, treatment providers, and policy makers need innovative, effective, and cost-beneficial approaches to help inmates with OUD successfully transition to the community.

We recently completed a Phase 4 pilot, open-label study of long-acting injectable naltrexone (XR-NTX), funded by Alkermes, with prisoners with pre-incarceration OUD. In this study, involving one XR-NTX injection in prison followed by 6 monthly injections in the community, XR-NTX was feasible; all 27 participants got their first injection.[12] XR-NTX was acceptable to correctional officials; it did not disrupt security and other prison routines and there was no concern about its diversion. An expected benefit of XR-NTX was opioid blockade for 30 days; there were no overdoses in the first month post-release. However, an important challenge was that while 78% of participants received their first community injection, only 37% received their 5th and 6th injections. In our multi-site study of parolees/probationers funded by NIDA,[13] 308 participants were randomized to XR-NTX across five sites in which 95% received the first injection; 65% received their 5th and 59% received their 6th injections. XR-NTX adherence rates were higher in parolees and probationers and roughly equal to opioid agonist treatment but still dropped off by month 6. Also, most parole/probation participants were recruited from community treatment programs and were nearing completion of treatment at study entry, which meant that they were more likely to have more stable lives than newly released prisoners. These results and many stressors faced by newly released prisoners, noted below, suggest that enhancements to prison initiation of XR-NTX are needed in order to ensure continued adherence to XR-NTX treatment.

Many of our XR-NTX prisoners left treatment because of the need for stable housing, legitimate employment, child care, securing health benefits, addressing medical and psychiatric issues, and meeting requirements regarding criminal justice supervision interfered with continued treatment. Thus, a ***Mobile Medical Treatment approach*** that will provide medication at the client's place of residence might improve adherence and expand capacity and treatment access by reducing travel time and cost.[14] Many programs have implemented mobile services, including for opioid addiction using LAAM,[15] methadone,[14,16,17] HIV education and testing,[18] HIV treatment,[19] for mental health services[20] and cancer information and support.[21,22] In summary, the above studies were successful in increasing access and engaging clients in treatment.

1.1. Design

The proposed study is a parallel two-group randomized controlled trial in which 120 incarcerated men and 120 incarcerated women will be randomly assigned within gender, to one of two conditions: (1) **XR-NTX+ MMTx.** One injection of XR-NTX in prison followed by 6 monthly injections post-release at the participants's place of residence utilizing mobile medical treatment; or, (2) **XR-NTX-OTx**. One injection of XR-NTX in prison, followed by 6 monthly injections post-release at a community opioid treatment program. All participants will be confirmed opiate-free prior to XR-NTX injection, and evaluated at 1-, 2-, 3-, 4-, 5-, 6-, 7- (safety visit) and 12-months after release from prison.

1.2. Specific Aims

Aim1. To compare the two study conditions in terms of: (a) XR-NTX treatment adherence; (b) opioid use; (c) criminal activity; (d) re-arrest; (e) re-incarceration; and (f) HIV risk-behaviors (i. needle use; and ii. risky sexual behaviors).

Aim 2. To determine if the number of months of post-release XR-NTX treatment is related to outcomes (a)-(f), and if so, is there a point at which XR-NTX v. Non-XR-NTX equilibrates. Such a finding could be potentially important because it would be informative about the needed length of XR-NTX treatment.

1.3. Significance and Public Health Impact

The proposed study is innovative because it would be the first randomized clinical trial in the US assessing effectiveness of receiving XR-NTX using mobile medical treatment compared to XR-NTX at an opioid treatment program. The public health impact of the study will be highly significant and far-reaching because most individuals with OUD do not receive treatment while incarcerated, thereby substantially raising their

likelihood of re-addiction, overdose death, HIV/AIDS infection, and re-incarceration. Finally, many individuals in the criminal justice system drop out of treatment and therefore increasing ways to improve adherence by attempting to: 1) expand capacity; and 2) implement access by providing treatment at their place of residence may positively impact outcomes.

2.0. SIGNIFICANCE

2.1. Opioid Use Disorder (OUD) among Incarcerated Individuals

OUD is a severe problem among jail and prison inmates. Inmates in the US, Canada, Australia, and many European and Asian nations have disproportionately higher rates of OUDs than their general populations.[3-7] In the US, there are over 1.5 million state and federal prisoners,[8] of whom an estimated 12-15% have histories of OUD.[9] Moreover, few resources are provided for corrections-based substance use treatment in many nations, and many inmates with OUDs remain untreated;[7,10] and less than .1% receive agonist treatment.[11]

2.2. Untreated Opioid Use Disorders among Inmates: Adverse Consequences

Scarce resources are available for corrections-based substance use treatment in many nations, and many inmates with OUD remain untreated.[3,6,7,23] As a consequence, opioid use either continues or resumes rapidly after release from incarceration,[3,7,24] placing newly released inmates at extremely higher risk for death from drug overdose[25-32] and for infections with human immunodeficiency virus (HIV) and hepatitis B and C.[3,5,33] Opioid use among newly released inmates also has adverse public safety consequences, as it typically results in increased criminal activity[33-36] and re-incarceration.[34,37,38] Individuals with OUD regularly engage in criminal activity, mainly illicit drug trafficking, often on a daily basis; such trafficking, in turn, typically leads to higher rates of violent crime.[39-42]

2.3. Need for Continuity of Care for Inmates with Opioid Use Histories

Extensive evidence documents that continuity of substance treatment from prison to the community is associated with superior treatment outcomes.[3,7,33,37,43-50] Continuity of care provides ongoing treatment, reduces rates of opioid and other illicit drug use and crime, as well as valuable support for newly released individuals to cope with problems related to re-entry into the community: unstable housing, unemployment, and pressure from drug-using peers to resume drug use.[7,33,51]

2.4. Pharmacotherapy in Criminal Justice Settings

A growing body of evidence supports the effectiveness of opioid agonist pharmacotherapy in jail and prison settings for both inmates who were using opioids at initiation of maintenance treatment[37,52-57] and inmates who were previously, but not currently, opioid-dependent.[43,45-47,58] However, many American prison and jail administrators are opposed to opioid agonist medication in their facilities, largely because of their preference for drug-free interventions[59-63] and concerns about diversion of medication, especially buprenorphine.[64]

2.5. Long-acting Injectable Naltrexone

The use of long-acting injectable naltrexone may be a promising form of treatment for pre-release prisoners. Naltrexone blocks the intoxicating and reinforcing effects of opioids, but has no opioid-like effects. When taken regularly, it reduces opiate-taking behavior. VIVITROL® (naltrexone for extended-release injectable suspension, XR-NTX) is supplied as a microsphere formulation of naltrexone for suspension and is to be administered by intramuscular (IM) gluteal injection every 4 weeks (once a month). In 2010, it was approved for the prevention of relapse to opioid dependence, following opioid detoxification. Administered as a monthly injection, long-acting naltrexone eliminates the need for adherence to daily oral therapy, and thus has the potential to improve clinical outcomes for this indication. Moreover, monthly administration avoids the daily plasma concentration fluctuations associated with daily oral administration of naltrexone and its major metabolite, 6β-naltrexol. Its lower frequency of administration, the fact it has no opioid-like effects and cannot be diverted by patients, may make long-acting naltrexone more acceptable to corrections officials than methadone or buprenorphine. The primary reason for failure of oral naltrexone treatment for both opioid addiction and alcoholism has been failure on the part of patients to adhere to the daily medication regimen.[65,66] Long-acting naltrexone reduces the adherence problem as confirmed by studies showing blockade of injected opiates for over 30 days. Importantly, a sustained release medication may protect participants from overdose death within the critical one month post-release period.[25,31] Long-acting naltrexone may also be more attractive to correctional officials than methadone or buprenorphine because there is no potential for abuse or diversion.

Because naltrexone has no abuse potential, and is not a controlled substance, there is greater flexibility in settings in which naltrexone can be prescribed, including correctional settings. Moreover, controlled environments offer an excellent opportunity to initiate long-acting, injectable naltrexone because individuals with OUD have a higher likelihood of being abstinent from opioids for the required length of time in the controlled correctional environment prior to initiating naltrexone treatment. Extended-release injectable naltrexone has been found effective in reducing opiate use compared to control participants for community corrections populations in the US;[67,68] jail inmates in the US[69] and for Russian heroin-dependent individuals.[70] Results from Russia are especially noteworthy given that in a nation with one of the highest rates of heroin addiction in the world, methadone and buprenorphine are not available.[70]

2.5.1. Why Long-Acting Injectable Naltrexone? Research has provided substantial evidence that the first month, and particularly the first week, after release from prisons is associated with extremely high death rates for former prisoners, mainly from drug overdoses.[27,29-31,71] Although methadone maintenance, initiated 3 months before release and continued in the community, is effective in reducing heroin use,[43,45,72-74] individuals still have to regularly go to treatment programs despite clients' lack of transportation and responsibilities regarding child care and employment. Furthermore, many are homeless, and finding safe and secure shelter is often a priority over attending drug treatment. There is also a need to take medication on a daily or near-daily basis. In contrast, with XR-NTX, medication is administered monthly and daily or near-daily attendance at drug treatment programs is not mandatory. Also, newly released prisoners, including those with pre-incarceration heroin addiction, face considerably more challenges to successful re-entry than in previous years, specifically regarding unemployment, lack of job skills/education, and fulfilling criminal justice related requirements.[75,76]

2.6. Mobile Medical Treatment

Mobile treatment for chronic diseases have been implemented in a variety of settings. Mobile treatment provides an opportunity to expand outreach to surmount barriers to traditional clinic treatment for chronic disease. A number of programs have implemented mobile services including for opioid addiction using LAAM,[15] methadone,[14,16,17] HIV education and testing,[18] HIV treatment,[19] for mental health services[20] and for cancer information and support.[21,22] In summary, the above-mentioned studies have been successful in increasing access and engaging clients in treatment. More importantly, the Greenfield et al.,[14] study indicated patients in the methadone mobile treatment group were retained in treatment for a median of 15.5 months compared to a median of 3.9 months for the patients at the fixed sites. It is well known that, regardless of type of treatment, greater treatment duration is associated with reduced substance use and criminal activity.

2.6.1 Why an XR-NTX mobile medical treatment study is needed. As emphasized by Hall et al.,[17] we need additional strategies that state and local governments can use to increase opioid treatment participation by broadening its reach to different types of patients such as pre-release prisoners, community corrections populations that are often socially disenfranchised and have high opioid use. Furthermore, the stigmatization of methadone and the difficulty for certain individuals to enter and continue treatment based on restrictions for individuals in the criminal justice system[61,62,77] might make mobile medical XR-NTX treatment more appealing to criminal justice professionals that have to monitor the movement and activities of parolees in the community.

2.7. Efficacy of Naltrexone with Criminal Justice Populations: Research by the Current Investigators

The current Investigators have considerable experience conducting pharmacotherapy trials with criminal justice populations using different medications. The three most relevant studies are: **1.** XR-NTX among Parolees, Probationers Pilot Study (Dana Foundation); **2**. Treatment Study Using Depot Naltrexone (5/6) Baltimore Protocol Treatment Site (NIDA# R01 DA024556); and **3.** A Phase 4, Pilot, Open-label Study of VIVITROL® in the Prevention of Re-arrest and Re-incarceration (Alkermes).

2.7.1. XR-NTX Among Parolees, Probationers Pilot Study. During 2007-2008, a multi-site pilot study (lead site PI Charles O'Brien of the University of Pennsylvania) examined depot naltrexone (Depotrex®) among opioid-dependent parolees and probationers. This feasibility study provided monthly injections to volunteers for 6 months. Sixty-one participants were recruited across five sites, including the present FRI research team site. Six-month outcomes showed that those who completed naltrexone treatment had significantly fewer opioid-positive urines and were less likely to have been re-incarcerated than participants who had not completed treatment.[67] There were a number of study limitations. There was a lack of a comparator group. There was a overall low follow-up rate of 66%, which varied considerably across sites. We compared a 3-month XR-NTX

treatment protocol from 1 site with a 6-month protocol from the other 4 sites. The statistical tests were bivariate with no control variable used in the analyses regarding outcomes.

2.7.2, Treatment Study Using Depot Naltrexone (5/6) Baltimore Protocol Treatment Site. The same investigators from the pilot study recently completed a 5-year multi-site study that examined the extent to which a monthly XR-NTX injection prevents relapse compared to treatment-as-usual (TAU) among probationers and parolees.[78] This 5-site open-label RCT compared 24 weeks of XR-NTX (*n*=153) to usual treatment (*n*=155). Participants randomized to XR-NTX had a longer median time-to-relapse (10.5 vs. 5.0 weeks, *p*<0.001), were less likely to relapse (43% vs. 64% of participants, *p*<0.001), and provided more opioid-negative urines (74% vs. 56%, *p*<0.001). There were several limitations to this study. An open-label effectiveness design increases generalizability yet is subject to increased attention, recall, and assessment bias. The agreement between this study's results and those of other recent trials are reassuring regarding validity. Eligibility criteria did not distinguish by disease severity or active vs. prior opioid use.

2.7.3. A Phase 4, Pilot, Open-label Study of VIVITROL® in the Prevention of Re-arrest and Re-incarceration. This was a Phase 4B, open-label, longitudinal, single cohort, pre-post study. Pre-release opioid-dependent inmates from four Maryland area prisons (three for men and one for women) receive one injection of XR-NTX prior to release from prison and are then offered six monthly injections of XR-NTX for six months post-release. Following prison release, participants were seen for study visits and receive XR-NTX at Glenwood Life Counseling Center in Baltimore, MD. Participants were assessed at 10 time points: at screening (study entry: approximately one month prior to release from prison), at baseline (approximately 1 week prior to release), and then monthly for 6 treatment visits, an end-of-treatment visit, and a safety follow-up visit following their release from prison. . We provided XR-NTX to 27 prisoners, of whom 100% received their first injection in prison; 21/27 (77.8%) received their first community injection, 18/27 (67%) received their second community injection; 13/27 (48%) received their third community injection; 11/27 (41%) received their 4th community injection, 10/27 (37%) received their 5th community injection, and 10/27 (37%) received their 6th community injection. Over the one–year enrollment period in this study, 97 individuals were screened for interest; 23 were initially not eligible, and 74 consented. Of these 74, 9 refused, 6 were released early and/or transferred to other prisons; 2 failed to meet the OUD criteria and 3 were positive for buprenorphine (all would have been ineligible for the presently proposed study). Fifteen inmates were excluded for medical reasons, 7 for psychiatric reasons and 5 for both psychiatric and medical reasons. According to the study physician and Co-I on the proposed study, Dr. Fitzgerald, most, if not all, of these 27 excluded for medical and/or psychiatric reasons would have been eligible for the presently proposed study, as the proposed study would not exclude individuals with appropriately treated medical and/or psychiatric conditions. Results indicate participants completing 6 compared to participants completing less than 6 injections were less likely to test positive for opioids in the community (0% vs. 63%, respectively; *p*=.003). Although not statistically significant, individuals who did not complete all 6 injections were more likely to be re-arrested compared to those completing all 6 community injections (31% vs. 0%, respectively; *p*=.12).[12] The limitations of this study included a small sample size which was highly selective and lack of a comparator group. Finally, because the rather long list of exclusion criteria were mandated by the funding agency, the ability to generalize results is limited. The proposed study will have a larger sample size, comparator group, and less stringent exclusion criteria.

2.8. Efficacy of Naltrexone with Criminal Justice (CJ) Populations: Other Research

To date, we are aware of only two RCTs using oral naltrexone with cj populations and one study using long-acting naltrexone with individuals leaving jail. Cornish et al.[79] randomly assigned federal probationers to receive either oral naltrexone or TAU. Probationers randomized to the naltrexone condition had fewer opiate-positive urines (8%) compared to the TAU group (30%), and lower rates of re-incarceration (26% *v*. 56%). More recently, Coviello et al.[80] randomly assigned 111 probationers/parolees to oral naltrexone or TAU. They found no significant differences between conditions in terms of both retention and negative opioid urine tests. Lee et al.[13] conducted an 8-week open-label randomized trial and randomized to XR-NTX (*n*=17) versus no medication (*n*=17) within 10 days prior to jail release. Acceptance of XR-NTX was high; with 15/17 initiating XR-NTX treatment. Rates of opioid relapse were lower among XR-NTX participants: 38% versus 88% (*p*<.004) and more XR-NTX urine samples were negative for opioids, 59% versus 29% (*p*<.009).

2.9. Major Differences between Individuals in Prisons, Jails, and Community Corrections

There are major differences between prisoners and offenders on community supervision. The criminal history of prisoners is more serious, frequent, and varied.[33,76] Therefore, the crime-reduction potential of XR-NTX may be greater when used with prisoners than with other criminal justice clients. Furthermore, and especially significant, there are extremely important physiological differences between prisoners compared to other offenders (those in jail and on community corrections). In contrast to parolees and probationers, who are at large in the community, who have full opportunity to use opioids and other illicit substances, most prisoners in the United States with histories of OUD do not have full opportunity to use drugs in prison (although use of illicit substances does occur, it is typically more occasional than on a regular basis).[7,81] Therefore, and unlike most jail inmates, who have relatively short incarceration stays and do not lose their tolerance to opioids, most such prisoners lose their tolerance to the respiratory depressant effects of opioids during incarceration. This distinction is critical, given the overwhelming evidence for the extremely high death rate from drug overdose among newly released prisoners.[27] Monthly XR-NTX injections, begun in prison, have the advantage of protecting such individuals from relapse to addiction, overdose death, HIV infection, increased criminal activity, and re-incarceration. In addition, most prisoners do *not* receive substance use counseling while in prison, as options in correctional institutions are limited compared to in the community. It is particularly noteworthy that the proposed sample and settings in which XR-NTX treatment is administered are distinctly different from that of the multi-site study (PI O'Brien) in which the current investigators participated. In PI O'Brien's study, participants were recruited in the community, not in a controlled environment (a prison), and must have had some criminal justice involvement (parole, probation, jail, arrest) during the past year. Further, all XR-NTX injections in the O'Brien study occurred in the community, while in the proposed study, the first injection will take place in prison.

3.0. INNOVATION

The proposed study is innovative because it would be the first randomized controlled trial (RCT) in the US assessing effectiveness of receiving XR-NTX using medical mobile treatment compared to XR-NTX at an opioid treatment program. The public health impact of the proposed study will be highly significant and far-reaching because most individuals with OUDs do not receive treatment while incarcerated, thereby substantially raising their likelihood of re-addiction, overdose death, HIV/AIDS infection, and re-incarceration following release. Furthermore, many individuals in the criminal justice system drop out of treatment; therefore, offering opportunities to improve adherence by attempting to: 1) expand capacity; and 2) implement access by providing treatment at their place of residence may positively impact outcomes. The proposed study is significant as to our knowledge it would be the first RCT with long-acting naltrexone in a prison population. While other investigations have reported that naltrexone is effective among parolees and probationers and pilot studies have found that it is feasible with prison inmates, the present study will focus on whether the addition of mobile XR-NTX treatment will increase adherence and thus efficacy of the medication. Finally, the importance of finding a point of equilibration will provide evidence of how many monthly XR-NTX injections will be needed. More importantly, there is a continuing need for RCTs to further examine the efficacy and effectiveness of opioid maintenance therapies within specific incarcerated populations such as prisoners because different criminal justice populations could respond to treatment differently and we could adapt treatment to work better for specific populations.[82]

4.0. APPROACH

4.1. Study Overview

This proposed five-year study will focus on whether the addition of mobile medical XR-NTX treatment will increase adherence and thus efficacy of the medication for pre-release prisoners. Project implementation will occur at four pre-release prisons: 1) Brockbridge Correctional Facility (BCF); 2) Dorsey Run Correctional Facility (DRCF); 3) Baltimore City Correctional Center (BCCC);4) Maryland Correctional Institution (MCIW) for Women; 5) Central Maryland Correctional Facility (CMCF); 6) Maryland Correctional Training Center (MCTC); and 7) Roxbury Correctional Institution (see Maryland Department of Public Safety and Correctional Services **Letter of Support**). Two of these Maryland prisons were sites in our recently completed XR-NTX pilot study (see Research Strategy, above). Following initial screening, informed consent, and medical examination, consenting prisoners at each facility will be block randomized within gender, to either: (See **Figure 1** below):
XR-NTX-OTx: One injection of XR-NTX in prison, followed by six monthly injections in the community post-

release at an opioid treatment program; or **XR-NTX+MMTx**: One injection of XR-NTX in prison, followed by six monthly injections in the community post-release at the participant's place of residence. All participants will be confirmed opiate-free by urine (all participants will receive two urine drug screens after consent) test and negative naloxone and oral naltrexone tests, and evaluated monthly for 7 months with follow up at 1-, 2-, 3-, 4-, 5-, 6-, 7- (safety visit) and 12-months after release from prison. We consider the proposed follow-up schedule advantageous from both a treatment and research perspective. Regarding treatment, it allows for quicker "rescue" for those overdue for XR-NTX injections. Concerning research, it enables us to stay in closer contact with participants and enhances post-release follow-up assessment completion rates, leading to greater generalizability of findings. The proposed study has two specific aims: **Aim 1.** To compare the two study conditions in terms of: (a) XR-NTX treatment adherence; (b) opioid use; (c) criminal activity; (d) re-arrest; (e) re-incarceration; and (f) HIV risk-behaviors (i. needle use; ii. risky sexual behaviors). **Aim 2.** To determine if the number of months of post-release XR-NTX treatment is related to outcome (a)-(f), and if so, is there a point at which XR-NTX v. Non-XR-NTX equilibrates.

4.2. Design Considerations

We considered XR-NTX vs. treatment as usual but it was felt strongly that it would not be ethical to deny services to participants during this crucial transition period from prison to community. We also considered XR-NTX vs. placebo but still were of the opinion of denying newly released prisoners access to an intervention was not ethical. While the methods of this particular design are very strong, the ethics of providing no treatment to newly released inmates can be called into question. Furthermore, although we do not know for pre-release prisoners, past research suggests that XR-NTX is efficacious for probationers. Therefore, it would be unethical to *withhold what we would assume to be an efficacious treatment from some participants. Moreover, our interest was not in whether XR-NTX worked in this population, but to address the unanswered question of whether mobile medical services (XR-NTX) increased medication compliance, thereby reducing opioid use, HIV risk behaviors, and re-arrest, and re-incarceration. *While we understand a control group that did not receive XR-NTX might be considered a potent comparator, we chose XR-NTX without a mobile component as the control group for two reasons: (a) it was the 'obvious' comparison group to our XR-NTX mobile intervention, because we would be able to determine the added benefit of mobile treatment above and beyond XR-NTX alone; (b) Other control groups would not be feasible [methadone or buprenorphine, due to medication regulations, daily dosing, need for increased staffing, and problem with diversion; or unethical (no treatment)].*

4.3. Investigators

The proposed research is a natural outgrowth and extension of the work conducted by the current investigators at FRI. This application for a Phase III RCT seeks to build on the investigators' ground-breaking research using pharmacotherapies with prisoners, probationers, and parolees with histories of opioid addiction.

PI Gordon has substantial experience conducting pharmacotherapy trials with opioid-dependent prisoners, parolees, and probationers. Dr. Gordon was PI on a XR-NTX for prisoners pilot study funded by Alkermes. He is PI on a five-year NIDA-funded Seek, Test, and Treat: HIV in CJS grant (R01DA030771). Importantly, he was Co-I on four NIDA-funded studies highly relevant to the present application: 1) Buprenorphine for Prisoners (R01 DA 021579); 2) Prevention of Relapse to Opioid Addiction Using XR-NTX for probationers/parolees (R01 DA 02455301); 3) a 2-year study, CJ DATS 2: Implementing treatment Initiatives for CJ Clients (R01 UO1 D025233) examining the implementation of pharmacotherapies with cj populations; and 4) Testing Client Linkage to Buprenorphine Treatment from Community Corrections (R01 DA021579-04S1). Dr. Gordon was project manager on the first RCT in the US examining the benefits of prison-initiated methadone;[43,45-47] and the first investigation of the feasibility of BUP-naloxone provided to pre-release prison inmates in Puerto Rico.[83] Furthermore, Dr. Gordon was Co-I of a pilot study examining the feasibility of XR-NTX with probationers and parolees[67] funded by the Dana Foundation.

Co-I Vocci is President of FRI, supervising 10 investigators researching substance abuse treatment. He has more than 30 years-experience in medication development and multi-site clinical trial research, and he administered NIDA's medication development program before accepting the position of President with FRI. Dr. Vocci has published over 100 articles in neuropharmacology and the treatment of substance use disorders.

Co-I Fitzgerald is a physician with over 15 years-experience in the treatment and study of pharmacotherapy for OUD. His research experience includes his collaboration with Drs. Gordon and Kinlock on the all of above-

mentioned investigations.

Consultant O'Brien is Kenneth Appel Professor and Vice Chair of Psychiatry at the University of Pennsylvania, Vice Director of the Institute of Neurological Sciences, as well as Director of the Center for Studies of Addiction. As Chief of Psychiatry at the Philadelphia VA Medical Center, his research has been responsible for numerous discoveries on the nature of addiction and improved the results of treatment for addictive disorders.

4.4. Successes in Research Implementation

4.4.1. Pilot Study on Naltrexone with Prisoners. In our pilot study conducted in Maryland prisons,[12] we achieved three main objectives: 1) we demonstrated that formerly opioid-dependent prisoners would accept XR-NTX treatment, beginning in prison; 2) strengthened our collaboration with the Maryland Division of Correction (DOC) custodial and medical staff by establishing logistics with correctional staff regarding XR-NTX administration; and 3) worked out logistics with our community treatment provider in terms of in-prison and community treatment, thus assuring continuity of care from prison to the community.

4.4.2. Recruitment and Follow-up of Drug-Involved Research Participants. We have been exceptionally successful in obtaining voluntary consent and cooperation of individuals with OUD to participate in research projects. In our previous study of methadone treatment for prisoners, 99% of eligible clients consented to participate, and over 95% of 1-, 3-, 6-, and 12-month post-release interviews were completed.[43,45-47] In our study of Buprenorphine for Prisoners, we have achieved follow-up rates exceeding 92% of study participants at 1-, 3-, 6-, and 12-months after release from prison. In our study of XR-NTX for Probationers/Parolees, we have achieved follow-up rates over 90% at 6-, 12-, and18-months. In our ongoing study involving HIV testing of parolees/probationers, we consented over 2000 probationers/parolees for testing and 100 for our HIV-positive intervention study; follow-up rates are 95% for each of our follow-up periods (1-,6-, 12-, and 15-months).

5.0 SPECIFIC APPROACH

5.1. Maryland Department of Public Safety and Correctional Services (MDPSCS)

Male and female inmates recruited for participation will be drawn from the following seven prisons: 1) Brockbridge Correctional Facility (BCF); 2) Dorsey Run Correctional Facility (DRCF); 3) Baltimore City Correctional Center (BCCC); 4) Maryland Correctional Institution (MCIW) for Women;5) Central Maryland Correctional Facility (CMCF) 6) Maryland Correctional Training Center (MCTC); and 7) Roxbury Correctional Institution (See **Letter of Support** from MDPSCS). The seven facilities are administered by the Maryland Division Department of Correction (DOC), and are staffed by administrative and custodial personnel and by case managers, who provide referral services and are responsible for preparing reports concerning inmates' institutional progress and adjustment. MDPSCS and FRI investigators have an extensive history of collaborating on pharmacotherapy studies for opioid-dependent prisoners.

5.2. Participant Eligibility: Inclusion/Exclusion Criteria

Eligible inmates must meet the following criteria: (1) adult male or female inmate at BCF, DRCF, BCCC, MCIW, CMCF, MCTC, or RCI and be eligible for release within 30 days; (2) history of opiate disorder [meeting DSM-V criteria of dependence at the time of incarceration; individuals who do not meet criteria at time of incarceration and become addicted during incarceration will be eligible];]; Inmates not meeting the opioid-dependence criterion will be eligible if they were treated in an opioid agonist treatment program during the year before incarceration. (3) suitability for XR-NTX treatment as determined by medical evaluation; (4) currently opioid-free by history, with negative urine for all opioids and no signs of opiate withdrawal; (5) willingness to enroll in XR-NTX treatment in prison [not currently in or planning to pursue agonist (methadone, buprenorphine) treatment at release]; and (6) planning to live in Baltimore City or County(individuals outside of Baltimore City/county will be allowed to participate as long as they agree to travel to the treatment clinic if randomized to OTX. Inmates with one or more of the following conditions will be excluded from the study: (1) Liver function test levels greater than three times normal (note: if a blood specimen is unable to be drawn the individual will not be excluded from participation); (2) Active medical illness that may make participation hazardous (e.g., unstable diabetes, heart disease). Adequately treated medical conditions are acceptable; (3) Untreated psychiatric disorder that may make participation hazardous (e.g., untreated psychosis, bipolar disorder with mania). Adequately treated psychiatric disorders and appropriate psychotropic medications will be allowed; (4) History of allergic reaction to XR-NTX; (5) Current chronic pain diagnosis for which opioids are

prescribed; (6) creatinine above normal limits; (7) pregnancy (for women); (8) Breast-feeding (for women) (9) suicidal ideation (within the past 6-months); and (10) Body Mass Index (BMI) > 40.

5.3. Participant Recruitment Procedures

The study will employ the following procedures, which have been successfully utilized in Friends Research Institute's (FRI's) previous randomized trials implementing pharmacotherapy with prisoners. Maryland Department of Correction (DOC) personnel will schedule project orientation appointments with research staff for the Baltimore area prison inmates with less than 60-90 days to serve. Group orientation sessions will be conducted at each prison, in which research staff will explain study procedures and eligibility requirements. Potentially interested inmates will then meet individually with research staff for an in-depth discussion of the purposes, procedures, risks, and benefits, of study participation, and to make a preliminary determination of eligibility, subject to confirmation during the physical examination (see below). Immediately after providing informed consent, each potential participant is scheduled for administration of the baseline measures. Following baseline assessment, which is used, in part, to confirm eligibility regarding histories of opioid addiction and nature and severity of medical and psychiatric problems, each potential participant will meet with the project medical staff for a medical history, physical examination, and laboratory tests to confirm eligibility and suitability for XR-NTX administration, and to discuss the potential risks and benefits of study participation. Individuals who do not meet medical eligibility based on physical examination or do not wish to initiate XR-NTX following a discussion of this treatment with the study physician will not be enrolled into the study. Potential participants who are determined medically eligible and remain interested in participating in the study will then be randomly assigned to one of the two treatment conditions (see **Random Assignment**, below). Finally, because of the possibility of coercion when working with prisoners, the study RAs will emphasize that the decision to participate or not will not affect the prisoner's status, institutional privileges, or release date. In addition to group orientations we will post IRB approved study flyers in the five prisons (these will be pre-approved locations decided upon by prison administration at each prison).

5.4. Random Assignment Procedure

Participants will be assigned to one of two conditions (**XR-NTX-MMTx** or **XR-NTX+OTx**) using a random permutation procedure, such that, within gender for each block of 2, 4, or 6 participants, half will be assigned at random to the XR-NTX-MMTx Condition [*n*=120: 60 men, 60 women] and half to the XR-NTX+OTx condition [*n*=120: 60 men, 60 women], ensuring that both male and female participants have an equal chance of being assigned to either condition.[85] [Random block sizes will be used in order to conceal allocation to treatment condition. Sealed envelopes will be prepared for the study physician based on this block randomization procedure so that he can explain the condition to which a participant has been assigned. He will open the designated envelope and inform the participant to which one of the two conditions s/he has been assigned. This assignment procedure will be performed by the study physician so that, immediately after assignment to treatment condition, consent to medication initiation can be obtained from participants.

5.5. Participant Attrition

Consistent with our previous studies, we will collect detailed locator information that has enabled us in the past to successfully locate participants for follow-up. Thus, we anticipate follow-up rates well over 90%, which is consistent with our previous studies conducted at FRI.[43,45-47,74,81]

5.6. Medical Services in Prison

5.6.1. Treatment Clinic. Glenwood Life Counseling Center (GLCC) has been in continuous operation for 41 years. It is a State of Maryland- and CARF-certified outpatient drug treatment program that treats over 600 patients. GLC provides individual and group drug abuse counseling, HIV assessment and risk-reduction counseling, and a limited amount of family-based therapy. Its medical director, Dr. Fitzgerald, served as the study physician on the PI's prison methadone, buprenorphine, and XR-NTX studies. The clinic is well-suited to continue its collaboration on the proposed study, in which it will provide XR-NTX services in the prison as well as in the community. Dr. Fitzgerald will perform all prison medical examinations and the nursing staff will provide prison-based injections under his supervision within10 days of release.

5.6.2. Pre-release extended-release XR-NTX. XR-NTX treatment will likewise be administered by the nursing staff of GLCC under Dr. Fitzgerald's supervision. Participants will receive one injection within 10 days prior to release. Long-acting, injectable naltrexone (Vivitrol ®) will be used, at a dose of 4cc (380mg of

naltrexone), administered by intramuscular injection to the buttocks (alternating sides monthly). Note: Participants can request to receive the intramuscular injection to the buttocks on the same side at each monthly visit. VIivivtrol® has the advantage of being FDA-approved for treatment of alcohol and opioid dependence, hence commercially available with strong safety data. Participants who deny opioid use in the past 10 days and who provide a specimen that tests negative for opioids on an instant urine test will receive a naloxone challenge test (Note: participants will receive two urine drug screens after consent: 1) one within 7-10 days of the injection; and 2) on the day of the injection). Naloxone is a short-acting opioid antagonist. This test consists of an intravenous (or intramuscular for participants' without venous access) injection of a 1.0mg of short-acting naloxone followed by a 20-minute observation period. A positive test will cause the temporary (up to 40 minutes) appearance of opioid withdrawal symptoms. Following a negative naloxone test, participants will be administered a low dose of oral naltrexone (12.5 mg) to further determine whether they will be able to tolerate depot naltrexone. If the participant has withdrawal symptoms in response to either the naloxone test or the oral naltrexone dose, the study physician will treat these symptoms with other medications. The medical staff of all prisons are highly experienced in treating opioid withdrawal, will be fully aware of the ongoing study, and will be able to provide symptomatic treatment to participants in the unlikely event that it is needed when study staff are not on the premises. Such issues may consist of the following: 1) withdrawal; and/or 2) injection site reaction. Prior to discharge, participants will receive an information card about naltrexone to carry with them at all times which will alert any medical providers about the characteristics of naltrexone. Ten days before anticipated release from prison, each participant will have an exit interview with the study's Research Assistant (RA). The RA will provide each such participant with a card with the address of GLCC outlining their schedule for their six monthly injections in the community. In addition, those randomized to XR-NTX+MMTx will receive a pamphlet 10 days before from the study RA detailing the procedures and operations of receiving medication at their place of residence. Follow-up injections will be scheduled 28 days (4 weeks) after first prison injection.

5.6.3. **Overdose Prevention*.*** The study physician and nurse will provide overdose prevention education at the time of XR-NTX injection in prison. We will use the overdose prevention video, "Staying Alive on the Outside" created by Green, Rich et al.[86] that was developed specifically for incarcerated populations and is currently used in Rhode Island Department of Corrections and other prison facilities. This video will be shown to all participants prior to release from prison. In addition, at each monthly follow-up visit in the community, the study nurse will provide prevention education information that was developed by the Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA's Overdose Toolkit[87] is a guideline and checklist focusing on the following: 1) how to avoid overdose, 2) what is naloxone, 3) preventing overdose, and 4) reporting side effects. This checklist will be reviewed with all participants at their monthly visits with the study nurse.

5.7. XR-NTX Treatment in the Community

5.7.1. Glenwood Life Counseling Center for XR-NTX injections. The participants randomized to XR-NTX-OTx will go to GLCC only to receive injections under the direction of Dr. Fitzgerald and the study nurse from prison in order to ensure continuity of care for those receiving XR-NTX in the community (injections will occur every 28 days). The study RA will be in close contact upon release and will provide the client with reminder calls and/or visits prior to each XR-NTX appointment. Prior to each injection (at GLCC and place of residence), the nurse will administer: 1) a drug use questionnaire, and 2) an instant urine drug screening test. If negative for opioid use participants will be administered XR-NTX. If the participant reports using opioids in the past 7-10 days or tests positive on the urine drug screen they will not be administered XR-NTX (see procedures below for missed XR-NTX injections). Once the participant receives the injection, he/she will be monitored for up to 1½ hours. In addition, the nurse will provide the participant with the Naltrexone Medication Card, and tell the participant that he/she should keep it at all times. The nurse or physician will follow the same procedures as in prison.

5.7.2. Place of Residence for XR-NTX injections. For those randomized to receive XR-NTX at their place of residence, specific procedures will be implemented. First, the study nurse will be accompanied by the study RA so two staff members are always physically present. The study RA will confirm the place of residence prior to release from prison using our locator form. Contact will be made with the participant immediately following prison release and subsequently one week before each scheduled injection to verify his/her home address as

many newly released inmates have difficulty acquiring stable housing. The study nurse/RA will make sure the scheduled injection will be at a date/time that is convenient for the participant. In addition, the nurse/RA will reiterate to the participant that they will be asking sensitive questions and providing long-acting naltrexone so the participant may want to make sure they will have privacy. If the scheduled date/time is not convenient or the client feels as they will not have privacy the appointment will be rescheduled for a more convenient date/time. The nurse will be responsible for making sure the study team have all the necessary medical equipment. The nurse and RA will first knock on the door of the participant's residence and explain who they are and ask if the participant is there. If upon entering the residence, the nurse, RA or client feel that privacy is not possible they will reschedule another date/time that is convenient for both parties within 7 days. Moreover, if upon arriving the client is not present we will not disclose the reason for our appointment. The nurse/RA will leave a business card/appointment card to reschedule. At the place of residence, the nurse will administer XR-NTX and follow the same procedures as they would at the clinic (See above). Participants who enter a semi-controlled environment, such as residential or inpatient treatment, will still be eligible to receive XR-NTX if the program continues to allow them to receive it. We have fostered a relationship with many of the Baltimore City treatment programs and we will coordinate with them to continue to provide XR-NTX whenever possible. Individuals that are homeless or become homeless during the course of treatment will be offered the opportunity to receive XR-NTX at GLCC or FRI field office. Based on our previous prison studies with medication we anticipate no more than 4-6 participants will be homeless. Participants who are receiving XR-NTX at their place of residence who require additional medical care will be referred by the study nurse or physician based on their level of need, similar to as they would at a standard outpatient opioid treatment program. Participants will also be encouraged access to individual and group drug abuse counseling, HIV assessment and risk-reduction counseling, and family-based therapy on an as needed basis*. The study nurse will follow the Department of Health and Human Services, National Institute for Occupational Safety and Health Hazards Review manual (NIOSH)[88]. This manual documents procedures and guidelines for providing medical care at a person's place of residence.*

5.7.3. Missed XR-NTX Injections. Participants who miss a monthly appointment will be contacted by the study RA within 24 hours of missing their appointment. The participant will be strongly encouraged to receive their next injection. If they miss a dose and return for a subsequent dose more than 7 days after their missed scheduled injection they will receive the following: 1) drug use questionnaire; 2) urine rapid test; and 3) naloxone challenge before the naltrexone injection. Everyone who reports opioid use or has a positive urine test for opioids during days 29-37 will be given the naloxone test and then the oral naltrexone (12.5mg) prior to the Vivitrol injection. If a participant misses a scheduled injection, he/she will have up to 37 days to receive their next XR-NTX injection. We will also record the number of successful rescues and number of delayed returns to XR-NTX treatment. Participants will no longer receive XR-NTX if they become incarcerated in jail or prison (if incarcerated less than 37 days, they will still be eligible receive their injection).

5.7.4. Withdrawal from Naltrexone: Treatment Safety. Participants may voluntarily stop taking XR-NTX doses at any time without penalty. Naltrexone is an opioid antagonist with no opioid agonist properties and no withdrawal upon discontinuation. Potential side effects relate to the medication itself and to the injection. The most frequent side effects of the medication include opioid withdrawal symptoms for those participants who still have some trace of opioids in their system. There had been reports of increased liver enzymes in individuals receiving high doses of oral NTX in a study of obesity. For this reason, we have an exclusion criterion regarding elevated liver function tests at baseline. The injection can lead to local irritation, infection, and potentially abscesses, which in the most extreme circumstance may require surgical debridement. Participants receiving XR-NTX who require acute treatment of pain will be told that they need to inform their physicians that they are on XR-NTX because XR-NTX is an antagonist and will block the effects of opioid-agonist pain medications. In addition, each participant will also receive a laminated card that indicates they are on XR-NTX that can be provided to their health care provider.

5.7.5. Additional Medical Concerns (Safety). Adverse events (AEs) and Serious Adverse Events (SAEs) will be tracked monthly at each follow-up appointment. In addition, in cases where participants have elevated liver enzymes and will be discontinued on XR-NTX, they will be linked with follow-up medical services to monitor liver function. All participants requiring additional medical or psychiatric care will be monitored and

followed up and be referred for additional care on a case-by-case basis. All participants are under the care of the study physician and GLC and will be monitored monthly through treatment phases. Where further medical treatment is required, appropriate referrals and consultation will be ongoing. Our study physician will follow the recommendations in the SAMHSA (2015) Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of opioid Use Disorder: A Brief Guide by referring a patient for more intensive or specialized care.

5.8. Measures

Assessment of participant characteristics and/or performance will involve a multidimensional set of instruments administered by trained research interviewers. See **Figure 2,** for a schematic of measures and when they are administered. Sources of information will include: (1) self-report; (2) official records; (3) urine drug screening results; and (4) treatment program records. Assessment at baseline will provide information on participant characteristics and pre-incarceration histories of substance use, substance use treatment, crime, incarceration, and HIV risk behavior. Participants in both conditions will be paid *$50 cash* for each follow-up visit. Participants

will not be paid for baseline assessments in prison due to the fact that such payments may be viewed as coercion.

5.8.1. XR-NTX Adherence. Data on post-release treatment status will be obtained from GLCC records. Treatment status will be measured at each follow-up point by whether or not a participant received an injection of XR-NTX at each follow-up point (yes *v.* no). We will also collect data on whether a person entered outpatient treatment (yes *v.* no) and the type of services utilized. Treatment duration for individuals who end treatment will be calculated based on the last date of clinic attendance (if a participant fails to receive his/her injection by day 37 s/he would be considered a drop-out). Thirty seven days is used in our current XR-NTX studies as this is how long the medication typically protects the participant. We will also collect data on whether or not participants entered other types of treatment. Follow-up assessments will collect self-report data on reasons why participants entered, did not enter, or dropped out of treatment.

5.8.2. Addiction Severity Index (ASI) with Timeline Follow-Back (TLFB). The ASI is a standardized 40-60 minute measure widely used in research to quantify problem areas in substance-using populations.[89,90] This instrument has excellent inter-rater and test-retest reliability.[89,90] We will also collect data on substance use frequency and criminal activity to cover the entirety of the follow-up periods post-baseline. In addition, we will use the DSM-5 opioid-related-disorder classification[91] to assess opioid use severity (mild, moderate, severe). In addition to the ASI, we will collect baseline data on crime severity which is determined on the basis of a 7-point scale (a higher number indicating greater severity of criminal involvement) and classifies crime severity according to the most serious level of criminal activity in their lifetime prior to the index incarceration.[92]

5.8.3. Biological Assays. Urine will be tested on-site with CLIA waived QuikScreen cups using an immunochromatographic assay for rapid (2-5 minute) qualitative results based on SAMHSA-standard cutoffs for alcohol (20mg/dl or 0.02% BAC), amphetamine/methamphetamine (1,000 ng/ml), cannabis (50 ng/ml), cocaine/ benzoylecgonine (150 ng/ml), and opiates/morphine (2000 ng/ml). In addition, we will test for methadone and buprenorphine, *and for commonly abused prescription drugs (oxycodone, hydrocodone, and codeine) (100 ng/ml), and for Fentanyl (10ng/ml).* Results will be used as outcome measures of heroin and other opioid use as well as to check on the validity of self-reported drug use information. Urine samples will not be obtained on the approximately 10% of participants who we expect to be re-incarcerated. Those participants in methadone or buprenorphine treatment who screen positive only on their respective treatment medication will be counted as negative for their urine drug screening results.

5.8.4. Risk Assessment of Battery (RAB). This self-administered questionnaire, designed to identify individuals engaging in acts that could transmit HIV and other infectious diseases,[93] contains 45-items consisting of three scales: a drug risk, sexual behavior risk, and an overall scale.

5.8.5. Opioid Overdose Scale. This self-administered questionnaire will ask participants to report the number of opiate overdoses where they did and did not receive medical attention. The questionnaire administered at baseline will cover the period prior to the instant incarceration while the questionnaire follow-up in the community, will cover post-release months 1-12.

5.8.6. Visual Analogue Scale (VAS). Participants are asked to place a mark across the line at the point that corresponds to their immediate craving for opioids. Anchors included 0 mm – 'no cravings' to 100 mm – 'most

extreme cravings possible'.[94,95] Participants will be assessed at baseline and at each follow-up visit and asked about peak cravings during the preceding 24 hours.

5.8.7. Health-related quality of life will be measured by the EuroQol 5D (EQ-5D).[108, 109] The preference weights obtained from the EQ-5D will be used to calculate quality-adjusted life-years (QALYs; see section D.4). The EQ-5D is the most widely used generic, preference-based health-related quality of life instrument.[110]

5.8.8. Official Records. As in our previous research,[96] official record data will be obtained from the MDPSCS at 12-months. Data will include type (e.g., charges involved) and number of arrests, convictions, and incarcerations; and the number and length of time of each imposed disciplinary period. Criminal record data will be used to assess the validity of self-report criminal activity data.

5.8.9. Biometric Measures. All participants will complete the following biometric measures for inclusion/exclusion criteria, participant monitoring, and serious adverse event (SAE) and adverse event (AE) reporting. The following biometric measures will be completed (see **Figure 3**): 1) history and physical; 2) liver function tests (note: if a blood specimen is unable to be drawn the individual will not be excluded from participation), hepatitis profile; 3) vital signs; 4) concomitant medications; 5) pregnancy, 6) HIV; 7) Urine toxicology; and 8) AEs.

5.8.10. Data Management/Quality Control. Assessments will be administered by trained RAs, and closely supervised by the PI. RAs will receive training concerning: (a) initiating and developing rapport; (b) sensitivity regarding culture, gender, and sexual orientation; (c) forms administration; (d) serious adverse event reporting; (e) responsibility for maintaining participant confidentiality; and (f) follow-up procedures.

5.9. Study Aims, Hypothesis, Rationale

5.9.1. Aims. The proposed study has two specific aims: **Aim 1.** To compare the two study conditions in terms of: a) XR-NTX treatment adherence; b) opioid use; c) criminal activity; d) re-arrest; e) re-incarceration; and f) HIV risk-behaviors (i. needle use; ii. risky sexual behaviors). **Aim 2.** To determine if the number of months of post-release XR-NTX treatment is related to outcome (a-f above), and if so, is there a point at which XR-NTX v. Non-XR-NTX equilibrates.

5.9.2. Hypothesis. Based on data from the research team's current studies (see above), It is anticipated that the XR-NTX+MMTx condition will have superior outcomes compared to the XR-NTX+OTx condition in terms of outcomes (a)-(f).

5.9.3. Rationale. We are not aware of RCTs using mobile medical treatment for the provision of XR-NTX. However, based on studies utilizing mobile treatment for HIV services, and methadone, which increased access, engagement, and retention, we believe the provision of medical treatment, provided at a participant's place of residence, is expected to yield better adherence, subsequently, improving outcomes mentioned above. If we find a point of equilibration it will tell us how many months we will need to provide mobile treatment (XR-NTX) and at what point it impacts on outcomes-significant given the cost of the medication. It is difficult to provide firm conjectures on this latter question given the lack of research in this area.

Figure 2: Data Collection Schedule

Measures	Source	Interval	Operational Definition
***Aim 1*: Outcomes (a)-(f)**			
a. XR-NTX adherence	Clinic records	B, 1-6	• # of injections due/completed
b. opioid use	ASI/TLFB/UDS	B, 1-6, 7, 12	• days of opioid use • positive opioid urine drug screen
c. criminal activity	ASI/TLFB	B, 1-6, 7,12	• days of crime
d. re-arrest	Official records	12	• time to re-arrest
e. re-incarceration	Official records	12	• time to re-incarceration
f. HIV risk behaviors i. needle use ii. risky sex behaviors	RAB/TLFB	B, 1-6, 7,12	 • scored 0-22 (higher risk) • scored 0-18 (higher risk)
***Aim 2:* Outcomes (a)-(f)**	Source	Interval	Operational Definition
(a)-(f) equilibrates	Above	1-6,12	Time to relapse
Supplementary	Source	Interval	Operational Definition
other treatment	ASI	B, 1-6, 7,12	• Days in other treatment
opioid overdose	OOS	B, 1-6, 7, 12	• # of times overdosed
opioid craving	VAS	B, 1-6, 7, 12	• 0-100 (higher cravings)
Quality of Life	QOL	B, 1-6, 7, 12	

Figure 3: Biometric Measures

Measures	**Data Collection Point**						
Biometric Measures (for inclusion/exclusion criteria, patient monitoring and AE determination)	Baseline in prison	1mo	2mo	3mo	4mo	5mo	6/7mo
History & Physical	✔						✔ (7only)
Liver Function Tests, Hepatitis Profile	✔						✔ (7only)
Vital signs	✔	✔	✔	✔	✔	✔	✔
Concomitant medication	✔	✔	✔	✔	✔	✔	✔
Pregnancy	✔	✔	✔	✔	✔	✔	✔
HIV	✔						✔ (7only)
Urine toxicology	✔	✔	✔	✔	✔	✔	✔
Adverse Events	✔	✔	✔	✔	✔	✔	✔

6.0. Statistical Analyses

6.1. Guiding Principle. Although the description of the statistical approach that follows is more in line with the language associated with a 'traditional' superiority trial, we endorse the "sensible formulation of the significance test" proposed by Jones and Tukey.[97] These authors outline an approach to significance testing that focuses not on the rejection of a null hypothesis, but on determining whether the data favor a determination of superiority or inferiority. As part of their approach, they suggest reporting not only a test statistic and its associated probability value but also a confidence interval and an effect size related to the determination of any difference. It would be our intention in reporting our results to adhere to Jones and Tukey's suggestions.

6.2. Intent-to-Treat Approach. All analyses will be conducted on available study-related data from all participants, regardless of whether or when they drop out of treatment; i.e., the intent-to-treat population is all persons consented and randomized to the study.

6.3. Outcome Measures. Except for criminal justice records, collected at study conclusion, outcome data will have been collected monthly during the project: at baseline (study entry), and at 1, 2, 3, 4, 5, 6, 7, and 12 months following release from prison (see **Figure 2,** above). The resulting dependent variables will be of three distinct types: 1) continuous random variables (e.g., RAB scale scores), assumed to follow a normal distribution; 2) discrete random variables (e.g., number of days of criminal activity), assumed to follow a Poisson distribution; and, 3) dichotomous variables (e.g., treatment adherence, urine drug screening results), assumed to follow a binomial distribution. [All distributional assumptions will be evaluated prior to the conduct of all analyses, and if such assumptions are not met, assumptions will be modified and statistical methods chosen accordingly, and/or outcome measures transformed appropriately. For example, it may be necessary to allow for under- or over-dispersion in the logistic and Poisson regression analyses, or use zero-inflated Poisson or negative binomial models rather than a Poisson model for the count variables.]

6.4. Explanatory Variables. The predictor variables in all statistical models can be categorized as either *Treatment Variables*, *Covariates*, or *Control Variables*. (From a statistical viewpoint, this categorization is arbitrary and is utilized here simply for ease of presentation.)

Treatment Variables. There will be a single treatment variable: Treatment Condition (XR-NTX-MMTx *v*. XR-NTX+OTx).

6.4.1*.Covariates.* Three additional predictor variables – Age, Gender, and age of onset of criminal activity – will be included as "main effects" in all analyses. These "main effects" test for the unique contribution of each of these variables in predicting outcome, above and beyond the effects of Treatment Condition. Each of these variables, as well as its respective interaction with Treatment Condition, will be included as a predictor in order to examine for potential differences in treatment outcome as a function of each covariate, and whether any of these three covariates moderate treatment efficacy.

6.4.2. *Control Variables*. Finally, because participants may know one another through contact at their respective prison, it is possible that participants' responses within a given prison will not be entirely independent of each other. This potential lack of independence must be controlled for by including Prison nested within Treatment Condition and Participants nested within Prison nested with Treatment Condition as random factors. [Although neither of these two effects represents a substantive effect of interest, both must be included in order to produce unbiased estimates and tests of significance for Treatment Condition.]

6.4.3. *Time.* Finally, the "repeated factor" in the statistical analysis of all outcome variables measured repeatedly will be assessment Time point, which will allow for the evaluation of both *differential course and impact* of the interventions as a function of the "between-subjects" Treatment Condition factor. (For information regarding which outcome variables are measured at what assessment time points, see **Figure 2,** above.)

6.5. Statistical Method. A Generalized Linear Mixed Model (GLiMM) will be used to conduct all analyses. [For the case in which the outcome is measured only at the end of study participation (e.g., reincarceration), GLiMM reduces to the generalized linear model (GLiM).] It is not necessary that the within-subjects set of observations either be complete or collected at the same points in time for GLiMM models. GLiMM will make use of all available data, and hence, is an ideal statistical procedure for "intent-to-treat" approaches to data analysis, as occurs in the study proposed herein.

6.6. Missing Data. GLiMM is quite flexible in the presence of missing data for outcome variables, and it is not necessary for participants to have complete outcome data to be included in GLIMM analyses; in general, GLMM will make use of all available data, and hence, is an ideal statistical procedure for intent-to-treat approaches to data analysis in the case of ignorable missingness (ie, MCAR and MAR). However, a pattern mixture model approach[98] to modeling the missingness as part of statistical estimation will be utilized if there are a sufficient number of identifiable patterns to the missingness. The potential impact of missingness and the operation of the missing data mechanism(s) will be examined from a multiple imputation perspective.[99,100]

6.7. Power. Stroup[101] (also see Littell et al.[102]) has outlined a four-step procedure to estimate power for general linear mixed models, which can also be applied to generalized linear mixed models as occur in the proposed study. This procedure was implemented in the current case. For each of the number of Times outcomes were measured (4, 5, 6, 7, or 9), three datasets for each hypothesis were created, assuming the dependent variable was continuous and normally distributed, discrete and Poisson distributed, or dichotomous and binomially distributed. For the normally distributed case, the only non-null effect in the model was the hypothesized effect of interest, with the XR-NTX-OTx condition mean set at 1 at Time 1, decreasing by .1 at each subsequent Time point, while the XR-NTX+MMTx condition means were set at 1 at Time 1, and then adjusted to reflect *"small"*[103] mean differences (.2 of the standard deviation at subsequent Time points) consistent with the hypothesis of interest. [Time was not included in the estimation of power for the criminal justice outcomes because these outcomes are measured only at 12-month post-baseline assessment.] Similar specifications were made for the datasets with outcomes following the Poisson and binomial distributions. Finally, observations were dropped from the data consistent with the expected loss of approximately 10% of participants at the 12-month assessment (see **Participant Attrition**, above). Hence, power was estimated for a design in which the effects were unbalanced in a manner similar to what was expected to occur in the proposed research. Therefore, simulations were conducted under what might be considered "worst-case scenarios." Power was then estimated for three different covariance structures (compound symmetric heterogeneous, first-order autoregressive heterogeneous, and unstructured) of the observations over Time. [Covariance structures can be specified for GLiMM models independent of the location (e.g., mean) structure, so it was only necessary to create a single dataset for the three cases.] Assuming a sample size of 240 and α=.05, the resulting power values (1 – β) for the Treatment Condition X Time effect varying between .81 and .85 in the simulations. From a more rudimentary and slightly less accurate perspective, assuming the primary outcome measures follow a normal distribution rather than binomial or Poisson distributions, power calculations based on the set correlation method[104] can be used to calculate effect sizes for desired power, including under the extremely conservative assumption that no other effect in the model is significant (with the resulting effect size estimates likely to be slight underestimates). In this case, assuming α=.05 and *N*=216 due to attrition (see **Participant Attrition**, above) in order to remain conservative, an effect size of $\mathbf{f}^2$=.037 in the population associated with a Treatment Condition main effect for statistical models in which there is no Time effect (e.g., reincarceration) and effect sizes ranging from a minimum $\mathbf{f}^2$=.046 to a maximum $\mathbf{f}^2$=.072 for the Treatment Condition X Time effects associated with the 4, 5, 6, 7, or 9 Time points for statistical models in which there is a Time effect, would yield a power of .8 for the respective effect. These effect sizes fall toward the "small-to-medium" range, with $\mathbf{f}^2$=.02 considered a "small" effect and $\mathbf{f}^2$ = .15 a "medium" effect.[103] In other words, and imprecisely, under the assumption that the effect in the population was ≥ .037 or ≥ .072, for the Treatment Condition and Treatment Condition X Time effects, respectively, there is an 80% chance of concluding that effect is significant if α is set to .05 and 216 participants are assessed at 12-month follow-up. *Power calculations do not utilize any estimates of treatment efficacy from prior studies. This latter approach to power analysis, although once popular, is often quite limited, as is the case for the proposed study, in that prior studies may have examined populations that are not comparable to the population in the proposed study and/or do not include the same experimental or control conditions, and in all cases, the effect sizes reported in prior studies are generally subject to wide fluctuation due to sampling variability.*[105] *Power was calculated to detect a stated effect size, as detailed in the proposal, an approach consonant with more recent writings regarding power analysis.*

6.8. Supplementary Analyses. We will tabulate (and test for treatment condition differences) for the relative frequency of each adverse event (AE) in each condition, where the examination is based on the proportion of

individuals who experience the AE, and the number of that AE reported. In addition, we will tabulate and test for treatment condition differences) for the relative frequency of opioid overdoses in each condition, where the examination is based on the proportion of individuals who report overdoses during the 12-months post-release. We will also calculate mean scores of cravings at each follow-up.

6.9. Additional Process Data *We will collect three additional process variables: (1) data on housing stability at each follow-up visit that will utilize a checklist to describe the participant's place of residence and the level of stability; (2) data on the distance travelled from place of residence to Glenwood Life Counseling Center (GLC) for participants randomized to TAU; and (3) data on the number of counseling sessions received during the course of the study (this will account for any community counseling received during treatment).*

6.10. Follow-up Analyses. *Follow-up analyses will include select covariates in the model, with a focus on the covariate X BI Intervention Condition (X Time, if an outcome is measured repeatedly).These follow-up analyses can be viewed as either sensitivity analyses or as subgroup analyses[106,107] intended to map the population(s) for which the intervention is maximally useful and/or examine the robustness of the findings under uncertainty in the model. Possible covariates include: (1) crime severity, (2) opioid severity, (3) housing stability, (4) distance travelled from place of residence to treatment clinic; and (5) number of counseling sessions received.*

7.0. Project Timeline

Months 1-5 will be devoted to start-up activities, including confirming logistic arrangements, recruiting and training staff, and developing detailed procedures with prison and treatment personnel, and obtaining IRB and OHRP approval. Recruitment of participants and delivery of interventions will begin in month 6. Five to six prison inmate/participants are projected to be enrolled per month, yielding a total of 240 participants (120 per condition), at the end of recruitment (month 40). Follow-up assessments will be completed by month 53. Months 54-60 will be devoted to dissemination activities (e.g., publication of the primary outcomes paper).

8.0. Impact

This proposed intervention addresses several public health and public safety problems. First, it will likely impact the problem that a substantial number of prisoners with histories of OUD are released to the community and untreated by treating their addictions. Second, by eliminating transportation costs and time, and the requirement that reliable transportation is required for treatment adherence, the treatment comes to the patient rather than the patient must go to treatment. This is likely to improve adherence, which tends to reduce the possibility of addiction. Third, by substantially impacting addiction, in turn, it has increased chances of reducing death from overdose, HIV and hepatitis infection, the frequency of criminal activity, and the likelihood of re-incarceration.

9.0. PROTECTION OF HUMAN SUBJECTS

This Human Subjects Research involves an NIH-Defined Phase III Clinical Trial.

9.1. Potential Risks

9.1.1. Extended-Release Naltrexone (XR-NTX). Participants may experience brief withdrawal symptoms with the naloxone test, although this will be uncommon as only patients with a history of no opiate use and negative urine for opiates will be given the test. Those receiving an XR-NTX intramuscular injection may experience side effects consisting of pain at the site of injection, nausea, or other opioid withdrawal symptoms. In rare cases, an infection at the site of injection has occurred. XR-NTX has been reported to cause increased liver enzymes when it was given in high dose oral form, but this has not been reported with the dose used in the injection. Participants in both conditions carry the risk of relapse to opioid dependence, as is the case for all individuals who have a history of opioid use disorder. Relapse to opioid dependence after a detoxification and opioid-free period, or after discontinuing depot naltrexone, carries a risk of opioid overdose and death because tolerance after a period of abstinence is low. Participants will be informed of these risks and of treatment alternatives, including agonist maintenance.

XR-NTX injections will block the effects of opioid pain medication and all participants randomized to the naltrexone condition will receive a card to present in case of emergency need for opioid analgesia. General anesthetics, nerve blocks, and non-steroidal pain medications are not affected. All individuals who will be administered depot naltrexone will be informed as follows**: "You should carry identification to alert medical personnel to the fact that you are taking depot naltrexone. A depot naltrexone medication card has been supplied to you for this purpose. Carrying the identification card should help to ensure that you can obtain adequate treatment in an emergency. If you require medical treatment, be sure to tell the treating physician that you are receiving depot naltrexone therapy".**

9.1.2. Other Risks. Other risks are expected to be minimal. Participants will be asked to provide sensitive information regarding a number of behaviors, including deviant and criminal behaviors, and are thus exposed to the risks associated with the potential for disclosure of confidential information outside the research context. Because participants will be discussing personal information, including information on psychological functioning, some participants may experience emotional discomfort.

9.2. Protection Against Risks

9.2.1. Risks Associated with XR-NTX. Participants may experience symptoms of opioid withdrawal from the naloxone challenge, oral naltrexone, or XR-NTX injection. In order to minimize the likelihood of withdrawal symptoms, potential participants will be carefully screened with exclusion criteria which include recent opiate use history and a urine test prior to naloxone administration. The study design was carefully crafted to minimize risk of withdrawal by first administering the short-acting naloxone followed by a small oral dose of naltrexone prior to XR-NTX administration. Individuals who do experience opiate withdrawal symptoms from the administered opioid antagonists will be treated symptomatically by the study's medical personnel.

To protect against risks of increase in liver enzymes, study applicants will be excluded if their liver enzymes are greater than triple the normal levels. Also, liver enzyme tests will be repeated during the course of the study and doses withheld if indicated.

Participants will be warned of the risk of opioid overdose should they discontinue XR-NTX and will be informed of alternative treatment, including methadone or buprenorphine treatment. Finally, participants will be informed that they should carry their study identification card with them and provide it to any medical personnel that will be treating them in the future so they can be aware of the need to provide appropriate alternatives to opioids for pain relief.

The study physician has extensive experience in the injection technique. This should minimize the likelihood of injection site reactions. Nonetheless, the FDA has provided the following information for healthcare professionals with regard to Naltrexone Injection Site Reaction [naltrexone for extended-release injectable suspension (marketed as Vivitrol)] FDA Alert [08/12/08] Vivitrol injections may be followed by pain, redness, itching, bruising, and swelling. Sometimes reactions at the injection site can quickly worsen and skin and other tissue can be permanently damaged and require surgery. If an injection site reaction does not improve within two weeks following the injection, or it worsens sooner than 2 weeks, the participant will be instructed to see his/her doctor. The dose of Vivitrol® (380mg) selected for this research has been studied in both normal healthy adults as well as in individuals who were using opioids, alcohol, and stimulants.

9.2.2. Vivitrol (naltrexone for extended-release injectable suspension): Medication Guide Required for Patients. Some people on Vivitrol treatment have had severe reactions at the site of the injection (injection site reactions), including tissue death (necrosis). Some of these injection site reactions have required surgery. The participant will be instructed to seek medical attention immediately if he or she has any of the following things happen at any of the injection sites: intense pain; an open wound the area feels hard; a dark scab large area of swelling; lumps; and blisters. FDA requires that a Medication Guide, which communicates this and other important information about treatment, be provided to all participants.

9.2.3. Risks Associated with Loss of Confidentiality. To assure participant confidentiality, as in our previous and ongoing research, we will obtain a federal Certificate of Confidentiality to protect all data against subpoena and criminal justice investigation; we will provide training to all research staff regarding

responsibilities for maintaining and protecting participant confidentiality. To ensure confidentiality, we will use of unique participant identifiers in the database. Baseline and follow-up measures will be linked by the unique identifiers employed and will be stored in the locked files to which only the Principal Investigator, Co-Investigators, and Project Manager have access. Study findings will make use of aggregate data only and publication or presentation of findings will not involve use of any individual or personalized information.

9.2.4. Risk Associated with Emotional Discomfort. All instruments to be employed have been used frequently and without incident with individuals who are using illicit substances. Research interviewers will be trained to be alert to indication of participant discomfort and will discontinue administration of research instruments if a study participant shows discomfort. In such cases occurring at baseline assessment, referral will be made to institutional medical/case management personnel as appropriate. For follow-up assessments, appropriate referral sources will be available to the interviewer in the event of an adverse reaction that requires intervention, and a clinical appointment to deal with this issue will be scheduled if the participant requests.

9.3. Risk/Benefit Ratio

Every effort will be made to minimize the risks to participants in this study. Exclusion criteria, (e.g., medical status), voluntary participation, and careful and constant medical monitoring and protection of confidentiality will help minimize risk to subjects. With regard to study benefits, all participants will receive long-acting naltrexone in prison and will be referred to substance use treatment in the community. In addition, participants will also receive treatment services in prison that may increase entry and retention into community-based treatment following release and thus decrease the likelihood of readdiction and its negative consequences. Results from this study may help determine the utility of administering long-acting naltrexone to inmates in prison with pre-incarceration opioid addiction histories prior to release and continued post-release either at a standard opioid treatment program or utilizing medical mobile treatment.

9.4. Importance of the Knowledge to be Gained

Although progress has been made in the development of effective treatments for opioid addiction that begin during incarceration and continue during the critical period of transition back to the community, further improvement in efforts at treatment entry and engagement is clearly needed. The development of effective treatment strategies for these individuals with histories of pre-incarceration opioid addiction, who are at especially high risk for HIV infection and death from overdose, is of high public health and safety importance. Therapeutic research that has established the effectiveness of XR-NTX in other settings and with other populations, suggests that the proposed intervention holds considerable promise for effectively treating inmates with histories of opioid addiction who are released to the community. It is especially significant that the proposed study is the first to examine naltrexone using mobile health strategies among soon-to-be released prison inmates with regard to a number of post-release outcomes: XR-NTX adherence, opioid use, criminal activity, and HIV risk behaviors.

9.5. Participation of Prisoners

The proposed study involves research on prisoners and therefore is subject to DHHS regulations that provide additional protections for research involving prisoners as research participants. In keeping with their vulnerable status as prisoners, all study participants will receive treatment prior to release (XR-NTX) in prison and in the community and information on how to access various treatment resources in the community. XR-NTX is approved by the FDA for the prevention of relapse to opioid dependence. Both treatment conditions will be receiving study medication. Thus, the study will not employ a “no treatment” control condition, inasmuch as all participants will receive an active substance use treatment (i.e., XR-NTX).

We are sensitive to the possibility that, given the limited financial resources of many prisoners at this point in time, providing cash compensation at baseline could unduly influence inmates to participate in this intervention study. Furthermore, we consider that the treatment that participants receive is ample compensation for the time that they devote to research procedures at baseline. Therefore, no cash compensation will be provided for baseline assessments. Cash compensation will be provided for follow-up interviews conducted following release in recognition of participants’ contribution of their time and efforts to the research.

We are also sensitive to ensuring that participants are not being coerced to enroll in the study. Thus, the process of participant enrollment (including participant screening, informed consent, baseline assessment, and medical examinations) will take place without correctional staff present, in private discussions with the research and medical staff of the study. Furthermore, as mentioned above, because of the possibility of coercion when working with prisoners, the study RAs will emphasize that the decision to participate or not will not affect the prisoner's status, privileges, or release date.

9.6. Data and Safety Monitoring Plan

9.6.1. Responsibility for Safety Oversight. As in our past and ongoing clinical trial of prison-initiated methadone and buprenorphine treatment, the Principal Investigator and his study staff, the FRI Institutional Review Board (IRB), and a Data Safety Monitoring Board (DSMB) will provide safety oversight for the project. In addition, an external medical safety monitor (an independent physician with expertise in pharmacotherapy and opioid addiction) will report his/her review of adverse events to the PI, the project's medical staff, and the FRI's IRB. The medical safety monitor will review reports on the study and be informed by the PI of any information that has bearing on the safety of the participants. Finally, the PI will be responsible for conducting a literature search on XR-NTX no less frequently than every six months to identify any emerging research findings that might influence study procedures. Finally, the PI and external medical safety monitor will stay alert to any changes in the labeling of naltrexone.

9.7. Report of Safety-Relevant Information to NIDA

The Principal Investigator is responsible for informing NIDA of any safety-relevant actions taken by the FRI's Institutional Review Board as a result of its regular semi-annual reviews and any special reviews of this project. In addition, the PI will inform NIDA of any major changes in the protocol or its status including: protocol amendments; procedural changes; suspension or termination of subject accrual or of the protocol itself; changes in the informed consent or IRB approval status; and other problems or issues that could have a significant impact on individuals' consent to participate.

9.8. Adverse Event Reporting

As in our other clinical trials, adverse event reporting will follow the usual FRI policy. Serious adverse events (SAEs) include any of the following outcomes for the participant: 1) death; 2) acute life-threatening incidents; 3) hospitalization or the prolongation of a hospitalization; 4) persistent or significant disability or incapacity; or, 5) birth defects. Should they occur, these events may be communicated to the PI by participants and/or staff, or may be observed directly by the PI. SAEs will be reported regardless of whether they are considered study related. Adverse events will be monitored by nursing and medical staff and will include: nasopharyngitis, insomnia, and injection site pain among other more frequently reported reactions.
The completed Serious Adverse Event Form will contain: subject's ID#, gender, age, the title and date of the Serious Adverse Event, and narrative explanation. The Serious Adverse Event Report Form tracks how the research staff was notified of the event, dates of consent, study medication, study screening for inclusion/exclusion, study treatment received, outcome of study treatment (e.g., was participant using illicit substances or abstinent, other relevant clinical information), dates and circumstances of the hospitalization/death, whether alcohol or illicit substances were known to be involved, and participant status at last clinical or research contact. In cases of participant death, the report also includes appropriate substantiation from clinic records, as well as copies of the death certificate, autopsy report, or medical record. The Principal Investigator will address whether there is a need to redesign or amend the protocol, and/or to inform current and future subjects of a change in description of risk (in consent form and protocol or other). The Principal Investigator will state whether the event was "expected" and assess its "relatedness" to the study medication or intervention.

9.9. Relatedness

The Principal Investigator (Dr. Gordon), Medical Co-I (Dr. Fitzgerald), and Medical Consultant (Dr. O'Brien) will review the information and offer an educated opinion about the relatedness of the event to the study drug.
1 = Definitely – The adverse event:
a) Follows a reasonable temporal sequence from drug administration.

b) Abates upon discontinuation of the drug (de-challenge).
c) Is confirmed by reappearance of the reaction on repeat exposure (re-challenge).
2 = Probably – The adverse event:
a) Follows a reasonable temporal sequence from drug administration.
b) Abates upon discontinuation of the drug (de-challenge).
c) Cannot be reasonably explained by the known characteristics of the patient's clinical state.
3 = Possibly – The adverse event:
a) Follows a reasonable temporal sequence from drug administration.
b) Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.
4 = Remotely – The temporal association between the adverse event and the drug is such that the drug is not likely to have had any reasonable causal relationship with the observed event. The assessment of whether the drug was present prior to the reaction or event could be made by history or by blood level.
5 = Definitely not – The adverse event is definitely produced by another known cause, and is not temporally associated with the drug.
9 = Unknown – only used while awaiting further information.

In any given case, the Ps will make an initial SAE report to the FRI IRB and the study's medical safety monitor within 48 hours. The PI will submit follow-up reports on participants who have experienced an SAE until the outcome of the event is known. This follow-up information will be reported to the external medical safety monitor and FRI's IRB. A summary of SAEs will be reported to NIDA Program staff through the annual non-competing renewal application mechanism. AEs will be aggregated weekly by nursing staff and reported to the PIs. The PIs will report these AEs in aggregate to the DSMB and IRB on a regular basis.

In addition to the above actions, all regulatory reporting required by the FDA will be closely followed.

9.10. Reporting of Unanticipated Risks or New Findings

Any unexpected Serious Adverse Events which occur during the course of this investigation and follow-up period, whether or not related to the study protocol, will be reported within 24 hours by telephone to NIDA (NIDA program official TBN), and the FRI IRB. The telephone report will be followed within 2 days by sending a completed Serious Adverse Event Form with demographic information and a narrative explanation of the event. The narrative will also provide details of relevant screening measures, medical history & physical, treatment compliance, participant reports of Serious Adverse Events and any other information the Principal Investigator deems appropriate. Attached to the Serious Adverse Event Form will be photocopies of relevant source documents (Case Report Forms). The Principal Investigator will address whether there is a need to redesign or amend the protocol, and/or to inform current and future participants of a change in description of risk, either in the consent form and protocol, or by other written or verbal communication. The written Serious Adverse Event report will also be sent to the FRI Institutional Review Boards.

The PI will also report any new information that may change the risk-benefit ratio to the FRI's IRB, medical safety monitor, and the NIDA Program Official. This information may consist of findings from the current study or other studies. Any changes in the protocol or informed consent as a result of this information will be promptly reported to the NIDA Program Official.

The PI will also report any irregularities in the conduct of the study, such as improper participant enrollment, obtaining of informed consent, and data collection or processing to the FRI's IRB, medical safety monitor, and the NIDA Program Official.

9.11. Quality Control of Data

Interviewers will be thoroughly trained regarding administration of interviews and completion of forms and their work will be reviewed on an ongoing basis. Interviewers will review case report forms (CRFs) for completeness and accuracy. Data processing staff will review CRFs the next day. The Project Manager will be advised of any forms needing correction, and he/she will bring these to the attention of the interviewer.
Prior to the conduct of inferential analysis, the raw data will undergo extensive examination for completeness and accuracy by the data entry staff, under direction of the project's statistician.

9.12. Data and Safety Monitoring Board (DSMB)

As in our previous clinical trials of prison-initiated opioid agonist maintenance treatment, a DSMB of outside experts in clinical trials, biostatistics, and criminal justice (prisoner advocate) will be created to review the progress of the study and monitor subject intake, outcomes, adverse events and other safety related matters. The DSMB will meet at the start of study enrollment and every six months for the first year of enrollment and annually thereafter. Members will include a physician expert in the opioid treatment of opioid disorder, a statistician, and a criminal justice expert (prisoner advocate). The DSMB will review all SAEs. The project's statistician will perform interim analyses, at times determined by the DSMB, to determine whether the study should be terminated early as a result of preliminary findings. The Board will also review study enrollment and feasibility as well as the nature and frequency of SAEs in reviewing the safety of the study. DSMB meetings will be convened as needed to discuss new findings, unexpected SAEs related to the interventions under study, or results of any other new findings in the literature that pertain to this study. All DSMB reports will be sent to the PI who will forward copies to the IRB and to NIDA.

9.13. Criteria for Suspending or Terminating the Study

The study may be modified, suspended, or terminated at the recommendation of the PI, DSMB, or by the FRI IRB in the interests of protecting study participants. The study will be modified to comply with any labeling changes for long-acting naltrexone administration made by its manufacturer or by the Food and Drug Administration. The PI, medical safety monitor, DSMB and/or IRB may recommend modifying, suspending, or terminating the study based on the SAE reports. Trials may be terminated for any one or more of four classes of reasons as determined by the DSMB, as specified below: 1) safety/adverse events; 2) favorable benefit-risk ratio; 3) unfavorable benefit-risk ratio; and 4) inability to answer questions regarding trial efficacy.

9.13.1.Termination Due to Safety/Adverse Events. The DSMB's decision to stop the study with regard to safety/adverse event considerations will be based on the number and severity of study-related adverse events, particularly those determined to be fatal and/or extreme. The study may also be terminated if the DSMB decides that there has been an emergence of an unexpected serious adverse event or events.

9.13.2. Termination Due to Favorable Benefit-Risk Ratio. If the results of an interim analysis of post-release outcome data performed by the DSMB provides compelling evidence for the efficacy of the experimental intervention(s), early termination may be recommended. Such a recommendation would not be made without consideration of other relevant information related to the trial and an assessment of the strength of evidence of benefit.

9.13.3. Termination Due to Unfavorable Benefit-Risk Ratio. If the interim efficacy analysis results show compelling evidence for a lack of clinically relevant outcomes, early termination may be recommended by the DSMB. Such a recommendation would not be made without consideration of other relevant information related to the trial (e.g., safety/adverse event issues).

9.13.4. **Termination Due to Inability to Answer Trial Question**. If there are serious flaws in the data or the implementation of the study, the DSMB may recommend termination because the questions concerning efficacy are unable to be adequately addressed. These problems include serious problems in the recruitment/enrollment of participants; threats to internal validity, external validity, construct validity, and/ or statistical conclusion validity. As with the other types of reasons for study termination, noted above, the DSMB will make this decision in consideration with other relevant information regarding the trial.

10. References

1. Lipari RN, Hughes A. *The NSDUH Report: Trends in Heroin Use in the United States: 2002 to 2013.* Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality;2015.
2. Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. *JAMA Intern Med.* 2015;175(6):978-987.
3. Dolan K, Khoei EM, Brentari C, Stevens A. *Prisons and drugs: A global review of incarceration, drug use and drug services.* Oxford: Beckley Foundation;2007. 12.
4. Fazel S, Bains P, Doll H. Substance abuse and dependence in prisoners: a systematic review. *Addiction (Abingdon, England).* 2006;101(2):181-191.
5. Kanato M. Drug use and health among prison inmates. *Current opinion in psychiatry.* 2008;21(3):252-254.
6. Kastelic A, Pont J, Stöver H. *Opioid Substitution Treatment in Custodial Settings. A Practical Guide.* BIS-Verlag: Oldenburg; 2008
7. Kinlock TW, Gordon MS, Schwartz RP. Incarcerated populations. In: Ruiz P, Strain E, eds. *Lowinson & Ruiz's Substance Abuse: A Comprehensive Textbook*. Fifth ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:881-891.
8. Carson EA, Golinelli D. *Prisoners in 2012: Advance counts.* Washington, D.C.: Department of Justice, Bureau of Justice Statistics; 2013.
9. Mumola CJ, Karberg JC. *Drug Use and Dependence, State and Federal Prisoners, 2004.* Washington, D.C.: U.S. Department of Justice, Bureau of Justice Statistics (NCJ 213530);2006.
10. Kinlock TW, Gordon MS, Shabazz H. *Pharmacotherapy for incarcerated individuals with histories of heroin addiction.* Hauppauge, NY: Nova Science Publishers, Inc.; In Press.
11. Fox AD. Opioid Addiction and Criminal Justice Systems: Opportunities to Break the Cycle of Incarceration. *SGIM Forum.* 2015;38(1).
12. Gordon MS, Kinlock TW, Vocci FJ, Fitzgerald TT, Memisoglu A, Silverman B. A Phase 4, Pilot, Open-Label Study of VIVITROL(R) (Extended-Release Naltrexone XR-NTX) for Prisoners. *Journal of substance abuse treatment.* 2015;59:52-58.
13. Lee JD, McDonald R, Grossman E, et al. Opioid treatment at release from jail using extended-release naltrexone: a pilot proof-of-concept randomized effectiveness trial. *Addiction (Abingdon, England).* 2015;110(6):1008-1014.
14. Greenfield L, Brady JV, Besteman KJ, De Smet A. Patient retention in mobile and fixed-site methadone maintenance treatment. *Drug and alcohol dependence.* 1996;42(2):125-131.
15. Kuo I, Brady J, Butler C, et al. Feasibility of referring drug users from a needle exchange program into an addiction treatment program: experience with a mobile treatment van and LAAM maintenance. *Journal of substance abuse treatment.* 2003;24(1):67-74.
16. Buning EC, Van Brussel GH, Van Santen G. The 'methadone by bus' project in Amsterdam. *British journal of addiction.* 1990;85(10):1247-1250.
17. Hall G, Neighbors CJ, Iheoma J, et al. Mobile opioid agonist treatment and public funding expands treatment for disenfranchised opioid-dependent individuals. *Journal of substance abuse treatment.* 2014;46(4):511-515.
18. O'Connor CA, Patsdaughter CA, Grindel CG, Taveira PF, Steinberg JL. A mobile HIV education and testing program: bringing services to hard-to-reach populations. *AIDS patient care and STDs.* 1998;12(12):931-937.
19. Dube C, Nozaki I, Hayakawa T, Kakimoto K, Yamada N, Simpungwe JB. Expansion of antiretroviral treatment to rural health centre level by a mobile service in Mumbwa district, Zambia. *Bulletin of the World Health Organization.* 2010;88(10):788-791.

20. Suggett J, Lloyd C, Meehan T, King R. Is there a difference? A comparative study of Mobile Intensive Treatment Team and Continuing Care Team consumers' clinical and other characteristics. *Advances in Mental Health.* 2012;10(3):293-297.
21. Foster C, Scott I, Addington-Hall J. Who visits mobile UK services providing cancer information and support in the community? *European journal of cancer care.* 2010;19(2):221-226.
22. Iredale R, Hilgart J, Hayward J. Patient perceptions of a mobile cancer support unit in South Wales. *European journal of cancer care.* 2011;20(4):555-560.
23. Taxman FS, Perdoni ML, Harrison LD. Drug treatment services for adult offenders: the state of the state. *Journal of substance abuse treatment.* 2007;32(3):239-254.
24. Strang J, Gossop M, Heuston J, Green J, Whiteley C, Maden A. Persistence of drug use during imprisonment: relationship of drug type, recency of use and severity of dependence to use of heroin, cocaine and amphetamine in prison. *Addiction (Abingdon, England).* 2006;101(8):1125-1132.
25. Binswanger IA, Stern MF, Deyo RA, et al. Release from prison--a high risk of death for former inmates. *The New England journal of medicine.* 2007;356(2):157-165.
26. Binswanger IA, Merrill JO, Krueger PM, White MC, Booth RE, Elmore JG. Gender differences in chronic medical, psychiatric, and substance-dependence disorders among jail inmates. *American journal of public health.* 2010;100(3):476-482.
27. Binswanger IA, Blatchford PJ, Lindsay RG, Stern MF. Risk factors for all-cause, overdose and early deaths after release from prison in Washington state. *Drug and alcohol dependence.* 2011;117(1):1-6.
28. Bird SM, Hutchinson SJ. Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996-99. *Addiction (Abingdon, England).* 2003;98(2):185-190.
29. Farrell M, Marsden J. Acute risk of drug-related death among newly released prisoners in England and Wales. *Addiction (Abingdon, England).* 2008;103(2):251-255.
30. Krinsky CS, Lathrop SL, Brown P, Nolte KB. Drugs, detention, and death: a study of the mortality of recently released prisoners. *Am J Forensic Med Pathol.* 2009;30(1):6-9.
31. Merrall EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction (Abingdon, England).* 2010;105(9):1545-1554.
32. Stewart LM, Henderson CJ, Hobbs MS, Ridout SC, Knuiman MW. Risk of death in prisoners after release from jail. *Australian and New Zealand journal of public health.* 2004;28(1):32-36.
33. Inciardi JA. *The War on Drugs IV: The continuing saga of the mysteries and miseries of intoxication, addiction, crime and public policy.* Boston, MA: Allyn and Bacon; 2008.
34. Hough M. Drug user treatment within a criminal justice context. *Substance use & misuse.* 2002;37(8-10):985-996.
35. Kinlock TW, O'Grady KE, Hanlon TE. Prediction of the criminal activity of incarcerated drug-abusing offenders. *Journal of Drug Issues.* 2003;33:897-920.
36. Kinlock TW, O'Grady KE, Hanlon TE. The effects of drug treatment on institutional behavior. *The Prison Journal.* 2003;83:257-276.
37. Dolan KA, Shearer J, White B, Zhou J, Kaldor J, Wodak AD. Four-year follow-up of imprisoned male heroin users and methadone treatment: mortality, re-incarceration and hepatitis C infection. *Addiction (Abingdon, England).* 2005;100(6):820-828.
38. Metz V, Matzenauer C, Kammerer K, et al. Evaluation of Opioid-Dependent Prisoners in Oral Opioid Maintenance Therapy. *Heroin Addiction and Related Clinical Problems.* 2010;12(1):5-16.
39. Brownstein HH. *Contemporary Drug Policy.* New York: Routeledge; 2013.
40. Latkin CA, Yang C, Tobin KE, German D. Injection drug users' and their risk networks' experiences of and attitudes towards drug dealer violence in Baltimore, Maryland. *International Journal of Drug Policy.* 2013;24(2):135-141.
41. Lobmaier PP, Kunoe N, Waal H. Treatment research in prison: Problems and solutions in a randomized trial. *Addiction Research and Theory.* 2009;18(1):1-13.
42. Yang C, German D, Webster D, Latkin C. Experiencing violence as a predictor of drug use relapse among former drug users in Baltimore, Maryland. *Journal of Urban Health.* 2011;88(6):1044-1051.

43. Gordon MS, Kinlock TW, Schwartz RP, O'Grady KE. A randomized clinical trial of methadone maintenance for prisoners: findings at 6 months post-release. *Addiction (Abingdon, England).* 2008;103(8):1333-1342 [PMCID: PMC2582162].
44. Inciardi JA, Martin SS, Butzin CA. Five-year outcomes of therapeutic community treatment of drug-involved offenders after release from prison. *Crime & Delinquency.* 2004;50:88-107.
45. Kinlock TW, Gordon MS, Schwartz RP, O'Grady K, Fitzgerald TT, Wilson M. A randomized clinical trial of methadone maintenance for prisoners: results at 1-month post-release. *Drug and alcohol dependence.* 2007;91(2-3):220-227 [PMCID: PMC2423344].
46. Kinlock TW, Gordon MS, Schwartz RP, O'Grady KE. A study of methadone maintenance for male prisoners: 3-month postrelease outcomes. *Criminal justice and behavior.* 2008;35(1):34-47 [PMCID: PMC24423939].
47. Kinlock TW, Sears EA, O'Grady KE, Callaman JM, Brown BS. Treatment retention and changes in motivation among drug court probationers. *Journal of Offender Rehabilitation.* 2009;48:1-18.
48. Prendergast M, Hall E, Wexler H, Melnick G, Cao Y. Amity prison-based therapeutic community: Five-year outcomes. *Prison Journal.* 2004;84(1):36-60.
49. Prendergast ML, Campos M, Farabee D, Evans WK, Martinez J. Reducing Substance Use in Prison: The California Department of Corrections Drug Reduction Strategy Project. *The Prison Journal.* 2004;84(2):265-280.
50. Wexler HK, Prendergast ML. Therapeutic communities in United States' Prisons: Effectiveness and Challenges. *Therapeutic Communities.* 2010;31(2):157-175.
51. Chandler RK, Fletcher BW, Volkow ND. Treating drug abuse and addiction in the criminal justice system: improving public health and safety. *JAMA.* 2009;301(2):183-190.
52. Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug and alcohol dependence.* 2003;72(1):59-65.
53. Hedrich D, Alves P, Farrell M, Stover H, Moller L, Mayet S. The effectiveness of opioid maintenance treatment in prison settings: a systematic review. *Addiction (Abingdon, England).* 2012;107(3):501-517.
54. Magura S, Rosenblum A, Lewis C, Joseph H. The effectiveness of in-jail methadone maintenance. *Journal of Drug Issues.* 1993;23:75-99.
55. Magura S, Lee JD, Hershberger J, et al. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. *Drug and alcohol dependence.* 2009;99(1-3):222-230.
56. Stover H, Michels, II. Drug use and opioid substitution treatment for prisoners. *Harm reduction journal.* 2010;7:17.
57. Tomasino V, Swanson AJ, Nolan J, Shuman M. The Key Extended Entry Program (KEEP): A methadone treatment program for opiate-dependent inmates. *The Mount Sinai Journal of Medicine.* 2001;68:14-20.
58. Dole VP, Robinson JW, Orraca J, Towns E, Searcy P, Caine E. Methadone treatment of randomly selected criminal addicts. *The New England journal of medicine.* 1969;280(25):1372-1375.
59. Friedmann PD, Hoskinson R, Gordon M, et al. Medication-assisted treatment in criminal justice agencies affiliated with the criminal justice-drug abuse treatment studies (CJ-DATS): availability, barriers, and intentions. *Subst Abus.* 2012;33(1):9-18. PMCID: PMC3295578.
60. Nunn A, Zaller N, Dickman S, Trimbur C, Nijhawan A, Rich JD. Methadone and buprenorphine prescribing and referral practices in US prison systems: results from a nationwide survey. *Drug and alcohol dependence.* 2009;105(1-2):83-88.
61. Rich JD, Boutwell AE, Shield DC, et al. Attitudes and practices regarding the use of methadone in US state and federal prisons. *J Urban Health.* 2005;82(3):411-419.
62. Rich JD, McKenzie M, Shield DC, et al. Linkage with methadone treatment upon release from incarceration: a promising opportunity. *Journal of addictive diseases.* 2005;24(3):49-59.
63. Zaller N, McKenzie M, Friedmann PD, Green TC, McGowan S, Rich JD. Initiation of buprenorphine during incarceration and retention in treatment upon release. *Journal of substance abuse treatment.* 2013;45(2):222-226.

64. Wish ED, Artigiani E, Billing A, et al. The emerging buprenorphine epidemic in the United States. *Journal of addictive diseases.* 2012;31(1):3-7.
65. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database of Systematic Reviews* 2006(Issue 1. Art. No.: CD001333. DOI: 10.1002/14561858.CD001333.pub.2).
66. Pettinati HM, Volpicelli JR, Pierce JD, Jr., O'Brien CP. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *Journal of addictive diseases.* 2000;19(1):71-83.
67. Coviello DM, Cornish JW, Lynch KG, et al. A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers. *Subst Abus.* 2012;33(1):48-59.
68. Cornish JW, Langleben DD, Nordeck CD, et al. Six-Month Depot Naltrexone Treatment Reduces Relapse in Parolees Formerly Addicted to Opioids. Poster presented at 51st Annual Meeting of the American College of Neuropsychopharmacology; December 2-6, 2012, 2012; Hollywood, Florida.
69. Lee S, Klein-Schwartz W, Welsh C, Doyon S. Medical outcomes associated with nonmedical use of methadone and buprenorphine. *The Journal of emergency medicine.* 2013;45(2):199-205.
70. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Current psychiatry reports.* 2010;12(5):448-453.
71. Binswanger IA, Nowels C, Corsi KF, et al. Return to drug use and overdose after release from prison: a qualitative study of risk and protective factors. *Addiction science & clinical practice.* 2012;7(1):3.
72. Kinlock TW, Battjes RJ, Schwartz RP. A novel opioid maintenance program for prisoners: report of post-release outcomes. *The American journal of drug and alcohol abuse.* 2005;31(3):433-454.
73. Kinlock TW, Schwartz RP, Gordon MS. The significance of interagency collaboration in developing opioid agonist programs for prisoners. *Corrections Compendium.* 2005;30:6-9, 28-30.
74. Kinlock TW, Gordon MS, Schwartz RP, Fitzgerald TT. Developing and Implementing a new prison-based buprenorphine treatment program. *J Offender Rehabil.* 2010;49(2):91-109 [PMCID: PMC2868193].
75. Lurigio AJ. *An evaluation of a safe haven's workshop for Illinois parole agents.* Chicago: Loyola University of Chicago; 2009.
76. Schmalleger F. *Criminal Justice Today: An introductory text for the 21st century* 10th ed. Upper Saddle River, NJ: Pearson Prentice Hall; 2010.
77. McKenzie M, Nunn A, Zaller ND, Bazazi AR, Rich JD. Overcoming obstacles to implementing methadone maintenance therapy for prisoners: implications for policy and practice. *Journal of opioid management.* 2009;5(4):219-227.
78. Lee JD, Friedmann PD, Boney TY, et al. Extended-release naltrexone to prevent relapse among opioid dependent, criminal justice system involved adults: rationale and design of a randomized controlled effectiveness trial. *Contemporary clinical trials.* 2015;41:110-117.
79. Cornish JW, Metzger D, Woody GE, et al. Naltrexone pharmacotherapy for opioid dependent federal probationers. *Journal of substance abuse treatment.* 1997;14(6):529-534.
80. Coviello DM, Cornish JW, Lynch KG, Alterman AI, O'Brien CP. A randomized trial of oral naltrexone for treating opioid-dependent offenders. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2010;19(5):422-432.
81. Gordon MS, Kinlock TW, Schwartz RP, Couvillion K, Schwartz RP, O'Grady KE. The severity, frequency and variety of crime in heroin-dependent prisoners enrolled in a buprenorphine clinical trial. *The Prison Journal.* in press.
82. Pecoraro A, Woody GE. Medication-assisted treatment for opioid dependence: making a difference in prisons. *F1000 Med Rep.* 2011;3:1.
83. Garcia CA, Correa GC, Hernandez Viver AD, et al. Buprenorphine-naloxone treatment for pre-release opioid-dependent inmate in Puerto Rico. *Journal of Addiction Medicine.* 2007;1(3):126-132.
84. Kinlock TW, Battjes RJ, Schwartz RP. A novel opioid maintenance program for prisoners: preliminary findings. *Journal of substance abuse treatment.* 2002;22(3):141-147.

85. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet.* 2002;359(9306):614-618.
86. Green TC, Bowman SE, Ray M, McKenzie M, Lord SE, Rich JD. Development of an incarceration specific overdose prevention video: Staying Alive on the Outside. *Health Education journal.* 2014:1-11.
87. SAMHSA. SAMHSA Opioid Overdose Prevention Toolkit. 2016; http://store.samhsa.gov/shin/content//SMA16-4742/SMA16-4742.pdf.
88. DHHS. NIOSH Hazard Review: Occupational Hazards in Home Healthcare. 2010; Publication No. 210-125:http://www.cdc.gov/niosh/docs/2010-125/pdfs/2010-125.pdf.
89. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *Journal of substance abuse treatment.* 1992;9(3):199-213.
90. McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. *The Journal of nervous and mental disease.* 1980;168(1):26-33.
91. Association AP. *Diagnostic and statistical manual of mental disorders.* 5th ed. Washington, DC 2013.
92. Kinlock TW. *Precursors and correlates of serious criminal behavior over a narcotic addiction career* [Doctoral Dissertation.]. College Park, MD, University of Maryland, 1993; 1995.
93. Metzger D, Woody GE, McLellan AT, Navaline H, O'Brien CP, International Conference on AIDS. Measuring risk behavior among IDUs: validation of the risk for AIDS behavior (RAB) scale. Paper presented at: Int Conf AIDS; Jul 19-24, 1992; University of Pennsylvania, Philadelphia.
94. Kaplan RF, Cooney NL, Baker LH, Gillespie RA, Meyer RE, Pomerleau OF. Reactivity to alcohol-related cues: physiological and subjective responses in alcoholics and nonproblem drinkers. *J Stud Alcohol.* 1985;46(4):267-272.
95. Childress AR, McLellan AT, O'Brien CP. Conditioned responses in a methadone population. A comparison of laboratory, clinic, and natural settings. *Journal of substance abuse treatment.* 1986;3(3):173-179.
96. Schwartz RP, Jaffe JH, O'Grady KE, et al. Interim methadone treatment: impact on arrests. *Drug and alcohol dependence.* 2009;103(3):148-154 [PMCID: PMC2699328].
97. Jones LV, Tukey JW. A sensible formulation of the significance test. *Psychological methods.* 2000;5(4):411-414.
98. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychological methods.* 1997;2:64-78.
99. Carpenter J, Kenward M. *Multiple Imputation and its Application.* New York, NY: Wiley; 2013.
100. Carpenter J, Kenward M. *Missing data in randomised controlled trials - a practical guide.* Birmingham: National Institute for Health Research;2008.
101. Stroup WW. Mixed model procedures to assess power, precision, and sample size in the design of experiments. Lincoln, NE: University of Nebraska, American Statistical Association; 1999:19-24.
102. Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O. *SAS for mixed models.* Second ed. Cary, NC: SAS Institute, Inc.; 2006.
103. Cohen J. *Statistical power analysis for the behavioral sciences (Second edition)* Hillsdale, NJ: LEA; 1988.
104. Borenstein M, Cohen J. *Statistical power analysis.* Hillsdale, NY: Erlbaum; 1988.
105. Miller J, Schwarz W. Aggregate and individual replication probability within an explicit model of the research process. *Psychological methods.* 2011;16(3):337-360.
106. Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol.* 2013;13:92.
107. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. *The New England journal of medicine.* 2007;357(21):2189-2194.
108. Dolan P. Modeling valuations for EuroQol health states. *Med Care.* 1997;35(11):1095-1108.
109. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health policy.* 1990;16(3):199-208.

110. Richardson J, Mckie J, Bariola E. Multiattribute utility instruments and their use. In: Culyer AJ, ed. *Encylopedia of Health Economics*: Elsevier; 2014:341-357.

11.0 APPENDIX (screening forms, medical forms, research instruments)