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RE: Improving Outcomes of Opioid Addicted Prisoners with Extended Release Injectable Naltrexone Before Reentry

NCT02617628

Sponsoring Agency: Patient Centered Outcomes Research Institute

DR. GEORGE E. WOODY (4413 -PS-Addictions)

This document serves as the cover letter for the attached protocol entitled: Improving Outcomes of Opioid Addicted Prisoners with Extended Release Injectable Naltrexone Before Reentry. The project began recruitment in August of 2016 and ended December 31, 2018. Please note that an approval was given for the PENN IRB Continuing Review for the submitted November 4, 2017 protocol from May 17, 2019 through May 16, 2020.

Sabrina A. Poole, Psy.D.
Project Director

George E. Woody, M.D.
Principal Investigator

Improving Outcomes of Opioid Addicted Prisoners With Extended Release Injectable Naltrexone Before Reentry

Version 10.0
November 4, 2017

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name:

Title:

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
CBC	complete blood count
CRF	case report form
CSA	Center for the Study of Addictions, University of Pennsylvania
DMU	Data Management Unit
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GGT	gamma glutamyltranspeptidase
HIV	human immunodeficiency virus
IDU	Injection Drug User
IM	intramuscular injection
IV	intravenous
IRB	Institutional Review Board
LDH	lactic dehydrogenase
LFT	liver function test
NXT	naltrexone
NAL	naloxone
RAB	Risk Assessment Battery
SAE	serious adverse event
UDS	urine drug screen
VIVITROL®	extended release injectable naltrexone (trade name)
XR-NXT	extended release injectable naltrexone

PROTOCOL SUMMARY

Title:

Improving Outcomes of Opioid Addicted Prisoners With Extended Release Injectable Naltrexone Before Reentry

Overview:

The collaboration between the University of Pennsylvania, the Philadelphia Prison System, and the North East Treatment Center (at the NETSteps site) proposes to study the impact of an injectable opiate addiction medication that can be given before reentry into the community to increase the health and reduce the population burden of untreated opioid addiction. In showing that there is a medication-assisted therapy such as extended release naltrexone (XR-NTX) that is likely acceptable to correctional facilities and opioid addicted prisoners, we can help to improve the outcomes achieved by the usual detoxification/treatment referral approach. If study hypotheses are confirmed and results disseminated to decision makers, we will have added to the knowledge about the treatment of opiate addiction in prisoners that can be used to facilitate policy changes that involve adding XR-NTX to correctional facility formularies for use before reentry, and the extension of collaborating with one or more outpatient treatment providers to maintain continuity of that care.

Objectives:

The primary objectives for this study include the potential to improve healthcare and related outcomes and reduce the risk of relapse and recidivism for opiate addicted prisoners reentering into the community after release from correctional facilities. The study we propose aims to show that there is a medication-assisted therapy (XR-NTX) that is likely to be acceptable to correctional facilities and opioid addicted prisoners and that can improve the outcomes achieved by the usual detoxification/treatment referral approach. If study hypotheses are confirmed and results disseminated to decision makers (dissemination plans described later), we will have obtained hard data that can be used to facilitate policy changes that involve adding XR-NTX to correctional facility formularies for use before reentry, and collaborating with one or more outpatient treatment providers to maintain continuity of care. Relapse is particularly high in the weeks after reentry because prisoners lose opioid tolerance when they are detoxified but do not lose their craving for drugs. The result is a dangerous situation because they often start using drugs in the same amount as before incarceration but to which they are no longer tolerant and overdose, sometimes with fatal results.

Population:

Two hundred (200) opioid addicted prisoners currently incarcerated in the Philadelphia Prison System who meet study admission criteria, express an interest in XR-NTX treatment, and give informed consent. Enrollment will be stratified to male/females, 18 years or older, and who are sentenced/not sentenced (e.g. meet/not meet with probation/parole officer).

Phase: III

Number of Sites: NETSTEPS-NorthEast Treatment Centers

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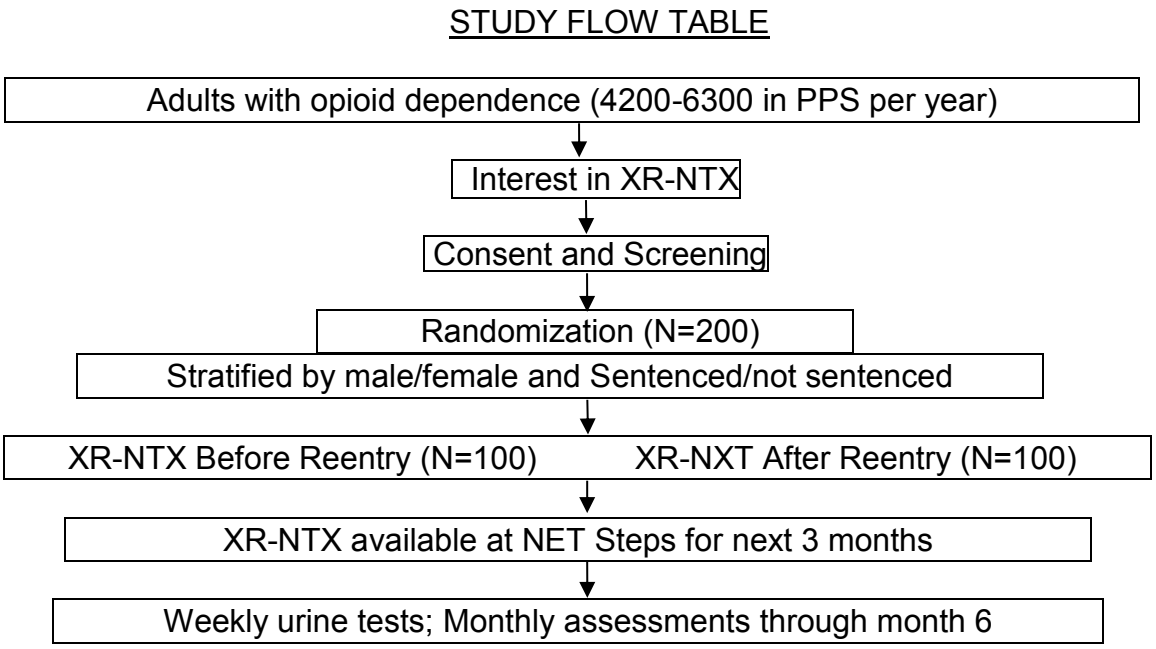
Description of Intervention: *XR-NTX* is a suspension containing naltrexone embedded in material comparable to surgical sutures. Following injection the normal metabolic process gradually erodes the suspension material and releases naltrexone continuously. Plasma concentrations of naltrexone and 6-beta naltrexol (the main metabolite) are detectable for at least 30 days after a single injection, and the medication must be re-administered to maintain its' effect. Continued use is not associated with tolerance or withdrawal, but naltrexone will precipitate withdrawal if given to a person who is physiologically dependent on opioids thus patients must be detoxified prior to dosing. There is a transient peak of naltrexone about two hours after injection followed by a second peak 2-3 days later that reaches approximately 25 ng/ml followed by a decline to about 12 ng/ml to day 7 with a more gradual reduction that reaches 1-2 ng/ml in 30 days. The once/month injection reduces first pass metabolism to 6-beta-naltrexol that occurs after the oral formulation, thus allowing for less total drug to be administered than the oral, though total naltrexone exposure is 3-4 times higher over 28 days than with a 28-day course of the 50 mg/day oral dose.

Study Duration: Three Years

Subject Duration: Six months

Estimated Time: to Complete Enrollment: 2019

STUDY SCHEMATIC



Windows for assessments:
Baseline = 14 days; weekly = ± 2 days; monthly = ± 1 week;
follow-up = ± 4 weeks.

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2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background Information

In 2014 the FDA and CDC declared opioid overdose deaths to be a national epidemic and NIDA and ONDCP identified prescription opioid and heroin use as national problems (http://www.whitehouse.gov/ondcp/drugpolicyreform#). These announcements constitute the first time that a single health problem has been declared a national emergency by four federal agencies. PCORI identified "Treatment Options for Opioid Substance Abuse" as a priority in January 2014, and Senators Portman and Whitehouse toured an Alkermes facility in Ohio where extended release injectable naltrexone, a medication that blocks opioid effects for a month after a single dose, is manufactured. (http://www.rollcall.com/news/-232507-1.html?). These Senators also introduced the Recidivism Reduction and Public Safety Act in 2014, a bill that reflects a growing interest in shifting our long-standing emphasis on dealing with substance use problems from a criminal justice approach to more and better treatment. Similar expressions of interest have been seen in newspaper articles and editorials (NY Times; Philadelphia Inquirer), and in medical journals and magazines such as the Atlantic Monthly.

In 2012 there were an estimated 2,056,000 persons aged 12 and older with a past-year prescription opioid use disorder and an estimated 467,000 persons aged 12 and older with a past-year heroin use disorder (SAMHSA, 2012). The prevalence of these disorders in specific locations varies but they are known to occur in Albuquerque, Baltimore, Boston, Camden, Chicago, Dallas, Denver, Los Angeles, New York, New Haven, Philadelphia, Phoenix, Portland OR and Portland ME, St. Louis, San Francisco, San Diego, Detroit, and Seattle (2014 summary of Community Epidemiology Work Group, available online via Google) and the have been growing in non-metropolitan areas, particularly regarding prescription opioids (Cicero et al, 2014).

Opioid use disorders are associated with a wide range of health and psychosocial problems. For one, many inject drugs and the prevalence of hepatitis C among injecting users ranges from 27-93% with 17,000 new cases of HCV identified annually, the strongest risk factor being injecting drug use (Ditah et al, 2013). Trading sex for drugs and unsterile injecting practices also spread HCV and HIV and can result in cellulitis, endocarditis, abscesses, and sclerosed veins. Tuberculosis is also more common among opioid users than in the population at large, as are injuries from accidents and violence. There is an increased prevalence of psychiatric disorders, most commonly depression and anxiety, some substance induced and others magnifications of underlying disorders, but both associated with an increased prevalence of suicidal ideation and behaviors. Educational and vocational performance is often impaired; family and personal relationships disrupted; preoccupation with obtaining and using drugs leads to poor adherence to medications for serious health problems such as HIV, diabetes, and cardiovascular disease; and the incidence of premature delivery is increased, particularly among women that are not in treatment, and can lead to expensive stays in neonatal intensive care units. These problems are documented in many publications and well summarized by Ruiz & Strain (2011) and in the DSM-5 section on Opioid-Related Disorders (2013).

In addition to health problems, criminal activities associated with drug-seeking behavior place burdens on entire populations. For example, opioid addicted individuals experience withdrawal 2-3 times/day if they do not have drugs and go to great lengths to get drugs to avoid it. The amount of money needed to support a "habit" can be estimated by reports from patients entering methadone programs who typically spend $50-$200/day for drugs, sometimes more. These funds often come from selling drugs or exchanging stolen goods (including those belonging to family members) for money via a "fence" that usually pays a small fraction of the retail value of

the goods and then sells them for a profit. Much of the activity to obtain these goods comes from burglary or robbery, sometimes associated with violence and harm to others.
Collectively, these behaviors increase the burden of opioid addiction on populations at many levels - families and friends whose possessions are stolen and see loved ones destroying their lives; emergency room visits to treat overdoses; hospitalizations to treat infections and psychiatric complications; interruption of education and inability to hold a job; financial costs due to unreimbursed medical care; increased taxes to pay for police, courts, incarcerations, and probation or parole officers; and marking individuals with criminal records that interfere with future employment and educational opportunities. Though nicotine and alcohol affect more individuals, opioid use disorders are arguably associated with a more rapid and greater number of serious health and social problems than any other substance use disorder.

2.2 Rationale

Extended release injectable naltrexone (XR-NTX Vivitrol®) is likely to encounter less resistance than methadone or buprenorphine-naloxone. It is an antagonist with no agonist effects, not a controlled substance because it has no abuse liability and thus not diverted or sold illegally, blocks opioid effects for a month after a single dose, does not produce tolerance and withdrawal, does not appear to have clinically significant interactions with antiretroviral medications or other therapies unless the patient needs opioids for chronic pain, and can be administered by existing correctional facility medical staff after 3-4 hours of training. Evidence of its acceptance by prisoners and correctional facilities is seen in the Alkermes Public Policy Directory of 2014 (available from robert.forman@Alkermes.com) that lists 9 facilities and other criminal justice settings where it is being used. Further evidence of its acceptability is seen in a review of medication assisted therapy (Einstein Expert Panel, 2013), a virtual tour of a XR-NTX program being used by the jail in Barnstable, MA for prisoners that have participated in their therapeutic community (http://www.rsat-tta.com/Special-Pages/RSAT-Virtual-Tour), and findings from patient interviews, surveys and a focus group that our research group recently completed and are described below.

Relapse is particularly high in the weeks after reentry because prisoners lose opioid tolerance when they are detoxified but do not lose their craving for drugs. The result is a dangerous situation because they often start using drugs in the same amount as before incarceration but to which they are no longer tolerant and overdose, sometimes with fatal results. This problem is seen in a study done in the United Kingdom (Farrell & Marsden, 2007); in another that found drug-related deaths in the first two weeks after reentry to be 3-8 times higher compared to weeks 3-12 (Moller et al, 2010); and in a third that found risk of overdose death to be 12.9 times higher during the first 2 weeks after reentry than among population-based controls (Binswanger et al, 2007). Despite the potential of XR-NTX to reduce relapse and its adverse consequences, only one controlled study has been completed with opioid addicted prisoners. It was a pilot study where 33 prisoners were randomized to receive XR-NTX before reentry or to the usual detoxification/treatment referral approach. Six of the 16 (38%) participants who received XR-NTX before reentry relapsed within two months as compared to 15 of 17 (88%) that relapsed within two months after receiving usual treatment (Lee et al, 2013; paper under review; personal communication, J. Lee 2014). NIDA has funded two similarly-designed studies but results are not yet available (Einstein Expert Panel, 2013). This limited amount of information points to a major gap in comparative effectiveness studies.

A different but related study was recently completed with opioid addicted ex-prisoners on probation or parole. They represented a subgroup that had not relapsed at the time they enrolled in the study since XR-NTX cannot be given to a person that is currently physiologically dependent because it will precipitate severe withdrawal.

The design involved randomization to 6 months of XR-NTX and monthly meetings with probation or parole officers, or to meetings with parole/probation officer meetings alone (usual treatment). Data on 274 of 308 participants that were eligible for 12-month follow-up in May 2014 showed that 57% of the XR-NTX patients received all 6 injections and there were no overdoses. However there were 7 overdoses in the usual treatment group with 3 deaths and 4 hospitalizations. The odds of abstinence from opiates in XR-NTX patients were 3.41 times the odds for controls (95% CI = (1.94, 6.00); other drugs were used at the same rate in both groups (O'Brien et al, 2014).

2.3 Gaps in evidence:

Illegal behaviors, combined with strict sentencing laws and "zero tolerance" policies, have resulted in a disproportionally high number of opioid addicted individuals in one or more of our approximately 3000 jails and 1800 prisons. For example, an article in NIDA Notes (Witten, July 1, 2011) citing data collected by Rich et al in 2000 (J. Rich, personal communication, 2014), estimated that 200, 000 heroin addicted individuals pass through U.S. criminal justice facilities every year; adding the tens of thousands addicted to prescription opioids that emerged since 2000 likely doubles or triples this estimate.

Most incarcerations of opioid addicted individuals are for less than a year and due to non-violent offenses. Many facilities offer substance abuse education, cognitive therapy, and mutual support groups such as Narcotics Anonymous or Alcoholics Anonymous but with few exceptions and despite the evidence that detoxification alone is ineffective (Kleber et al, 1999; Woody et al, 2008; Weiss et al, 2012), and the proven efficacy of medication assisted treatment (MAT), they are routinely detoxified and released without MAT. The result is relapse, often on the way home from jail (see information from ex-prisoners, below), with lost motivation to enroll in treatment, the adverse health and population burdens described above, and cycling in and out of correctional facilities for problems such as not keeping appointments with probation or parole officers, positive urine tests, drug dealing, burglary, possession, receiving stolen goods, and public intoxication.

The practice of not using MAT for opioid addicted prisoners is different from what usually happens to those with other health problems such as HIV, diabetes, and cardiovascular disease. Prisoners with those problems are typically prescribed medication while incarcerated and given a medication supply or prescriptions to bridge the gap between reentry and enrollment in follow-up care. In the case of opioid addiction, there are three medications – methadone, buprenorphine-naloxone (Suboxone®), and extended release injectable naltrexone (XR-NTX; Vivitrol®) – that are safe and highly effective when used according to accepted guidelines (Dole and Nyswander, 1965, 1968; Johnson et al, 1992, 2000; Krupitsky et al, 2011), but rarely used.

A few studies have been done showing that treating opioid addicted prisoners with methadone or buprenorphine-naloxone and transitioning them to continuing care after reentry prevents relapse (Kinlock et al, 2007; Gordon et al, 2008; 2009; Magura et al, 2009; Hedrick et al, 2011), but resistance to using these medications is high and detoxification continues to be the usual treatment (Nunn et al, 2009; Pecoraro & Woody, 2011; Friedman et al, 2012). Reasons for this practice have not been studied but likely include: administrators do not see addiction as a chronic relapsing disorder; some view the main role of incarceration as punitive and reject the idea of treating addiction; methadone carries a massive regulatory burden; methadone and buprenorphine-naloxone are narcotic agonists that can be diverted, sold, and abused within the facility; methadone and buprenorphine-naloxone, being agonists, are sometimes viewed as "substituting beer for whiskey" and not considered "real" treatment. Interestingly, resistance to agonist therapy is not limited to correctional facilities, as seen by community protests that typically occur when someone tries to start a new methadone program, a problem known as the "NIMBY Syndrome" e.g. not in my backyard.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

It is important to keep in mind that medication assisted treatments (MATs) do not cure addiction in the way that antibiotics cure infections, but MATs can help to control addiction, much like medication for diabetes, hypertension, HIV, and other problems that are often chronic and relapsing (McLellan et al 2000). We theorize that MAT can markedly reduce the adverse health and population consequences of opioid addiction, including HIV risk (Metzger et al, 2011). Unlike some health problems that last a lifetime, opioid use disorders often remit over time but it usually takes 10-15 years (Wu et al, 2011), thus in controlling them we can expect to produce short and long-term as well as long-term benefits by preventing further health and psychosocial problems that markedly reduce an addicted person's chances of ever leading a healthy and productive life. However, in doing studies such as these we can incur the following risks associated with infectious disease and psychosocial testing:

- ***HIV Testing:*** These include violation of confidentiality or affective reactions including suicidal ideation or suicide attempts if found to be HIV+. All efforts will be made to minimize these risks by pre and post-test counseling and referral, if the study performs the HIV test, to the most appropriate treatment provider for those who are HIV+. It is expected that HIV pre and post counselling was already conducted if the HIV test was performed by PPS. We expect that some HIV+ patients will be in treatment at the time of study enrollment and it will be continued while they are in the PPS as per usual procedures.
- ***Hepatitis C (HCV) and Hepatitis B (HBV)Testing:*** Risks are similar but even greater to those associated with HIV for injecting users since HCV is more easily transmitted by unsterile injecting practices than HIV. Pre and post-test counseling will include education about what hepatitis does to the body, how it is transmitted, how to protect oneself from being infected or infecting someone else, and referral to the most appropriate treatment available if positive.
- ***Behavioral Ratings:*** Risks are minimal and limited to breach of confidentiality or becoming anxious or embarrassed by some of the questions. Procedures to protect confidentiality and reduce study-related anxieties are described in other parts of this application.

2.4.2 Potential Benefits

This study has been designed to assess different ways of providing a medication that has the potential to improve the health of opioid addicted prisoners and reduce the population burden of untreated opioid addiction. The mechanism for this effect will be preventing relapse along with improving quality of life and facilitating treatment participation after reentry. XR-NTX was chosen for this study because it is an antagonist with no addiction liability and thus more likely to be used by correctional facilities than methadone or buprenorphine that have abuse liability because they have potent opioid agonist effects. Participants in both treatment conditions will be offered more help and attention than they would normally receive and if hypotheses are confirmed, correctional facilities will have hard data they can use to justify adding XR-NTX to their existing medical services. Adoption of XR-NTX by many facilities could help prisoners across the country and be a meaningful step toward reducing the opioid-related problems that are described in other parts of this proposal.

3. STUDY OBJECTIVES

The objectives of this study is to address the questions about the concerns of patients and their caregivers regarding quality of life and relapse after prisoner reentry into the community. To do this, we will examine an extended release vehicle (XR-NTX) as a comparative tool to treatment as usual.

3.1 Study Outcome Measures

3.1.1 Primary

Proportion not relapsed by month three.

3.1.2 Secondary

1) Quality of life;
2) Weeks in treatment through month six;
3) Time to relapse;
4) Rearrests;
5) Psychiatric symptoms;
6) Opioid use;
7) Alcohol and other drug use;
8) HIV risk;
9) Reincarceration;
10) Deaths.

4. STUDY DESIGN/TIMELINE/ AND RESEARCH SITES

4.1 Study Design:

To address these questions we will identify opioid addicted prisoners who appear to meet study admission criteria and express interest in XR-NTX treatment, explain the study to them in detail, encourage them to ask questions, and obtain consent from those who remain interested. We will then complete baseline assessments to confirm eligibility (criteria described later) and the first 200 that meet enrollment criteria will be stratified according to male/female and sentenced/not sentenced (e.g. meet/not meet with probation/parole officer), and randomized 1:1 to receive XR-NTX before reentry with the offer of having three additional doses of XR-NTX at NET Steps after reentry, or be given an appointment to be seen at NET Steps same day or up to 7 calendar days after release to receive their first dose of XR-NTX after reentry with the opportunity for 3 additional doses at NET Steps. Follow-ups for participants who have difficulty going to the NETSteps site can have their follow-up injections and assessments done at the 3535 Market Street site, 5th floor. All participants will be assigned a Patient Benefits Manager to help reinstate benefits that were lost during incarceration and all will receive the usual counseling and other services available to NET Steps patients (described later in more detail). A urine drug toxicology screen , adverse events, and an alcohol breathalyzer test will be done weekly and brief assessments will be done at months 1, 2, 4 and 5 with more detailed assessments at months 3 and 6. Criminal justice information on arrests and re-incarcerations will supplement the assessments.

4.2 Project Timeline

This study will require approval by the Office of Human Research Protections, the Penn IRB, and the City of Philadelphia IRB, which is used by the Philadelphia Prison System. We will also register this study on clinical trials.gov. We will train research and clinical staff in study procedures, and write the study procedures manual before implementation of any procedures. These activities will be completed by month 3. Randomization and treatment will occur in months 4-33, with data cleaning, analyses, and final reports completed by month 36. This schedule projects an average enrollment of 8.3 subjects randomized/month. This rate is feasible based on the number of opioid addicted individuals that enter the PPS every year; the level of interest in XR-NTX that we identified in our interactions with former or current opioid addicted prisoners (details in other parts of the proposal); the broad enrollment criteria that will not exclude many potential candidates; the staffing requested to implement the study; NET Steps capacity to treat participants; research experience by NET Steps and its leaders, who have met recruitment and follow-up targets in other studies; and support from administrators and staff in the PPS. We have found that that recruitment for clinical trials can be slower or faster than expected at various times thus it is difficult to know exactly what proportions of the final sample will have been recruited at specific points. Our best estimate is that 25% will be recruited by the end of month 9, 50% by the end of month 15, 75% by the end of month 21, recruitment finished by the end of month 27, and treatment finished by the end of month 33.

Interim progress and engagement reports will be submitted every 6 months and include summaries of ways that patients and stakeholders were involved in the development of study materials and implementation of the study according to PCORI requirements. We do not plan to do interim analyses unless requested by PCORI or an

IRB. Final analyses will be completed by the end of month 35 and a final report will be submitted at the end of the contract period. Copies of submitted and published manuscripts will be provided to PCORI staff and de-identified data along with a codebook and analytic data sets made publically available on the clinical trials NIH web site within 9 months of acceptance of the primary outcome paper.

4.3 Research Site(s)

4.3.1 Site Descriptions & Data Collection

Site selection was based on interest from PPS administrators and the Philadelphia Department of Behavioral Health to do something that might improve the poor outcomes of opioid addicted prisoners and stop the revolving door of incarceration, relapse and re-incarceration. Another contributing factor was the unique relationship between NET Steps and PPS in which a research trained medical staff is available on site and "behind the walls" in NET@PPS; the structured treatment available at NET Steps including the BRIDGE program with the Patient Benefits Managers to help restore benefits to prisoners that have lost them while incarcerated; the approved treatment capacity of NET Steps that will allow them to treat study patients; the medication development research experience of Dr. Yu and his long-standing working relationship with the Penn research team; and a second study trained doctor from the NET Steps medical staff that can back up Dr. Yu if he is unavailable due to vacation or illness.

NET Steps is directed by Ms. Amy McNamee and the site operates the "BRIDGE" program which helps methadone maintained prisoners restore health benefits and link them to continuing care after reentry. PBMs are an essential part of this program and we will use their expertise to help study patients restore health benefits that they lost while incarcerated. Ms. McNamee replaces Mr. John Carroll who founded NET Steps after participating in a SAMHSA HIV risk reduction project to help homeless opioid addicted persons with HIV. The target was to provide treatment for 700 or more new people. The site met this goal by recruiting 644, achieving

6-month follow-ups on 539 (84%), and creating NET Steps. The site also participated in the CTN "START" study that compared liver enzyme changes associated with a 6-month course of methadone or buprenorphine-naloxone (Weiss et al, 2011). The site recruited 117% of their target and primary outcome data were obtained on 97%. NET Steps and members of the DV Node are participating in a 5-year follow-up of all 97 START patients and have exceeded their recruitment target. The site also participated in an earlier CTN study of HIV risk reduction for males and females on methadone maintenance and also met recruitment and follow-up goals (Calsyn et al, 2010; Tross et al, 2008). Dr. Yu, the Medical Director at NET Steps, directed pharmacotherapy studies at the Philadelphia VA before coming to NET Steps and has worked with Dr. Woody and others in the Penn/VA addiction treatment research center for 20 years.

Participants can also receive their Vivitrol Injections and complete their assessments at the University of Pennsylvania's clinical site, 3535 Market Street, 5th floor. Study trained nurses and doctors will facilitate this process. Every effort will be made to help the participant keep their counseling appointments.

4.3.2 Philadelphia Prison System (PPS*):*

NET@PPS *i*s part of NET Steps, both part of North East Treatment Centers (NET), a non-profit substance abuse facility that operates 10 programs. NET Steps has an IOP with step down programs for patients in its methadone maintenance and non-agonist programs. NET@PPS staff interacts with thousands of opioid addicted inmates in the PPS each year but only 150-200 are on methadone at the time of incarceration and eligible to receive it from NET@PPS. NET@PPS staff consists of a physician (Dr. Yu), who directed substance abuse medication studies at the Philadelphia VA in the Penn/VA Addiction and Treatment Research Center; nurses; a clinical coordinator (Mr. Hirschman); counselors with a maximum of 35 patients as per PA regulations; and support staff. The NET@PPS consists of 5 main facilities and 7 smaller Alternative and Special Detention facilities. Each is under the direction of a warden and all are located on 100 acres in Northeast Philadelphia. The PPS operates on the concept of unit management to reduce inmate movement by delivering services where inmates reside. Most daily functions including dining, outdoor exercise, medication, and sick call are provided on the units. The Inmate Services Division provides counseling, job placement, addiction prevention education, individual, family, and group therapy, AIDS awareness programs, interdenominational religious services, and self-help programs including AA and NA. PPS has a community reintegration program, 14 industrial training programs, and 8 vocational training programs. Prison Health Services provides primary care, including detoxification, HIV, dental, and mental health services. As described above, NET@PPS operates a methadone program for inmates that are on an approved methadone program at the time of incarceration, and has access to all PPS units. The approximately 90% of opioid dependent Inmates that are not on methadone, including those on buprenorphine, are detoxified and referred to treatment at re-entry. The PPS has an approved census of 6800 but typically houses over 8000 due to strict sentencing laws and has been sued in Federal Court for overcrowding. Approximately a third of inmates have been sentenced; others are awaiting sentencing or in for probation violations such as positive drug tests, failure to pay fines or enroll in drug treatment, missing appointments with probation or parole officers, or new crimes. Turnover is rapid, and about 50% are released within two weeks. A total of 240,729 individuals were admitted and released between 1996 and 2003 but this figure represented only 106,849 different persons. About half of these 106,849 were incarcerated and released an average of 3.5 times, accounting for 187,501 incarcerations and releases, or

78% of all releases (Roman et al, 2006). Blind testing found that 3.4% are HIV+ (personal communication, B. Herdman, 2012). Counseling and case management are done in private rooms, and counseling hours are pre-approved by PPS administration. Continuing care for NET@PPS patients is provided by NET Steps or referral back to their "home" program via the BRIDGE program. Of 409 inmates for whom NET@PPS provided services over a recent two-year period, 75% were eligible for insurance coverage, approximately 25% were female, 25% African-American, 60% Caucasian, and 15% Hispanic (mainly Puerto Rican). Most Hispanic inmates speak and read English, which has been true of other addiction studies done in Philadelphia. Charges for NET@PPS patients were Drug Possession (20%), Drug Sales (18%), Theft (24%), Assault (25%), and "Other" (13%).

4.3.3 Electronic Verification System (EVS): NET@PPS has funding that requires it to obtain the Medicaid status of each inmate patient, which is done via the PA Department of Welfare EVS. About 25% of inmates are ineligible for various reasons, often welfare fraud, and thus not accepted into NET@PPS.

4.3.4 "Lock & Track": This PPS database is used to manage inmate interactions (Evans & Ricker; http://www.locktrack.com) and has tools to identify user authorizations, data security and backups, network management and other functions vital for prisoner management; and information on correctional living locations, inmate tracking numbers, release status, and criminal offenses. Sample fields include: Booking and Release, Cases and Charges, Sentencing, Date of Incarceration, Time-Served, Release Date Calculations, Housing Assignments, Court Dates, Inmate Movements, Segregations, and Probation/Parole status. NET@PPS staff has permission to access to Lock & Track and uses it to identify the movement of patients within the PPS, and patients that have been arrested and returned to the PPS.

5 ENROLLMENT AND WITHDRAWAL

5.1 Enrollment

Two hundred (200) prisoners meeting enrollment criteria will be enrolled and stratified according to male/female and sentenced/non-sentenced (e.g. required vs. not required to meet with a probation officer), and randomized to receive XR-NTX before re-entry with follow-up XR-NTX treatment at NET Steps, or randomized to receive their first dose of XR-NTX when they report to NET Steps same day of release up to 30 calendar days post release. Should a prisoner not be released from PPS at the reported release date, and has received his baseline injection of Vivitrol, and the extended incarceration exceeds 30 days, the study will reset his baseline date and administer a 2nd pre-release restart shot prior to the new release date. Additional reset injections may be needed if new release dates are not met. Prisoners will be told that three additional XR-NTX doses will be available at NET Steps and that if they change their mind after reentry they can receive another treatment of their choice. Urine drug tests, adverse events, and a breathalyzer will be done weekly with brief assessments at months 1, 2, 4 and 5, and more detailed assessments at months 3 and 6. PPS data and publicly available criminal justice system information (http://ujsportal.pacourts.us/docketsheets/cp.aspx) will document rearrests and re-incarcerations. Reasons for screen failure will be recorded; those who relapse will be restarted on XR-NTX or offered the most appropriate treatment at NET Steps or another program of their choice. Efforts will be made to obtain follow-up data on all participants according to the intent to treat design.

5.2 Inclusion criteria:

Opioid dependent with physiological features according to DSM-5; interested in XR-NTX treatment; eligible to have health benefits reinstated; detoxified; age 18 or above; not being transferred to serve a longer sentence in a State or Federal prison; provide their address or phone number along with the names and contact information of

3 or more persons likely to know where they can be reached with permission to contact them if unable to be reached in other ways; able to speak and read English, provide informed consent and correctly answer 9 of 10 study quiz items. Women who are sexually active (except women who are no longer having menstrual cycles or have had both ovaries removed, or have had their uterus removed, or have had tubal ligation) must agree to use one of the following methods of birth control from the date they sign this informed consent until a month after their final dose of study drug:

a. Hormonal contraception (oral contraceptive, contraceptive implant, or injectable hormonal contraceptive
b. Double-barrier birth control (condom plus intrauterine device, diaphragm plus spermicide, etc.)
c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy. Participants must also be able to have access to NET Steps via car or public or other transportation after reentry.

5.3 Exclusion criteria:

Planning to move from the Philadelphia area within the next 6 months; being mandated to inpatient substance abuse treatment greater than 30 days; neurological, cardiovascular, renal, hepatic (ALT, AST or GGT >3 times top limit of normal) or another medical disorder that seriously impairs or makes hazardous ability to participate; active tuberculosis; currently psychotic, homicidal, suicidal; uncontrolled seizure disorder; history of allergy to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent; chronic pain for which opioids are needed; sentenced to naltrexone.

5.4 Strategies For Recruitment And Retention

The Philadelphia Prison System (PPS; city jail) is an outstanding location to study XR-NTX for the following reasons: (1) All opioid addicted prisoners are detoxified except those that were on a licensed methadone program at the time of incarceration; these patients represent less than 5% of all opioid addicted prisoners. For those on methadone, their dose and the last date they received it are verified and they are continued on methadone via a contract with NET Steps, a nearby program that has treatment staff in the PPS and provides it "behind the walls" via a satellite site, hence "NET@PPS". At reentry, NET@PPS patients are transitioned to NET Steps or back to their original program. This treatment infrastructure within the PPS will be adapted and used to implement the study proposed here; (2) NET Steps has participated in CTN studies, achieved high recruitment and follow-up rates, and has the capacity to treat study participants; (3) The Medical Director at NET Steps and NET@PPS directed pharmacotherapy studies at the Philadelphia VA before coming to NET Steps where he participated in XR-NTX studies and worked with Dr. Woody and other members of the Penn research staff; (4) The Director of the PPS Medical Services is a PhD economist that worked for Blue Cross/Blue Shield before coming to the PPS, is familiar with the health and population burdens of untreated opioid addiction, and is very interested in this study as is the PPS Commissioner and Commissioner of the Philadelphia Department of Behavioral Health.
The research team (Penn, NET Steps, and NET@PPS) will organize a Community Advisory Board (CAB) consisting of 10 members, half recovering opioid addicted individuals that have been incarcerated and half members of the local community. The CAB will be led by the two Recovery Specialists mentioned above and meet bi-monthly throughout the study, and be attended by members of the research team who will observe and respond to questions. In addition to leading CAB meetings, the Recovery Specialists will participate in weekly research and treatment staff meetings, provide advice on solving problems that emerge in the course of the study including how to interest and engage prisoners, answer questions about study-related issues, and help locate and schedule participants for follow-up appointments.
The design is summarized below; a detailed description of the measures is provided later.

All admissions to the PPS are medically screened on the first day, including questions about drug use. Screening will help identify study candidates, as will daily interactions between NET@PPS staff and PPS healthcare providers. In addition, Dr. Herdman and the Director of Social Work Services at PPS have suggested that the PPS can make announcements and hand out study information and sign-up sheets during the initial days of confinement. Additional information could be provided via a brief video on the PPS closed circuit TV system.

5.5 Participant Selection

The study staff distributes study flyers to prisoner representatives at PPS prisoner-staff meetings that occur once a month. These flyers are then posted in each unit. Interested inmates are requested by the flyer to put in a sick call slip to the medical provider who notifies us by secured email of the request. Study staff then goes up to the prison and requests a private visit with the inmate. At this visit, the research staff will provide detailed information about the study and provide the inmate with an opportunity to ask questions. Those continuing to be interested will be asked to review, discuss, and sign the informed consent and take a 10-item quiz testing their understanding of the study. Those who cannot read or answer 9 of 10 quiz questions after 3 retries will be ineligible. Upon signing the consent and passing the quiz screening assessments will be begin. Historical data will be gathered from PDP through the medical database using the PPS contractor. Existing historical data cannot be older than 60 days with the exception of HIV and PPD tests. If the research study performs the HIV tests, then pre-test counseling for the HIV test will be conducted.

Candidates who complete all inclusion procedures will be randomized into two groups; group A who will be scheduled to return to the research office prior to re-entry for a drug test, a breathalyzer test, another pregnancy test (females), and naloxone challenge, and group B who will be scheduled to for a drug test and naloxone challenge after release within 7 days at the NET treatment clinic. Those with a opioid positive drug test will be asked to return in 3 days for a repeat test; failure to have an opioid negative test on the second occasion will count as a relapse. Patients who fall into this category will be referred for other treatment or can be restarted on study medication if they are detoxed and elect to continue. These patients will continued to be followed for their weekly and monthly assessments. Those in group A or B with an opioid negative drug test and who pass the naloxone challenge will receive their first dose of XR-NTX with continuing XR-NTX for 3 months thereafter at NET Steps.. A benefits manager will schedule an appointment with the participant after they have met the inclusion criteria, have been randomized, and have a valid release date. Those who change their mind about XR-NTX will be eligible for methadone, buprenorphine-naloxone, intensive outpatient treatment without medication, or referral to another program if they so choose. If a subject in Group A, who received an injection before release from PPS is held over in PPS pass the expected release date by 30 days but not greater than 6 months, the subject will not be given a second injection inside the prison. The subject will be considered in the study but not injected until the new established release date for his next injection. The injection visit dates will be reset to begin as his first injection, with the next injection post release.

If a subject in Group A, who received an injection before release from PPS is held over in PPS more than the expected release date but less than or equal to 30 days from his first injection, the subject's next injection will be considered his 2nd injection and his visit schedule will not change.

Table 1: **Study Interventions and Assessments Flow Chart**

	Months 1-3	Month 6

XR-NTX Before Reentry (N=100)	**XR-NTX** + Therapy + Follow Up	Therapy + Follow Up
XR-NTX After Reentry (N = 100)	**XR-NTX** + Therapy + Follow Up	Therapy + Follow Up

5.6 Randomization Procedures:
Randomization will be stratified according to male/female and sentenced/not sentenced (e.g. meet/not meet with probation/parole officer. Those who relapse will be referred to the most appropriate alternative at NET Steps or a program of their choice, or offered XR-NTX if they so choose after completing detoxification and the testing procedures described above to make certain they are free of physiologic dependence before receiving XR-NTX. Follow-up assessments will be done every 4 weeks through month 6, as described above. HIV and hepatitis risk reduction counseling is provided at NET Steps as part of ongoing treatment, as is counseling about the possibility of infections, adverse drug reactions, and overdoses from illicit drug use.

5.7 Subject Withdrawal
5.7.1 Reasons for Subject Withdrawal
Subjects can withdraw from the study at any time. Subjects who discontinue from the study medication will be asked to continue their study visits even though they are no longer receiving study medication.
5.7.2 Handling of Subject Withdrawals or Subject Discontinuation of Study
All subjects will complete an End-of-Study Form before being discontinued from the study and counselled as to the available options for other treatments. Should a subject become lost to follow-up, study staff will attempt to contact them after the scheduled 6-month assessment date.

5.8 Premature Termination or Suspension of Study
This trial will use the University of Pennsylvania Center on Studies of Addiction Internal Data and Safety Monitoring Board (DSMB). There are no plans for interim analysis of safety data however the PI and DSMB will review safety data every 6 months and annually, as required by the protocol, or more often if necessary. Adverse experience and safety contrasts will be performed as indicated, in response to recommendations by the PI and DSMB.
5.9 Potential Problems and how they will be addressed:
5.9.1 Recruitment:
We will print brochures describing the study and will have access to all PPS units. Inmates meeting criteria for opioid dependence with physiologic features are usually easy to identify because they go into withdrawal shortly after entering the PPS. We will review recruitment information at weekly research meetings and consider increasing the number of staff or staff time available to identify study candidates if we fall behind. 2) Not meeting an 80% follow-up rate. Mr. Taylor is working with NET Steps on the START study and has been highly effective but if we are not meeting goals, we will use the van that he uses to meet participants in the community for HIV studies led by Dr. Metzger. 3) Difficulties within PPS. We will ask the Recovery Specialists, other PPS staff, Dr. Herdman, or the Commissioner for help if this occurs. 4) Illness of key staff members. Though we have no indication that such a problem will occur, other senior faculty could be called upon to manage the study. Dr. Poole . (PsyD) is a highly experienced Project Director who has had significant experience in managing other studies.

5.9.2 Dropout and Follow-up:
5.9.2.1 Locator Data Collection: A detailed contact sheet will be completed for all patients at baseline and updated at each subsequent assessment. We will ask patients to provide contact information on themselves and

three others (treatment programs, friends, relatives) with whom they are most likely to stay in contact, and also ask about places where they might be able to be contacted if we cannot locate them directly or via contacts. Research staff will ask for updates about changes in contact information at each assessment.

An attempt to obtain follow-up data for relapse will also be done by the Study staff for those subjects who have been lost-to-follow-up. Staff will call active subjects who have not completed their final visit, but have been lost-to-follow-up, and if reached, ask a series of questions using a follow-up CRF. The staff will also attempt to get the patient to reconnect to the study by scheduling a visit. If the subject has completed the last visit (week 24), staff will attempt to reach the subject by telephone to also completed the questionnaire. This will be a onetime contact call for ended subjects. No compensation will be paid for calls. Subjects who have expressed not to be contacted by the study will not be contacted.

5.9.2.2 Clarity and Appointment Reminders*:* Future appointments for treatment and assessments will be scheduled on a calendar at the time of enrollment and a copy given to the patient at his first outpatient visit. Research staff will give a reminder call seven days prior to each monthly assessment, and a follow-up call the day before the assessment. Missed calls will be noted in a telephone contact log, and three or more repeat attempts will be made. For those unable to be contacted directly, attempts will be made to contact them through locator information.

5.9.2.3 Response to Missed Appointments: At the end of each day research staff will try to contact patients who missed an assessment. If unable to make contact after 5 days staff will begin outreach procedures including contacting persons whose names and numbers were provided on the locator form.

6. STUDY INTERVENTION

6.1 Description of Study Medication:

Vivitrol® (XR-NTX) is a suspension containing naltrexone embedded in material comparable to surgical sutures. Following injection the normal metabolic process gradually erodes the suspension material and releases naltrexone continuously. Plasma concentrations of naltrexone and 6-beta naltrexol (the main metabolite) are detectable for at least 30 days after a single injection, and the medication must be re-administered to maintain its' effect. Continued use is not associated with tolerance or withdrawal, but naltrexone will precipitate withdrawal if given to a person who is physiologically dependent on opioids thus patients must be detoxified prior to dosing.

6.2 Acquisition:

Vivitrol® will be acquired free of charge to the study and provided by Alkermes®.

6.3 Formulation, Packaging, and labeling:

VIVITROL is supplied in single-use cartons. Each carton contains one 380 mg vial of VIVITROL microspheres, diluent for suspension, one 5-mL prepackaged syringe, and customized 1.5- and 2-inch administration (thin-walled) needles with needle protection devices.
For complete instructions be see the Manual of Operations (MOP) which contains the package insert.

6.4 Product Storage and Stability:

VIVITROL® is shipped and should be stored under specific temperature-controlled conditions to ensure proper delivery and help secure patient safety. The handling
instructions that are shipped with the medication should be read before administering to patients:
VIVITROL® should always be refrigerated at 2° to 8°C (36° to 46°F) and not frozen
Store VIVITROL® separately from food, in accordance with Occupational Safety and Health Administration Guidelines. Unrefrigerated, VIVITROL® can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. The product expiration date is printed on the carton.

6.5 Dosage, Preparation and Administration for a subject:

VIVITROL® is currently marketed in the US for use in adults with alcohol dependence. It was administered in this study at the currently marketed dose (380 mg).
The dose of 380 mg was selected after evaluation of VIVITROL® 150 mg and 300 mg in an opioid blockade study, with both doses demonstrating complete blockade of exogenous opioids for greater than 28 days, and after evaluation of VIVITROL® 190 mg and 380 mg in a phase 3 clinical study conducted in patients with a diagnosis of DSM-IV alcohol dependence. In that phase 3 study, doses of 190 mg and 380 mg were selected in order to provide systemic exposure of naltrexone on the same order of magnitude as is observed following oral dosing.

6.5.1 Administration Procedures:

For complete instructions see the Manual of Operations (MOP) which contains the package insert.

6.6 Accountability Procedures:

XR-NTX will be stored in temperature-controlled environments at NET@PPS and NET Steps at temperatures ranging from 36-46, as specified by Alkermes. Dispensing records will be kept by research nursing staff at NET@PPS and NET Steps. Drs. Woody and Yu are familiar with how to administer XR-NTX due to work on other studies. They will participate in training PPS and NET Steps medical staff how to administer it, however Alkermes staff may be involved in training because they are providing the medication at no charge, as was the case in our study of XR-NTX for amphetamine addiction in Iceland.

6.7 Study Behavioral or Social Intervention (s) Description:

All participants will be offered a psychosocial intervention that focuses on recovery and adherence to treatment and will be delivered in the Re-Entry track at NET Steps by certified addictions counselors in an Intensive Outpatient (IOP) format or an Outpatient Program (OP) track as specified by the PA Client Placement Criteria. The primary modality for IOP is 9 hours/week of group and .25 to .5 hours/week of individual supportive therapy for 3-4 months followed by 3-4 hours of group and individual therapy/week that focuses on reentry into sober, law-abiding society. The OP track is 2.5 hours per month of which 1 hour or all of the 2.5 hours per month can be individual counseling. NET Steps has operated a reentry track for 4 years because staff found that newly released inmates have unique issues and do not mix well with standard IOP patients. The primary treatment component is described in a NIDA monograph (http://archives.drugabuse.gov/adac/ADAC5.html) and based on "Living in Balance: Moving from a Life of Addiction to a Life of Recovery," developed by Hoffman et al. (2003). It consists of 12 Core Topics that provide basic information about addiction and recovery that patients explore using session-specific, reproducible worksheets and is supplemented by 20 sessions that build on the core topics using worksheets supplemented by Gorski's relapse prevention techniques as described in Technical Assistance Publication series No. 19: "Counselor's Manual for Relapse Prevention with Chemically Dependent Criminal Offenders" (http://kap.samhsa.gov/products/manuals/taps/19.htm#top).

6.8 Pharmacokinetics and Pharmacodynamics: There is a transient peak of naltrexone about two hours after injection followed by a second peak 2-3 days later that reaches approximately 25 ng/ml followed by a decline to about 12 ng/ml to day 7 with a more gradual reduction that reaches 1-2 ng/ml in 30 days. The once/month injection reduces first pass metabolism to 6-beta-naltrexol that occurs after the oral formulation, thus allowing for less total drug to be administered than the oral, though total naltrexone exposure is 3-4 times higher over 28 days than with a 28-day course of the 50 mg/day oral dose.

***6.9 Metabolism and Elimination*:** The liver metabolizes naltrexone to 6-beta-naltrexol. The P450 system is not involved thus reducing chances for interactions, including drugs used to treat HCV and HIV. Naltrexone and its metabolites form glucuronide conjugates and are excreted in urine. The elimination half-life of naltrexone and 6-beta-naltrexol is 5-10 days.

6.10 Safety: XR-NTX was approved for preventing relapse to alcohol dependence in 2005 and for opioid dependence in October 2010, thus most safety data are from patients treated for alcohol dependence. Local reactions at the injection site have been the most common side effects, and they typically resolve in a few days.

Liver damage has not been observed in patients treated with Vivitrol ® for alcohol or opioid dependence. Additional safety details are in the Human Subjects section and Package Insert.

6.11 **Patient Benefits Manager (PBM):** About 80% of opioid addicted prisoners in the PPS rely on public benefits for treatment (personal communication, J. Carroll, 2013) and about 50% have benefits suspended while incarcerated. Restoring benefits is a bureaucratic process that can take several weeks and occurs more quickly with help from a PBM. An overview of the process in Philadelphia is as follows: The Pennsylvania Department of Public Welfare (DPW) uses an Internet-based claims processing and management information system called Pennsylvania Medical Assistance (MA) PROMISe. Providers access its website for claim status, online claim submission, and other necessary information at http://promise.dpw.state.pa.us/. To discover the patient's status, providers must complete an electronic registration form using the 13-digit provider number, SSN or EIN number. Provider staff create their own unique user ID and password, answer three challenge questions, and enter a passphrase to complete the registration process. Once this process is completed and a registration form is obtained, the staff may begin to submit claims, check recipient eligibility and determine candidate history. Staff can directly apply for patient benefits using an online web based application process operated by the Department of Public Welfare called "COMPASS". To receive this information it is necessary to access an Eligibility Verification (EVS) module from "PROMISe" using the patient's 10-digit ID and 2-digit Medical Assistance Access Card Issue Number, or the SSN and date of birth**.** For inmates whose eligibility has expired or is not established, the initial health insurance application is completed using "COMPASS", which is the point for renewal and establishment of health benefits, medical assistance, food stamps, cash assistance, and other services. An encryption process protects patient information during electronic transmission on COMPASS, a user identification/password ensures confidentiality, and a "Medical Eligibility" form signed by a physician must be completed. All prisoners need to complete a "Criminal Justice" form certifying they do not owe court fines or other financial penalties. Benefits can be restored when the processes described above have been completed and the information on this form is verified and signed by the inmate's Probation Officer or by someone at the Philadelphia Justice Center.

7. STUDY SCHEDULE OF EVENTS

ASSESSMENT SCHEDULE **7.1 Screening:**	- Quiz completed, scored, and reviewed - Informed consent completed and signed - Check of inclusion and exclusion criteria - DSM-5 Checklist - medical/surgical history, including neurological and psychiatric history - physical exam, including a neurological assessment - Vitals- heart rate and blood pressure - height and weight - hematology-Hb,Ht,WBC-diff, platelets* - biochemistry (ALT, AST, ALP, creatinine)* - HCV test, HBV* - HIV test - urine or blood pregnancy test (for women of childbearing potential)

	- Prior/concomitant meds • Drawn by Study if not using historical data - ASI (baseline) - EuroQol - BDI - TLFB - RAB - smoking status
7.2 Baseline/ Enrollment (Week 1)	- Randomization - urine drug tox screen - breathalyzer - urine or blood pregnancy test (for women of childbearing potential) - naloxone challenge* - XR-NTX administered (Day 1)* - recording of AEs/SAEs, if any- Locator Data - Non medical services form - pt satisfaction questionnaire - Check counselling enrollment * pre-release or post release
7.3 Week 2 through end of Month 5	- naloxone challenge (at monthly injections/can be clinical observation) - XR-NTX adminis. (mo 2, mo 3, mo 4) - ASI (month 3) - EuroQol (month 3) - BDI (month 3) - urine or blood pregnancy test (monthly) - TLFB (mo 1, mo 2, mo 3, mo 4, mo 5) - RAB (Month 3) - urine drug tox screen (weekly) - alcohol breathalyzer test (weekly) - Non medical services form - record all primary and secondary efficacy in CRF - recording of AEs/SAEs, if any- recording of concomitant medications - check for protocol violations - check time to restoration of benefits - check deaths report -check re-incarceration report - Locator Data

	- Check counselling enrollment - End–of-study CRF (if needed) - Pt Remuneration made
7.4 End-of-study visit (month 6):	- ASI - EuroQol - BDI - urine drug tox screen - alcohol breathalyzer test - TLFB - RAB - urine or blood pregnancy test (for women of childbearing potential) - HCV, HBV tests** - HIV test** - Non medical services form - record all primary and secondary efficacy in CRF - recording of AEs/SAEs, if any - - check deaths report - check re-incarceration report - recording of concomitant medications - check for protocol violations - pt satisfaction questionnaire - complete End-of-Study Form- chk time to restoration of benefits - Check counselling attendance - Pt Remuneration made ** if negative to date
7.5 Withdrawal Visit **If patient does not wish to continue in the study and misses his visit, complete end of study form.**	<u>Perform End of Study Visit</u> - ASI - EuroQol - BDI - urine drug tox screen - alcohol breathalyzer test - TLFB - RAB - urine or blood pregnancy test (for women of childbearing potential) - HCV, HBV tests** - HIV test** - Non medical services form

	- record all primary and secondary efficacy in CRF - recording of AEs/SAEs, if any - check deaths report - check re-incarceration report - recording of concomitant medications - check for protocol violations - pt satisfaction questionnaire - complete End-of-Study Form- chk time to restoration of benefits - Check counselling attendance - Pt Remuneration made ** if unknown

8. STUDY MEASURES/ PROCEDURES

8.1 Study Assessments

1) Study Quiz: The study quiz is a 10-item questionnaire given to make sure that the patient understands the study. The patient must answer 9 of the 10 questions correctly in order to qualify for the study. If the patient only answers 5 of the 10 items correctly on the first try, he cannot be in the study. If the patient answers 6 to 8 of the questions correctly he will be given 3 more chances to answer the questions again until he scores 9 of the 10 items correctly. Those who answer 9 or more items correctly will be asked to sign the informed consent and will go on to complete more screening tests.

2) Record of inmates screened, randomized, and reasons for screen failure: Will include inmates expressing interest in participating, those screened and randomized, and reasons for screen failure.

3) Opioid Dependence and Other SUDs: Done at baseline to confirm opioid dependence with physiologic features and other SUDs using the DSM-IV checklist (Hudziak et al, 1993) that we will modify for DSM-5 (e.g. delete the item on recurrent legal problems; insert the item on craving).

4) Screening Physical Examination and Laboratory Tests: height, weight, BP, pulse, temperature, chest, abdomen, HEENT, extremities, CBC, electrolytes, liver panel, creatinine, routine urinalysis, TB and urine or blood pregnancy tests – will be collected to rule out medical conditions that exclude patients from study enrollment. Pregnancy tests will be collected at screening and baseline by study staff and repeated monthly prior to XR-NTX injections for females who have not relapsed. ALT, AST, and GGT will performed at screening only. Patients will be referred to their primary care provider for further evaluation if levels is 3 or more times the top limit of normal.

5) Addiction Severity Index (ASI; McLellan, et al, 1992) with items added to the legal section to calculate average number of crimes/day on days when illegal activity occurred (French, Salomé, et al, 2002). This addition estimates criminal activity in the 30 days prior to incarceration and at 12 and 24-weeks by multiplying the number of days of illegal activities by the average number of crimes/day. We will add a question, "Since the last assessment, how many days have you been incarcerated in a facility other than the PPS" to obtain data that is not available in Lock & Track (described below) or the ASI for use in calculating primary and secondary outcomes (e.g., Rajkumar, 1997; French et al, 2002).

6) Urine (UDS) : A Urine Drug toxicology screen will be done at week 1 and thereafter using a urine tox dip stick method. If confirmation or other outside tests are needed by the study, NET Steps will utilize Atlantic

Diagnostic Laboratories (ADL). Atlantic Diagnostic Laboratories (ADL). uses a specialized profile that tests for 14 commonly abused drugs (details in Appendix). All tests performed within PPS will utilize the PPS medical contractors. The lab picks up specimens 5 days/week and results are transmitted electronically to NET Steps or NET@PPS within 24-48 business day hours. Testing costs are reasonable and detailed in the budget justification.

7) Self-Reported Opioid & Other Drug Use: Done using the Time Line Follow-Back (TLFB; Sobel & Sobel, 1992) to assess use of various substances over a specified period of time. For this study it will assess drug and alcohol use over the 30 days prior to incarceration, and during the past 30 days at each monthly assessment.

8) Naloxone challenge: A baseline COWS is administered prior to the naloxone challenge by administering 0.4 to 0.8 mg of naloxone I.M. and observing the patient for 15 - 30 minutes to establish absence of physiological dependence (score of <5 on the COWS). A second COWS is administered after the naloxone challenge is given and the patient is also observed for 15 – 30 minutes. The naloxone challenge is done prior to subsequent XR-NTX doses unless it is clear that there has been no relapse, or that relapse has occurred, in which case it will not be done. Determination presence/absence of relapse is a clinical evaluation based on self-report, urine test results, reports from significant others (if available), and physical examination (rhinorrhea, lacrimation, fresh tracks or puncture marks). If withdrawal occurs after a naloxone challenge, clonidine 0.2 to 0.6 mg will be administered to suppress it and the participant will be observed with blood pressure checks every 15 minutes until symptoms subside and there is no evidence of clonidine-induced hypotension.

9) Relapse to Opioid Dependence with Physiological Features: Determined from self-report, physical assessment, urine tests, reports from significant others if available, and/or a positive naloxone challenge in cases where it is administered prior to a XR-NTX.

10) Time to Relapse: Determined by time between absence of physiologic dependence and time that relapse occurred, and documented using methods described above.

11) Weeks in Addiction Treatment: Data obtained from NET Steps clinical records, patient self-report, and verification from other treatment provider (for those reporting treatment elsewhere). A week will be counted as beginning on Monday and ending the following Sunday. Having 5 or more days of protected time from a previous XR-NTX injection, or receiving 5 or more days of methadone or buprenorphine-naloxone, or having a counseling appointment lasting 30 minutes or more will be counted as a week in treatment.

12) Quality of Life: measured by the EuroQol (EuroQol Group, 1990), a standardized measure for describing and valuing health-related quality of life. It consists of two components: one that describes current health in five domains, by choosing one of three levels in each of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; and the other a visual analogue scale where patients rate their current global health state by choosing a number from a visual analogue scale that ranges from 0 to 100- where 0 represents the worst imaginable health and 100 is the best imaginable health. It was used in the cost-effectiveness study of short vs. longer-term buprenorphine-naloxone treatment for opioid addicted youth where it showed improvement with addiction treatment (Polsky et al, 2010), and will be done at baseline using the timeframe "when you entered the PPS", and at 12 and 24 weeks using the timeframe "since your last assessment".

13) Psychiatric Symptoms: measured by the Psychiatric Composite Score of the ASI and the Beck Depression Inventory (BDI; Beck et al, 1961) for 30 days prior to incarceration at baseline and at 12 and 24 weeks after reentry.

14) HIV Drug and Sex Risk: Done at baseline and at 12 and 24 weeks using the Risk Assessment Battery (RAB), a self-report of drug use and injection and sex risk behaviors (Navaline et al, 1994; Metzger et al, 2001) that will assess HIV risk over the 12 weeks prior to incarceration at baseline and the past 12 weeks at each follow-up. The RAB has 38 closed end items that cover issues of substance use including frequency, needle sharing and cleaning, and condom use. Responses on the RAB have been equivalent to those collected by

personal interview, and scores were able to discriminate between cocaine and opioid abusers as well as those who converted to HIV+ from those who remained HIV negative (Metzger et al, 2001).
15) Re-arrest and re-incarceration: This information is available via the Lock & Track Database (http://ujsportal.pacourts.us/docketsheets/cp.aspx) and will be supplemented by information about crime and illegal activities from the Addiction Severity Index (described above). *"Lock & Track"* is used to manage inmate interactions (Evans & Ricker; http://www.locktrack.com) and has tools to identify user authorizations, data security and backups, network management and other functions vital for prisoner management; and information on correctional living locations, inmate tracking numbers, release status, and criminal offenses. Sample fields include: Booking and Release, Cases and Charges, Sentencing, Date of Incarceration, Time-Served, Release Date Calculations, Housing Assignments, Court Dates, Inmate Movements, Segregations, and Probation/Parole status. NET@PPS staff has permission to access to Lock & Track and uses it to identify the movement of patients within the PPS, and patients that have been arrested and returned to the PPS. Most re-incarcerations will be in the PPS since all subjects will be city residents, but a few may occur elsewhere and these can be identified by "Lexus-Nexus", a program that provides information about individual-specific incarceration throughout the U.S and to which we have access due to participation in the follow-up study of participants in the Clinical Trial Network "START" study where NET Steps was a site.
16) Death: Reports from significant others and the National Death Index as in prior studies (Zanis et al, 2004; Woody et al, 2007).
17) Time to restoration of benefits: Available from the Eligibility Verification form on PROMISe.
18) Money Spent on Drugs: determined from the ASI.
19) Employment: measured by the composite score on the Employment section of the ASI for 12 weeks prior to incarceration at baseline, and at 12 and 24 weeks after re-entry.
20) Non-Study Medical Services (NSMS; *French et al, 2000):* Measures outpatient and inpatient medical treatment; questions will be added about non-study substance abuse treatment. The timeframe will be 90 days prior to incarceration at baseline, and at the 12 and 24-week assessments using the timeframe of "since your last assessment."
21) Hepatitis B and C Tests: Performed by study at baseline if historical data is > 60 days or status is unknown, and performed at 24 weeks for those testing negative.
22) HIV Tests: Will be collected at baseline if historical data is not available, and at 24 weeks for those testing negative.
23) *Pre and Post Counseling* for HIV and other Infectious disease positive tests.
24) Adverse Event Report Form (AERF): This form will be similar to the one used in the study of buprenorphine-naloxone treatment for opioid addicted youth (Woody et al, 2008). Patients will be asked about adverse events since their last visit at each assessment point, and reports will be categorized as AEs or SAEs and followed up to determine their outcome, as described later in more detail.
25) Prisoner views of XR-NTX: Patients will be asked why they are interested in XR-NTX and why they chose it rather than methadone or buprenorphine-naloxone. A form with the questions is in the Appendix.
26) Staff views of XR-NTX: A questionnaire will be developed to assess attitudes of 10 NET@PPS and PPS staff (identified by Amy McNamee, and Dr. Herdman) on their views of XR-NTX treatment. It will be modeled on one we are using in a study at Christiana Medical Center in Delaware to assess nurses' attitudes about addicts and addiction treatment where peer counselors meet with medical inpatients who have untreated substance use problems and try to get them into treatment. This questionnaire will be administered when 3/4ths of the subjects have been enrolled and will provide information about acceptability of XR-NTX in the PPS and at NET Steps.
27) Alcohol Breathalyzer Test: is performed at baseline and at all weekly visits.
28) Relapse CRF: is performed each week and monthly for each subject. Each positive opioid urine equals 5 days; Time Line Follow back days opioid use equals # of days indicated (self-report use).

29) Follow-up Questionnaire: is performed in-person or over the telephone throughout the study for active subjects, and done over the telephone for subjects who are active but have been lost-to-follow-up; and including subjects who have completed their final 24 week visit but were lost-to-follow-up.

8.2 LABORATORY PROCEDURES/MEASURES

8.2.1 Clinical Laboratory Tests

1) The study will use historical data if available from PPS. The study will use the OraSure Rapid oral test (swab) for HIV if study performs test. Study screens will be confirmed via laboratory if positive.
2) CBC, Blood Chemistry,HBV and HCV tests. Will use historical data if < than 60 days old. We will use PPS medical contractor to draw blood if >60 days.
3) Liver Tests (ALT, AST, GGT). Will use historical data if < than 60 days old. Will use PPS medical contractor to draw blood if >60 days.
4) Will use historical data from PPS at screen. PPD tests will be performed at screen by the PPS medical contractor if status is unknown.
5 Historical Urine or blood pregnancy test used at screening if < 60 days old, but will be readministered at baseline before the administration of Vivitrol, and then urine or blood pregnancy dip tests monthly after reentry throughout the study.

8.2.2 Specimen Preparation and Handling

All rapid test kits will be labeled with the patient's ID number before testing and reading. The kits come one kit per package. Will be stored in locked cabinets before use.

9. DATA MANAGEMENT AND CASE REPORT FORMS (CRFs)

Mr. Petro and Ms. Li will construct a web-based system modeled on ones they developed for other studies. Data will be password protected and entered on desktop or laptop computers by research staff. Only study numbers will identify subjects, and data linking subjects to numbers will be kept in a locked cabinet in a secure office at PPS that is designated for that purpose. The system will be programmed with range checks and stops that will not let data entry proceed if important pieces of information are inconsistent or missing. Investigators will be alerted to problems with missed assessments or other protocol deviations. Data will be backed up daily and secured using password protected Login IDs.
Study data will be collected via the web-based system. A complete, cleaned and de-identified copy of the dataset will be made available upon request within a month of receiving a request but not more than nine months from the end of the final year of funding, The dataset will be entered into the NIH system as was done with the NIDA study of buprenorphine-naloxone for opioid addicted youth (Woody et al, 2008) and with other studies in the Clinical Trails Network.

9.1 Data Handling & Record Keeping

9.2 Confidentiality: Subject visits are conducted in a private study office. Interviews are monitored visually by prison security personnel who are located outside of the room, but will not be able to hear the interviews. Source documents collected from the interviews will be kept in a locked file cabinet within a locked room in the study office. Subject data will be kept confidential and managed according to the HIPAA requirements that include a signed authorization informing the subject of what protected health information (PHI) will be collected; who will have access to that information and why; who will use or disclose that information; and their rights to revoke authorization for use of their PHI. If a subject revokes authorization to collect or use PHI, the investigator retains the ability to use information collected prior to the revocation of authorization. For subjects who revoke authorization to collect or use PHI, attempts will be made to obtain permission to collect vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.3 Source Documents: Source data include all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are in documents such as: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at laboratories, or at medico-technical departments involved in the clinical trial.

9.4 Case Report Forms (CRFs): These include all primary data collection instruments and are entered and accessed through the web-based data management system. The system will be programmed so that each form is validated to check for blank fields and inconsistencies.

9.5 Records Retention*:* Source documents will be retained for at least 7 years after data lock.

10. ASSESSMENT OF SAFETY

10.1 Potential XR-NTX (Vivitrol ®) Risks):

10.1.2 Injection Site Reactions:

XR-NTX is administered as a gluteal intramuscular injection and inadvertent subcutaneous injection may increase the likelihood of severe injection site reactions. To reduce this possibility, each needle provided in the XR-NTX kit is customized and no other needle can be used. Because needle length may not be adequate in every patient because of body habitus (e.g. severe obesity that reduces the chances for intramuscular administration), each participant will be assessed prior to injection to assure that needle length is adequate and those whose subcutaneous tissue is so thick that the needle is unlikely to reach the muscle will not be enrolled. Patients will be educated to report concerning injection site reactions to the attention of the clinician and research staff.

Injection site reactions are the most common AEs and have been reported in 50% of the placebo group and 69% of the 380 mg Vivitrol ® group in alcohol treatment studies. They include pain, tenderness, induration, swelling, erythema, bruising, or pruritus and typically resolve in 1-3 days but can be severe. In clinical trials for alcohol dependence one patient developed hardening of tissue at the injection site that continued to enlarge after 4 weeks and required surgical excision. In the post-marketing period additional cases of injection site reactions with induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis have been reported. In some cases, these problems required surgical intervention including debridement of necrotic tissue with some resulting in significant scarring. These cases occurred primarily in female patients. A physician will examine patients exhibiting abscess, cellulitis, necrosis, or extensive swelling to determine if referral to a surgeon or other specialist is needed.

10.1.3 Unintended Precipitation of Opioid Withdrawal:

XR-NTX will precipitate or exacerbate opioid withdrawal unless the patient has been opioid-free for 7-10 days, which is expected to be the case in all but a very few potential study candidates. An opioid negative urine test, drug use history, psychiatric interview and observation for signs and symptoms of current opioid use or withdrawal will be done prior to the first naloxone challenge and the challenge will not be done unless the person appears to be free of physiologic opioid dependence. The absence of current physiologic dependence will be confirmed by self-report, clinical observations, and a score of <5 on a COWS that is administered 15 -30 minutes after receiving 0.4 - 0.8 mg naloxone I.M. Clonidine 0.2 to 0.6 mg will be used to suppress withdrawal if it occurs, and blood pressure will be checked every 15 minutes until there is no evidence of hypotension and/or withdrawal over the next 45-60 minutes. Similar procedures will be followed prior to subsequent XR-NTX injections, however the naloxone challenge will not be re-administered if the clinical situation clearly indicates the absence of relapse. Patients that have relapsed will be referred to the most appropriate available treatment, as previously described.

10.1.4 Opioid Overdose From an Attempt to Overcome Opioid Blockade: Patients will be told that attempting to overcome the XR-NTX blockade by administering large amounts of opioids is dangerous and may result in fatal overdose.

10.1.5 Liver Toxicity: The most serious adverse effect associated with naltrexone is hepatocellular injury, which has almost always been associated with oral doses of 1400 to 2100 mg per week. These doses produce much greater naltrexone exposure than the 380-mg/monthly doses from a XR-NTX injection. At oral doses below 600 mg/week only relatively minor changes in liver tests were reported and these were not clearly attributed to naltrexone. In addition, a study of actively drinking alcoholics who received a once-monthly injection found no evidence of liver toxicity. This study enrolled 624 patients (68% male; median age 44), and randomly assigned them to XR-NTX 380 mg (n=205), XR-NTX 190 mg (n=210) or placebo (n=209). There were no significant differences in ALT, AST, or bilirubin levels between study groups at any post-baseline assessment; GGT in the 380 mg group was lower compared with placebo at weeks 4, 8, 12, and 20 and high (> 3 times upper limit of normal) liver chemistry tests (LCTs) and hepatic-related adverse events were infrequent in all treatment groups. In a subset of patients who were drinking heavily throughout the study, or who were obese or taking NSAIDs, there was no increase in frequency of high LCTs or hepatic-related adverse events in those receiving either dose of Vivitrol ® (Lucey et al, 2008).

10.1.6 Hepatic Impairment: XR-NTX pharmacokinetics has not been shown to alter hepatic states in patients with mild to moderate hepatic impairment, and dose adjustment is not required for these individuals. However they have not been evaluated in subjects with severe hepatic impairment, thus individuals with severe renal disease will be excluded from the study. *Gastrointestinal Effects*: The most common gastrointestinal AEs are nausea (11% placebo group; 33% XR-NTX 380 mg group) and vomiting (6% placebo group; 14% XR-NTX 380 mg group).

10.1.7 Renal Impairment: A pharmacokinetic analysis indicated that mild renal insufficiency (creatinine clearance of 50-80 mL/min) had little or no influence on Vivitrol ® pharmacokinetics and that no dosage adjustment is necessary. XR-NTX pharmacokinetics have not been evaluated in subjects with severe renal insufficiency thus these individuals will not be included in this study.

Gender: In a study of healthy subjects (n=18 females; 18 males), gender did not influence the pharmacokinetics of XR-NTX.

10.1.8 Age and Race: The pharmacokinetics of XR-NTX has not been evaluated in the geriatric population, nor has the effect of race on pharmacokinetics.

10.1.9 Drug Interactions: The metabolic pathway of naltrexone suggests that it does not appear to have significant interactions with other drugs but studies evaluating interactions have not been performed.

10.1.10 Reversal of Blockade for Pain Management*:* In an emergency situation, suggestions for pain management are regional anesthesia or non-opioid analgesics. If opioids are required for anesthesia or analgesia, patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by persons specifically trained in the use of anesthetic drugs and the management of respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

10.1.11 Depression and Suicidality: In controlled trials among patients with alcohol dependence, AEs of a suicidal nature (suicidal ideation, attempts, completed suicides) were infrequent overall, but more common in patients treated with XR-NTX than placebo (1%). In some cases, the suicidal thoughts or behavior occurred after medication discontinuation but were in the context of an episode of depression that began while the patient was on the study drug. Two completed suicides occurred in alcohol treatment studies, both in patients treated with XR-NTX Depression-related events were also more common in patients treated with XR-NTX than in those on placebo (1%).

10.1.12 Contraindications: Patients should not receive XR-NTX if they are taking opioid analgesics; have current opioid dependence, are in opioid withdrawal, failed a naloxone challenge, or have a positive urine

screen for opioids; exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent; or have acute hepatitis or liver failure.

10.1.13 Eosinophillic Pneumonia*:* In clinical trials, there was one diagnosed case and one suspected case of eosinophilic pneumonia. Both cases required hospitalization and resolved with antibiotics and corticosteroids. Should a person receiving XR-NTX develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered.

10.2 Unanticipated Problems

10.2.1 Adverse Events

AEs will be noted on CRFs similar to those used in the study of buprenorphine-naloxone treatment for opioid addicted youth (Woody et al, 2008). Medical staff will evaluate the intensity, seriousness, and causal relationship of the AE to study medication and procedures. The PI, Project Director, and NET@PPS or NET Steps medical staff will ask participant what adverse events have occurred since the last visit. Medical Staff will judged "possibly" or "definitely" related to the study, and record the event in the AE CRF. A report describing it will be sent to the Penn and Prison IRBs within the defined reporting period unless otherwise defined as serious. Then it must be reported in 5 days and followed up to determine its outcome. Unanticipated problems involving risk to subjects or others will be reported for any incident, experience, or outcome that meets any of the following criteria: 1) Unexpected in nature, severity or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, product information, etc.); 2) Related or possibly related to research participation (i.e., a reasonable possibility that the experience or outcome may have been caused by procedures involved in the research); 3) Suggests that the research places subjects or others at risk of physical, psychological, economic, or social harm.

10.2.2 Definition of Adverse Event (AE): These are defined as any symptom, sign, illness, or experience that develops or worsens during the course of the study. Abnormal results of diagnostic procedures are considered AEs if they result in study withdrawal, are associated with a serious adverse event, lead to additional treatment or further diagnostic tests, and/or are considered by the investigator to be of clinical significance.

10.2.3 Recording Adverse Events:

At each patient contact the research team will seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs will be recorded in the source document and also on the appropriate CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures or results should be in the source document. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that study treatment or participation is not the cause. SAEs that are ongoing at the end of the study must be followed up to determine the final outcome. Any SAE that occurs after the study and is considered possibly related to the treatment or study participation should be recorded and reported immediately.

10.2.4 Unanticipated Problems for Immediate Reporting of an AE(s):(

1) Any AE that, even without detailed analysis, represents a SAE that is rare in the absence of drug exposure (i.e. agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).

(2) Any AE that would cause a change in the product information, protocol or informed consent, or would prompt IRB action to assure protection of human subjects.

10.2.5 AE Relationship to Study Intervention

Consider date and time of on-set, severity, and relatedness to known side effects.

10.3 Serious Adverse Events

10.3.1 Characteristics of a Serious Adverse Event

An SAE is an AE that is fatal, life threatening, requires or prolongs a hospital stay, results in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important unanticipated medical event. Such events may not be life threatening but may jeopardize the subject or require intervention to prevent a serious outcome. For example, drug overdose, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would be considered serious.

10.3.2 Reporting SAEs: Disability, hospitalization or prolongation of hospitalization, congenital defects, and life-threatening events are SAEs that must be reported (orally, e-mail, fax) to the Penn and Prison IRBs at the time they are identified if they are judged related or possibly related to the study, or unexpected. A written report is to be filed within 5 working days to these IRBs and the sponsor. When additional clinical information is available, a follow-up and/or final SAE report is to be filed. If the report is supplied as a narrative, the minimum necessary information at the time of the initial report includes: study identifier, subject number, description of event, date of onset, current status, if study treatment was discontinued, reason why event was considered serious, and whether it was related to study treatment or procedures. Copies of each report and documentation of IRB notification and receipt will be kept in the study file.

10.3.3 Reporting Deaths: The Penn IRB requires that investigators report a death within 24 hours when it is unexpected and indicates participants or others are at increased risk of harm. Other deaths are to be reported within 72 hours, regardless of whether they were related to study participation.

10.4 Adverse Event Reporting Period: The period during which AEs must be reported begins at study initiation, including assessment of any preexisting conditions and ends at the last follow-up.

10.5 Post-Study AEs: At the last scheduled assessment subjects will be instructed to report any subsequent event(s) that they, their physician, or treatment staff believe might reasonably be related to study participation. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to the study. The sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly in the subsequently conceived offspring of a subject that participated in the study. Patients who become pregnant during the study will not be eligible for continuing XR-NTX since it is not approved for use during pregnancy, but will be followed up to determine if there was any evidence of fetal harm or an abnormality.

10.6 Other Considerations for Reporting AE(s) or SAE(s):

10.6.1 Abnormal Laboratory Values:

A laboratory abnormality should be documented as an AE if any of the following conditions are met: 1) It is not refuted by a repeat test that was done to confirm it; 2) It suggests a previously undetected disease and/or organ toxicity; 3) It requires active management; e.g. discontinuation of medication, more frequent follow-up assessments, further diagnostic investigation, etc.

10.6.2 Hospitalization, Prolonged Hospitalization & Surgery:

Any AE that results in hospitalization or prolonged hospitalization will be documented and reported as a SAE unless otherwise instructed in the protocol. In this study, re-incarceration or admission for detoxification will not be considered SAEs since they are common and expected among the study population. Conditions that require surgery could be AEs or SAEs depending on the clinical situation.

(1) Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition.
(2) Hospitalization for detoxification or rehabilitation of opioid or other substance use disorder, unless it is a worsening or increase in the condition.
(3) Information that indicates a change to the risks or benefits of the research, in terms of severity or frequency. For example:

- Safety monitoring indicates that a side effect is more severe or more frequent than expected.
- An arm of the study is clearly shown to be of no therapeutic value paper.

10.6.3 Unanticipated Problems Reporting to IRB

(1) Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
(2) Breach of confidentiality
(3) Change to the protocol without prior IRB review in order to eliminate apparent immediate hazards.
(4) The research team cannot resolve a complaint that indicates unexpected risks.
(5) Protocol violation (an accidental or unintentional deviation from the approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of subjects.

10.7 Women and the Reporting of Pregnancies

Pregnancy is an exclusion criterion for entry into the study. Women who test positive during the pregnancy test at screening will not be permitted to be in the study. Pregnancy tests will be repeated monthly prior to XR-NTX injections for females who have not relapsed.
Lactating females must agree not to breast feed. Sexually active females of child-bearing potential (i.e., women who are not menopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) must agree to use one of the following methods of birth control from the date they sign the ICF until 24 hours after their final dose of study drug:

a. Hormonal contraception (i.e., oral contraceptive, contraceptive implant, or injectable hormonal contraceptive
b. Double-barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide, etc.)
c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy.

Patients who become pregnant during the study will not be eligible for continuing extended-release naltrexone since it is not approved for use during pregnancy, but delivery will be followed up to determine if there was any evidence of fetal harm or an abnormality. These patients will be referred to other treatments. The investigator must notify the IRB and study sponsor of patients who become pregnant during the study as an adverse event (AE).

11. PATIENT REMUNERATION:

Patients will receive $100 cash dispersed through the use of a Greenphire ClinCard , or equivalent voucher at a local retail outlet for months 1, 3, and 6 for the time they spend doing these monthly assessments. Patients can

receive an additional $30.00 on their Greenphire ClinCard for coming in for their first scheduled visit in Week 1 as scheduled by the study staff. Patients will receive $20.00 for their month 2, 4 and 5 visits which are briefer. Participants will also receive $15.00 for travel and time for weekly visits not including the monthly visits at weeks 1 -3, 5 -7, 9 – 11, 13 – 15, 17 – 19, and 21 – 23. Estimated costs for travel expenses are in the budget justification.

***Travel Costs*:** Many inmates lose public assistance and welfare benefits upon incarceration and typically have no legal income, no medical benefits, and no medical transportation benefits after re-entry. The Patient Benefits Managers will seek and secure benefits for subjects that lost them, a process that currently averages 6 weeks post re-entry but will be shortened by starting it before reentry. The maximum amount of reimbursement they can receive if they keep all assessment appointments is $660.

12. CLINICAL MONITORING

The Study Coordinator will monitor the sites on a weekly basis to review logs and procedures. The Quality Assurance Monitor will visit the sites on a monthly basis to review source documents and procedures, and she will visit the study offices weekly to monitor regulatory requirements.

13 STATISTICAL HYPOTHESES AND PLAN

13.1 Primary Aims

Before performing analyses, we will apply the following data screening and cleaning procedures: 1) screen for data-entry errors; 2) check for outliers; 3) assess the extent and pattern of missing data, and 4) check that appropriate assumptions of normality are met, as necessary. In all analyses, we will examine whether the assumptions underlying the application of statistical methods have been met, principally through use of standardized residuals, influence diagnostics, and graphical displays. We will check to confirm that the groups do not differ on baseline relevant background variables using analyses of variance (ANOVA) for continuous variables and log-linear models for binary or ordinal responses. The randomization process should minimize the need for inclusion of covariates to reduce bias in treatment comparisons. However, we will consider relevant covariates for inclusion in analyses to improve precision of estimation of treatment effects (Hauck et al. 1998). The statistical procedures that will be used to examine each outcome are listed below.

13.2 Primary Aim 1—Proportion Without Relapse by Month 3:

At each monthly assessment we will determine whether a subject has relapsed based on self-report, physical examination, response to a naloxone challenge, or information from program staff of significant others. Using these data, we will create a binary outcome reflecting whether or not the participant relapsed during the 3 months post-release. We will compare the proportion of participants who relapsed in the two groups using a logistic regression analysis. The analysis will include group as a predictor variable along with all relevant covariates (including the stratification variables). Relapsed will be defined by self-report of 10 or more days in the past 30 days or by two or more opiate positive urine samples in the last 30 days. Positive urine samples will be computed as 5 days of opioid use for each sample. The analysis will be performed using SAS's PROC LOGISTIC.

13.3 Power Analyses for Primary Aim:

There are relatively few data to estimate power for this study since so little work has been done in this area. We know that most relapses from various substance dependencies occur in the first 3-6 months (Woody & Cacciola, 1994). For opioid addiction it typically occurs in the first days or weeks (Binswanger et al, 2007) and for opioid addicted prisoners, often on the way home from jail, according to reports from the two Recovery Specialists and

more than half of the focus group participants. We also know that XR-NTX will prevent relapse for a month and that more than twice as many prisoners that did not receive it before reentry relapsed by the second month after reentry as compared with those that received it before reentry (Lee et al, 2013). Regarding the issue of how long patients will continue on XR-NTX, 79% of the XR-NTX patients in the O'Brien et al study received their first 3 injections and 73% received their first 4. In the Krupitsky et al study (2011) 78% received their first 3 injections and 70% received their first 4 (data provided by J. Stoddard, Alkermes, 2014).
The Lee et al study most closely resembles the one proposed here, however our study has a stronger control group than Lee et al because patients in our control group will be offered XR-NTX at NET Steps after reentry and all participants will have a Patient Benefits Manager to help reinstate benefits that were lost while incarcerated. Putting these data together, we estimate a 23-33% group difference in relapse rates by month 3. Power estimates calculated using this estimate and following the recommendations of Cohen with a 2-sided alpha of .05 and a baseline sample size of 100 per group result in 80% power to detect a difference in relapse rates of approximately 20% (OR = 2.4) between the two groups assuming a relapse rate of 50% in the control condition and 10% and 20% attrition by the 3- and 6-month follow-ups. These outcomes are clinically meaningful based on the severe consequences from untreated opioid addiction, the evidence that continuing in treatment reduces them, and confirmation of their importance by conversations with ex-prisoners and the Recovery Specialists, and focus group participants.

13.4 Secondary Aims*:*
1) Quality of life;
2) Weeks in treatment through month six;
3) Time to relapse;
4) Rearrests;
5) Psychiatric symptoms;
6) Opioid use;
7) Alcohol and other drug use;
8) HIV risk;
9) Reincarceration;
10) Deaths.

We will use linear mixed effects models (Littell, Milliken, Stroup, & Wolfinger, 1996) to examine group differences on continuous longitudinal outcomes (i.e., 1) quality of life scores, 5) Psychiatric symptoms, 8) HIV risk scores,) and non-linear mixed effects models (Diggle, Heagerty, Liang, and Zeger, 2002) to compare the groups on binary longitudinal outcomes (i.e., 6) opioid, 7) alcohol, and other drug use). Mixed effects models have advantages over conventional repeated measures methods as they allow for missing observations, provide greater flexibility in modeling the variance-covariance matrix, and permit the estimation of both group and random subject-specific effects. Models will be calculated using SAS's PROC GLIMMIX and MIXED, respectively. We will use a Poisson regression model to compare the groups on 2) weeks in treatment through month 6. We will use a Cox proportional hazards regression model to determine whether the time to relapse (3) differs across the two groups. The analysis will account for the fact that the data will likely be right-censored as some participants may experience a relapse during the period of observation. The analysis will include relevant covariates and will be performed using SAS's PHREG. The models will include a terms for group, time, and their interaction as well as any necessary covariates. Finally, we will use logistic regression to compare the two groups on binary cross sectional outcomes (i.e., 4) rearrest, 10) death, and 9) reincarceration). The models will be similar to that described for the primary outcome.

13.5 Missing values:

Missing data will not be an issue for several of the outcomes (i.e., days in treatment, re-arrest, re-incarceration). The most important source of missing data is likely to be dropout. As recommended by Lavori (1992), we will analyze the data under an intent-to-treat principle, in which all participants initially randomized will be included. Logistic regression models predicting dropout, based on patient characteristics and prior measures, will be used to determine whether the dropout process is ignorable (i.e. whether missed visits are well explained by observable data). Although these models provide a formal framework for assessing sensitivity to missing data, much of their implementation proceeds in an exploratory manner.

13.6 Maintenance of Data on Retention Efforts:

To assist in follow-up we will utilize "Participantfile", a computerized record of participant information. This software was designed and programmed by our research team over the past 10 years and was used in the CTN "STRIDE" study of exercise for stimulant dependence. It provides secure, immediate access to a variety of follow-up information on each patient. All contact information will be included in this database including: names, phone numbers and addresses of friends or relatives who might know where the patient can be located, aliases and "nicknames," hangouts, other study subjects known, and treatment programs. Access to these encrypted data is strictly controlled through a database security system. The database will be stored on a removable disk that will be locked in a safe storage area at the end of each day. All attempts to locate subjects will be recorded in Participant file. This allows staff to know the status of any missed patient so others can assist in follow-up work if necessary. It also allows supervisors, the site PI, or project manager to monitor workloads, schedule calls, personalize letters, etc. For example, if all calls are unanswered in the morning, calls at another time are indicated. Leads will continue to be recorded and discussed at weekly staff meetings.

14 Training Plans

14.1 Engagement Plan

The Penn research staff will train NET@PPS counselors and nurses in the use of XR-NTX and review procedures with Dr. Herdman, Ms. McNamee, Drs. Yu and Taylor, and the NET Steps staff. The lead staff will schedule weekly or biweekly meetings with the NET team at NET Steps until the study is well underway at which time we will reduce the meetings to weekly or biweekly. Lead staff will visit the PPS weekly or biweekly, and Dr. Woody will likely visit it weekly to check with the research and medical staff until the study is well underway when he will reduce the frequency of visits to biweekly or monthly. Dr. Herdman, Chief of Medical Operations at the PPS, will be in weekly contact by e-mail, phone or fact-to-face meetings with Ms. McNamee and Dr. Woody to review study progress and help solve problems that may emerge.

The two Recovery Specialists will have partial salary support from the study and will help guide it in the context of daily contacts with research and clinical staff, weekly research meetings, and serving as Co-Chairs of bimonthly Community Advisory Board meetings where study progress with be discussed and former opioid addicted prisoners that are in stable recovery along with other community members will be asked to provide feedback and advice on the conduct of the study.

Disseminating study results: Study results will be presented to PPS and NET Steps staff as soon as they are available. Dr. Herdman has suggested specific meetings, conferences, and publications where results can be disseminated, as described in more detail in the Dissemination and Implementation Potential section. The two Recovery Specialists and Community Advisory Board members will be asked for suggestions about how to communicate results to interested parties and will be included in presentations to local officials, members of their community, and at meetings sponsored by the Philadelphia Department of Health, prison administrators, or local or national research meetings.

14.2 Principles for Engagement:

14.2.1 Reciprocal Relationships: NET@PPS, NET Steps patients and staff, and PPS medical staff and administrators will be involved in different ways, as described in other parts of this proposal. PPS officials will have decision-making authority about study procedures within the PPS. The PI will have decision-making authority about research procedures but his decisions will be guided by input from the Project Director and research and clinical staff, and from Dr. Herdman and his staff, the Recovery Specialists and Community Advisory Board members. This collaborative style has been followed in all of our other clinical research projects because we have found that it gets the best results.

14.2.2 Co-learning: Study procedures, and aims and hypotheses will be communicated to research, clinical, and PPS staff during the training and study start-up period in the first three months. The informed consent process will educate prospective study participants about the study as will printed information and videos about the study that are made available to prisoners. All members of the research team will be trained on study procedures, and the involvement of patient and community stakeholders will be described to other researchers in presentations and publications.

14.2.3 Partnership: In addition to the bidirectional communications between research staff and patient partners described above, the Recovery Specialist will receive 10% salary support from the study for his/her effort duringt the project, Community Advisory Board members will be compensated for their time participating in CAB meetings, and study participants will be compensated for their time and travel to complete assessments. The amounts of these compensations are detailed in the Penn and NET Steps budget justifications.

14.2.4 Trust, Transparency, Honesty: The study design has been discussed with PPS officials and NET Steps patients, and all thought it was a good idea. Details of study implementation, problems that arise, and how they will be addressed will be a continuous focus at weekly staff meetings and CAB meetings. Communications will be very open and study results will be presented to NET Steps and PPS staff. Local community leaders will be contacted to explore the possibility of presenting study results at local community meetings. The study interventions and design are not complex and there should be no problem communicating them to a wide range of audiences.

15. PROTECTION OF HUMAN SUBJECTS AND CONFIDENTIALITY

Informed consent to participate will be voluntary, participants can drop out of the study at any time, and persons sentenced to naltrexone will be excluded. Informed consent will include information about the pharmacology of XR-NTX and its possible side effects (described below and in "package insert" found in Physician's Desk Reference). There may be unanticipated situations where the investigator reserves the right to terminate a subject's participation. Such situations would likely entail the development of a serious adverse event or new findings that impact the conduct of the study. Participants will be told that if suicidal or homicidal ideation develops that is judged to pose a significant risk to themselves or others, staff will be obligated to take emergency action that may involve communicating with a third party or involuntary commitment to a psychiatric facility. Urine and alcohol breath test results that are part of the study will not be shared with treatment staff, prison administrators, or probation or parole officers, a Confidentiality Certificate will be obtained once the study has been approved to protect data from forced disclosure, and patients will be informed of this protection. However they will be told that this Certificate will not prevent research or treatment staff

from disclosing evidence of child abuse or threatened violence to self or others.

In the event that a participant fails the naloxone challenge by testing positive for opioid use, the research clinical staff (study physician and/or nurses) will treat and observe him until the withdrawal symptoms caused by the naloxone challenge are resolved. This will be done in a private room in the medical suite. Information about the participant's drug use symptoms will not be reported to the PPS administrators or staff.

The informed consent will state that contact information may be shared with research staff to help locate participants for follow-up. At baseline, a medical examination will be done to rule out individuals that are suicidal, homicidal, psychotic, or have medical problems that may make it difficult or impossible to participate, or are unable to provide informed consent. Approvals from - IRBs serving the University of Pennsylvania and the PPS will be necessary. XR-NTX was approved for treatment of alcohol dependence in 2005 and for opioid dependence in 2010 and has been used with few serious adverse events among thousands of patients. Potential risks are summarized below.

In the

15.1 Study-Related Medical Problems: All patients will be provided with a study identification card stating that they are in a study of XR-NTX. Those that have a medical emergency will be told to consult with a study physician, their primary care provider, or go to the nearest emergency room and tell them if they have received XR-NTX in the last 30 days. Patients will be told to tell the doctor or other medical staff that they are in a research study being conducted at the University of Pennsylvania and ask them to call the telephone numbers that are listed on the study identification form for further instructions or information. In the event that a patient is hurt or injured as a result of participation, he/she is to contact the investigator listed on the consent form and study identification card. In the event of physical injury resulting from research procedures, medical treatment will be provided without cost to the patient but the University of Pennsylvania will not provide financial compensation. The patient's insurance will be responsible for the cost of medical care if the patient has an illness or injury that is not directly related to participation in the study.

16 STUDY OVERSIGHT

16.1 Notifying a non-Penn IRB*:* The City of Philadelphia IRB serves the PPS and must approve this study., thus the P.I. and research staff are responsible for complying with Philadelphia, the University of Pennsylvania's IRB, and PCORI requirements, and also those of Alkermes since it will provide study medication. Copies of each report and documentation of IRB notification and receipt will be kept in the study's regulatory binder.

16.2 DSMB Members: David Oslin, M.D., a faculty member in the Department of Psychiatry at the University of Pennsylvania School of Medicine, serves as the Chair. Members include Dan Weintraub, M.D., Kevin Lynch, Ph.D., and David Metzger, PhD., who are also faculty members, Deb Dunbar, MSN, CRNP and Cynthia Clark, PhD, CRNP, of the University of Pennsylvania School of Medicine, Department of Dermatology. Prior to the review of protocols each member of the DSMB discloses in writing any potential conflicts of interest, actual or implied by appearance. Should an unanticipated situation arise that a Board member feels represents a conflict of interest, the Board member is recused. Drs. Lynch and Metzger may opt to recuse themselves from reviews since they are members of the research team.

The DSMB will meet every 6 months and annually, as required by the protocol, or more often if necessary , and will conduct a review of the protocol to insure that: 1) The protocol captures the information necessary to evaluate the safety and efficacy of the study and provide recommendations that may improve the protocol; 2) That the protocolincludes a Data Safety and Monitoring Plan (DSMP) that must be approved by PCORI. This plan references any recommendations made by the DSMB as well as necessary protocol modifications. The DSMP includes stopping rules that specify the outcome differences to be detected in the event an interim analysis is requested, or an analysis of AEs/SAEs that would indicate a trial should stop. In general, stopping rules reflect one of the following: 1) There is clear evidence of harm or harmful side effects of the treatment; 2) There is no likelihood of demonstrating treatment benefit, or; 3) There is overwhelming evidence of treatment benefit.
The DSMB will review this study as indicated above and make recommendations to continue, amend, or terminate it based on safety data (e.g., terminate a trial because of high incidence of a particular SAE that is related to the study). This study is not double blinded, so the DSMB will be able to compare group outcomes and determine whether it should have an early termination. The DSMB will review study performance (e.g., protocol violations, improper entry criteria, slow accrual, low participation, failure of randomization, inadequate treatment adherence, inadequate follow-up rate, severely compromised validity), and independently make recommendations for improvement or termination if the trial is judged unable to prove anything meaningful.

16.3 Annual Reviews by the Penn and City IRBs: In addition to reviews by the Center's DSMB, PCORI requires annual reports of study progress including AEs and SAEs, and the Penn and City IRBs require annual reviews that include AEs and SAEs and can stop the study if they detect problems that justify it.

17. QUALITY ASSURANCE

17.1 Study Monitoring and Quality Assurance: A Quality Assurance Monitor is budgeted for this study (see budget justification). The monitor will review data and submit audit reports monthly using forms similar to those used in CTN studies such as the buprenorphine-naloxone study of opioid-addicted youth. The P.I., Project Director, and Co-Investigators will review reports and follow up to correct identified problems.

18. ETHICAL CONSIDERATIONS:

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312; International Conference on Harmonization guidelines) and all applicable governmental regulations and institutional policies and procedures. The protocol and any amendments will be submitted to the Penn and City IRBs for approval before procedures are changed unless they require immediate action to protect participants' safety.
All subjects will be given a copy of the consent describing the study with sufficient information to make an informed decision about participation. Information obtained in connection with the study that can be used to identify participants will be kept confidential, and any decision about study participation will be independent of decisions made by the PPS or other members of the criminal justice system on the legal status of participants. An informed consent will be written and submitted along with the protocol for review by the Penn and City IRBs if this study is to be funded. No study procedures will be commenced unless the participant has reviewed and been given the opportunity to ask questions about the purpose and procedures in the study, understands the risks and benefits, and signs the informed consent. The research team will apply for a Federal Confidentiality Certificate and no patients will be enrolled until it has been approved.

19. PUBLICATION PLAN:

The main findings will be submitted for presentation and dissemination at criminal justice, state, city and addiction treatment meetings as described in the dissemination plan, and to one or more refereed journals after data lock. Additional papers will be submitted later based on a publication plan developed during the study.

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APPENDIX

21. STUDY SCHEDULE OF EVENTS