STUDY PROTOCOL

Injectable Pharmacotherapy for Opioid Use Disorders (IPOD)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ASI-Lite	Addiction Severity Index-Lite
CAP	College of American Pathologists
CJ-DATS	Criminal Justice Drug Abuse Treatment Studies
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
DATCAP	Drug Abuse Treatment Cost Analysis Program
DE	Drug Education
DEA	Drug Enforcement Agency
DL	Dose Logs
DMC	Data Management Center
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IND	Investigational New Drug
LFT	Liver Function Test
Mg	Milligrams
NDA	New Drug Application
NTX	Naltrexone
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
PN	Patient Navigator
PNV	Patient Navigator and Vivitrol Condition
PI	Principal Investigator
RAB	Risk Assessment Battery
SAE	Serious Adverse Event
SOWS	Subjective Opiate Withdrawal Scale
SSI-M	Modified Scale for Suicide Ideation
UDS	Urine Drug Screen
TEA	Treatment Effects Assessment
TES	Treatment Effectiveness Score
TLFB	Time Line Follow Back
VAS	Visual Analog Scale
VI	Extended-Release Naltrexone (as Vivitrol®)

2.0 ABSTRACT

2.1 Study Objective

The aim of this trial is to assess the clinical utility, effectiveness, and cost implications of treatment for incarcerated offenders with opioid use disorders who are randomly assigned to one of three treatment conditions to include a depot formulation of naltrexone (Vivitrol®) only (VI), a patient navigation (PN) procedure plus Vivitrol (PNV), and a drug education procedure (DE) before being released to the community. This trial will investigate whether effective medication therapy used in non-incarcerated populations will also be effective in incarcerated individuals. Empirical evidence demonstrates that starting treatment before release greatly increases the probability of successful outcome including reduced alcohol and drug use, increased employment rates, and reduced recidivism rates.

2.2 Study Design

This four-year randomized, open-label trial will examine the feasibility, efficacy, and net economic benefits of VI for opioid addiction delivered with and without a platform of PN provided for six months compared against a DE condition. Before release from jail, participants in the VI and PNV conditions will receive their first Vivitrol injection (and those in the PNV condition will meet with a Patient Navigator) and will then be scheduled for medication management sessions twice monthly for months 1-3, with monthly injections in months 4-6. Participants in the PNV condition will meet with a PN who will provide behavioral assistance to overcome possible barriers to community outpatient treatment and will be provided with a schedule of possible community treatment programs. Participants in the DE condition will receive education designed to reduce the likelihood of overdose on the same schedule as the VI and PNV groups. All participants will receive weekly study phone calls to assess well being and possible adverse events.

2.3 Study Participants

Participants will be 150 individuals, who meet DSM-5 criteria for opioid use disorders, are 18 years and older, who have been detoxified from opioids in the Metropolitan Detention Center in Albuquerque, New Mexico. This study will include only those participants for whom the study physician determines that possible treatment with the study drug is in the best interest, and informed consent will be obtained.

2.4 Interventions

All participants will be scheduled for twice-monthly medical management and assessment appointments for the first three months of the 24-week post-release intervention phase, with monthly appointments for months 4-6. Eligible participants will be randomly assigned to treatment condition (VI, PNV, DE) in equal numbers. VI and PNV participants will undergo a naloxone challenge to ensure opioid abstinence at the time of Vivitrol induction. Those in the PNV condition will be provided with a PN who will facilitate attendance at outpatient treatment programs as well as assist with other needs. The DE group will not receive any medication but will be scheduled for assessments and education on drugs of abuse, maintaining abstinence, and methods for avoiding overdoses on the same schedule as the other two groups. The DE group will also be

provided with naloxone kits to be used in the event of overdose. All groups will also be provided with referrals to community-based substance abuse treatment programs.

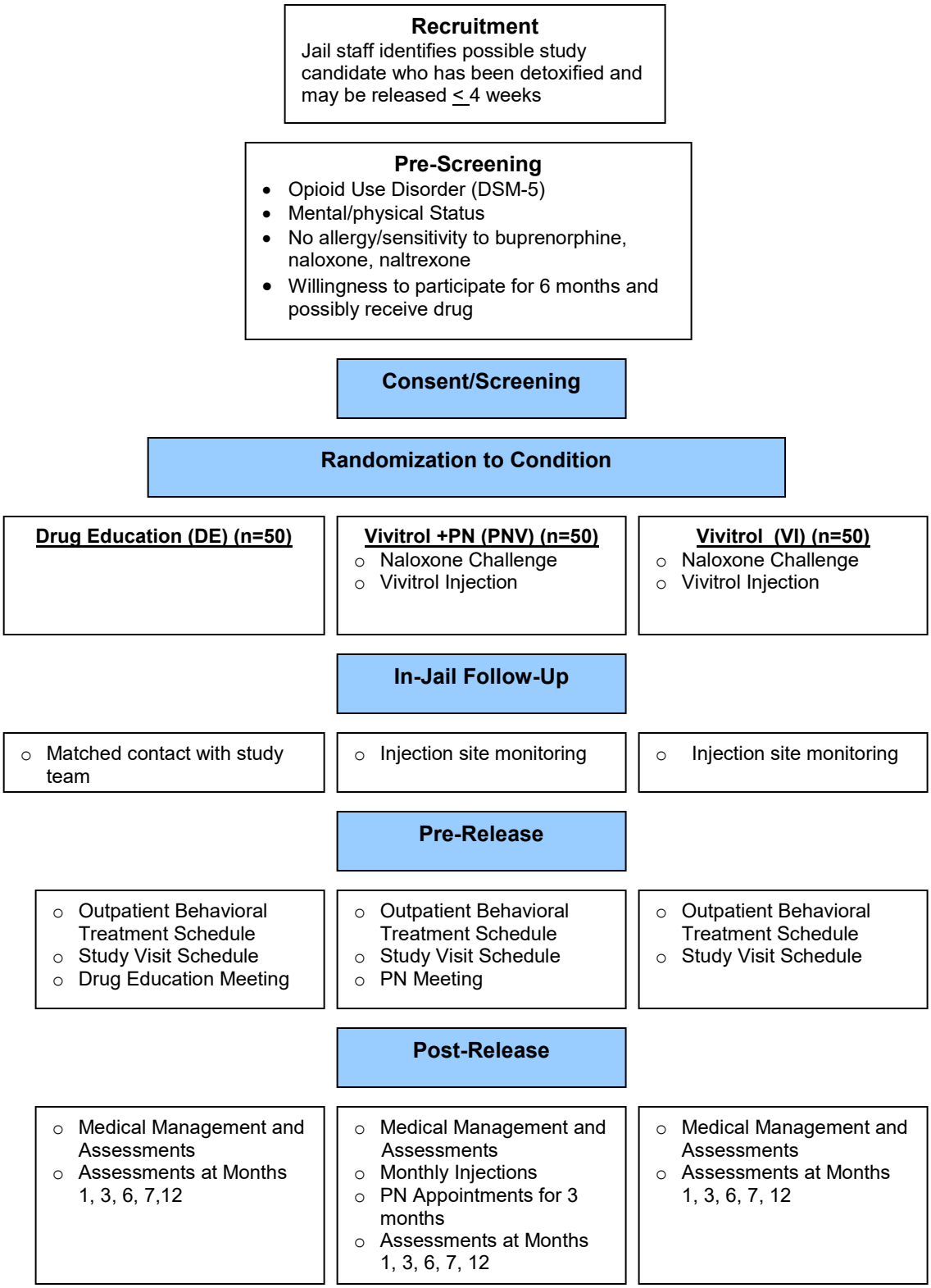
2.3 Assessments

Screening/baseline assessments will include a medical and psychiatric history, physical examination, clinical lab tests (blood chemistry, hematology, urinalysis and hepatitis screening), 12-lead electrocardiograph, vital signs, pregnancy test (for females), and urine toxicology screen. Assessments completed at months 1, 3, 6, 7, and 12 include drug use, dosing and protocol compliance, pregnancy tests for females of child-bearing potential, and other measures of status and functioning. Safety of study participants and intervention tolerability will be assessed throughout the study by collection of adverse events, suicidality, and measures of drug use. Participants who experience an adverse event deemed as compromising their safety will be discontinued from participation and provided referrals for medical care.

2.4 Analyses

The primary outcomes include opioid use and DSM-5 diagnosis of opioid use disorder via modified CIDI-2 Substance Abuse Module at 6-months post-intervention. Opioid use will be computed from the Timeline Follow-Back (TLFB) as the number of days of self-reported opioid use in the past 30 days at the 6-month assessment. The cost analysis will measure and value resources associated with VI, including medical personnel (physician/nurses), labs, and medications. To ascertain cost-effectiveness ratios of VI and PNV, cost data will be compared to changes in key clinical measures of effectiveness.

3.0 STUDY SCHEMA



4.0 INTRODUCTION

4.1 Background and Rationale

Although prison and jail can be effective at reducing levels of crime and drug use during the period of incarceration, resumption of these behaviors upon release is the norm. Nearly 7 in 10 released offenders are re-arrested within three years (Bureau of Justice Statistics, 2002; Pew Center on the States, 2011). Data regarding drug use are even more disquieting, indicating that in many cases offenders are re-addicted within one month of release from incarceration (Bird & Hutchinson, 2003; Kinlock et al., 2011) and their drug use and/or crime levels following prison can even exceed use levels prior to incarceration (Hough, 2002).

Not surprisingly, such persistent patterns of drug use and crime are associated with comorbid health problems and even premature death. In a given year, a quarter of all people in the United States who have HIV, a third who have HCV infection, and more than 40% who have tuberculosis disease will pass through a correctional facility that same year (Bergier et al., 2010; Hammett et al., 2002). Likewise, the risk of death among parolees during the first two weeks following release from prison is nearly 13 times greater than those of similar demographic background—with drug overdose being the leading cause (Binswanger et al., 2007). As dire as this finding is, it may be an underestimate of the problem. A study of newly released prisoners in England and Wales found that mortality rates among males were 29 times higher than the general population during the first two weeks of release. Female offenders' mortality rates were *69 times higher* (Farrell & Marsden, 2007). These studies are included in a recent meta-analysis of drug-related deaths following prison release that revealed a three- to eight-fold increase in the risk of drug-related deaths during the first two weeks following release (relative to the subsequent 10 weeks), with relatively high risk of death remaining throughout the first month of reentry (Merrall et al., 2010). These authors concluded that "further research is urgently needed on mortality after release from prison, as well as interventions to reduce the risk of drug-related deaths during the transition from prison to the community" (pp. 1552-1553).

A substantial body of research now exists supporting the safety and efficacy of naltrexone and buprenorphine, in both their oral, daily-dose forms and in depot long-acting formulations (e.g., Chiang et al. 2003; Krupitsky et al., 2011; Ling & Wesson, 2003; Ling et al., 2010; Lobmaier et al., 2010; Mattick et al., 2008; Mello & Mendelson, 1980). Nonetheless, MAT, particularly pharmacotherapies other than methadone, has not been readily adopted in correctional settings. A survey of correctional agencies (conducted as part of NIDA's CJ-DATS collaborative) revealed that two-thirds of the jails surveyed provided methadone (primarily for detoxification), but *none* offered naltrexone to opiate-dependent inmates (Friedmann et al., 2012). Although the use of MAT is more common in jails than in prisons (used primarily to manage opiate withdrawal), it is important to note that MAT remains unavailable in most jails for purposes beyond detoxification (Oser et al., 2009).

The efficacy of naltrexone has been well established. Naltrexone, an opioid receptor antagonist, blocks the euphoric effects of heroin and other opioids. This characteristic has fostered growing acceptance of naltrexone by correctional authorities who wish to avoid the perception that they are merely replacing one drug with another (Farabee, 2006). However, it must be taken orally on a daily basis, making adherence a problem among all but the most committed patients. Cornish et al. (1997) randomly assigned federal probationers to a 6-month program of probation plus naltrexone and brief drug counseling or to probation plus counseling alone and found that opioid use was significantly lower in the naltrexone group, with the mean percent of opioid positive urine

tests among the naltrexone subjects at 8%, versus 30% for control subjects ($p < .05$). Likewise 56% of the controls and 26% of the naltrexone group ($p <. 05$) had their probation status revoked within the 6-month study period and were returned to prison. But treatment compliance was a problem, with only 52% of subjects in the naltrexone group continuing for the 6-months duration of the study.

Still, the effectiveness of oral naltrexone is mitigated by poor compliance hampering clinical utility in real-world settings. In one study of a prison-based naltrexone program, only 7% of the enrolled patients remained in treatment for six months (Shearer, Wodak, & Dolan, 2007). To address this issue, Vivitrol® (~380mg naltrexone delivered intramuscularly every four weeks; Alkermes, Inc.) was developed to provide long-acting pharmacotherapy for one month per dose. The purpose of this proposed study is to assess the relative effects and net economic benefits of this pharmacotherapy in comparison with a patient navigator (PN) and drug education (DE) conditions for criminal-justice-involved offenders.

4.1.1 Issues of MAT in Correctional Settings

Although many have called for expanding the use of medication-assisted treatment in prison (Cropsey et al., 2005; Kinlock et al., 2011), there are several features of jails that make the latter more promising settings for MAT. Perhaps the most critical difference is that detoxification typically occurs in jails, not prisons. Virtually all prison inmates spend time in local jails while awaiting trial or sentencing. Therefore, whether an offender is serving a brief jail sentence or is awaiting transfer to prison, detoxification typically falls under the purview of the jails. The second reason for focusing on jails relates to the time period of incarceration. Jails tend to house offenders for a few days to several months, whereas prisons are reserved for those serving sentences for a year or more—on average 29 months (Kuziemko, 2007). As a result, the costs of maintaining prison inmates on naltrexone, buprenorphine, or methadone for the entire duration of their sentence would likely be prohibitive. The third consideration is that more offenders pass through jails than prisons. This is an important point that is often missed: Although prisons house more inmates than jails at any one time (1,512,576 in prison versus 780,581 in jail at year-end 2007 [BJS, 2008a]), the number of *entrants* to these two systems tells a very different story, with 751,593 admissions to prison during 2007 versus approximately 13 million admissions to jails during that same period (BJS, 2008a,b). The increased flow between jails and the community likely accounts for reports that the availability of drugs in jails exceeds that in prisons.

A recent survey of criminal justice agencies affiliated with NIDA's Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) collaborative found that MAT is underutilized in the treatment of substance use disorders (Friedmann et al., 2012). Offenders most likely to receive MAT were pregnant women and those experiencing withdrawal. Offenders *least* likely to receive MAT were those re-entering the community after serving a prison or jail term. Among the primary factors influencing the use of MAT in these correctional settings were preferences for drug-free treatment and limited knowledge of the benefits of MAT. Addressing these philosophical- and knowledge-related barriers requires relevant research, specifically, data collected in real-world settings testing practical MAT administration models on offender populations. It is also important to note that even if philosophical barriers shift in favor of MAT, tight local and state budgets may require a higher threshold of evidence—particularly related to costs—before allowing a wider adoption of MAT for offenders.

4.1.2 Preventing relapse to opioid addiction and reducing HIV transmission

Research has shown that substitution or maintenance medication is an effective way of managing opioid dependence, preventing relapse to drug use, and concomitantly resulting in reduced HIV/AIDS infection by curtailing drug-related behaviors that promote transmission of HIV (Metzger, Woody, & O'Brien, 2010; Morris, Levine, & Weaver, 2004; WHO, 2004). This aspect is especially pertinent among the criminal justice population, where the prevalence of confirmed AIDS is more than double that of the general U.S. population (Maruschack, 2009). Effective MAT also provides an opportunity to educate about unsafe sexual activities and to reduce HIV-risky sexual activities such as having concurrent/multiple sexual partners, especially in overlapping networks that greatly increase HIV infection liability (Copenhaver et al., 2006; Morris, 1997; Morris & Kretzschmar, 1997). Research has documented significant reductions in HIV risk behavior and overdose deaths and improved outcomes from antiretroviral treatment in HIV-infected opioid users when treated with buprenorphine (Johnson et al., 2000).

Naltrexone offers an approach to combat the spread of HIV predicated on its opioid antagonist mechanism of action, in contrast to the full or partial agonists (methadone or buprenorphine). Vivitrol may be especially useful where cultural and regulatory conditions inhibit use of opioid agonists with reinforcing aspects, because of perceived "coddling" of addicts. As promising as this long-acting pharmacotherapy may be, however it is unlikely to be widely adopted by correctional agencies or community treatment systems until their expected net economic benefits are established.

4.2 Significance of the Project to the Field

The efficacy of naltrexone has been well established in numerous controlled clinical trials conducted in community settings, however little research is available examining its impact among correctional populations. A recent study compared depot naltrexone with methadone among heroin-dependent inmates released from prison and found that both pharmacotherapies were associated with reductions in opiate use and criminal activity (Lobmaier et al., 2010). However, post-release retention in the methadone condition was extremely low (relative to the 100% adherence rate for those in the depot naltrexone group). Poor attendance/adherence is a vexing issue in offender treatment, with typical rates of admission of one-third to one-half of parolees referred to drug-free counseling programs, and about half of those referred to MAT (Cornish et al., 1997; Lobmaier et al., 2010; Olson, Rozan, & Powers, 2009). Vivitrol potentially obviates the problem of non-compliance with medication dosing, eliminates concerns about potential diversion as medication is provided once monthly by the medical study team, and lessens the need for frequent patient presentation in the clinic or primary care physician's office—issues that are concerns associated with oral naltrexone.

The development of long-acting depot formulations of naltrexone (e.g., Vivitrol) has also provided a new approach for treating opioid addiction, especially in terms of preventing relapse once abstinence has been attained (Comer et al., 2006). Naltrexone implants reliably prevented relapse within one month after detoxification (Foster, Brewer, Steele, 2003), and multi-site research in Russia found Vivitrol effective for treating heroin addiction over six months (Krupitsky et al., 2011). Vivitrol was approved in 2010 by the U.S. FDA for opioid addiction.

The pharmacotherapy examined in this study offers important advantages to its orally administered counterparts, including the eradication of concerns regarding medication

compliance, maintenance of consistent plasma levels of medication, and elimination of potential diversion and misuse. The proposed project intends to provide new empirical data from a correctional population on the utility of depot naltrexone in preventing relapse and associated behaviors by examining the long-acting medication in a context that takes advantage of its strengths to bring about positive and meaningful net economic benefits. Comparisons will be made between two medication conditions provided with and without a Patient Navigator component (VI, PNV) and a drug education (DE) condition.

4.3 Objectives

The project emphasizes evaluation of the clinical utility of pharmacotherapy with Vivitrol (VI) or Vivitrol + PN (PNV) in comparison to a drug education (DE) condition. Descriptive statistics will provide an overall assessment of the implementation of the protocol. The aims of this project include:

Aim 1: Assess the feasibility and clinical utility of a 24-week protocol of long-acting naltrexone (by intramuscular *injection*; VI) provided with and without a PN component (VI, PNV). Measures include side effects, adverse events, retention, and acceptance of the procedures by participants and clinicians. Acceptance will also be assessed among correctional staff.

Aim 2: Examine the effectiveness of Vivitrol provided with and without a PN component (VI, PNV) for its ability to prevent relapse to illicit opioid use, reduce drug-related criminal activity, curtail engagement in HIV-risk behaviors, and increase employment compared to a group receiving only drug education (DE) to assist in relapse prevention after release from jail. The VI and PNV groups will receive VI monthly for the entire 6-month intervention phase. Th PNV group will be provided with PN for 3 months to provide assistance in accessing community treatment after release from jail. Primary measures include DSM-5 diagnosis at time to relapse (defined as self-report of daily opioid use for one week), protocol adherence, and opioid-negative urine samples during the study.

Aim 3: Collect cost data using the Drug Abuse Treatment Cost Analysis Program (DATCAP) and estimate savings from reduced drug use, reduced criminal activity and re-incarceration, and increased employment. Data will support benefit-cost and cost-effectiveness analyses of depot pharmacotherapy with Vivitrol for released offenders with opioid use disorders.

4.3.1 Primary Objectives

The primary objective is to compare outcomes of the three intervention groups, measured a The opioid use and DSM-5 diagnosis of opioid use disorder via modified CIDI-2 Substance Abuse Module at 6-months post-intervention.

4.3.2 Secondary Objectives

*Secondary objectives include: (*1) HIV risk behaviors (compared using repeated measures procedures to evaluate possible change in sexual and drug-related behaviors that may inhibit or promote HIV infection) measured by the HIV-GAIN; (2) Self-reported number of days incarcerated during the intervention and follow-up phases; (3) Self-reported number of days of opioid and other drug use measured by TLFB, and objective measures of drug use by urine drug screens (UDS) at the 6-month post-release assessment (end of the intervention phase); (4) Self-reported days in drug abuse treatment; (5) Self-reported number of arrests; (6) Self-reported craving for opioids, and (7) Self-reported number of overdoses.

5.0 STUDY DESIGN

5.1 Overview of Study Design

The proposed four-year study is a randomized, open-label trial that will examine feasibility, efficacy, and net economic benefits of a depot medication for opioid addiction, alone or in conjunction with PN, and a drug-education condition receiving no medication. All participants receive standard medical management. Before discharge from jail, participants randomized to one of two medication conditions (VI, PNV) receive Vivitrol and subsequent injections every four weeks for 24 weeks. Those in the PNV condition will meet with a PN before discharge and regularly after release to discuss barriers to treatment, possible treatment program participation following release, and will address social support and other participant needs. Before discharge, the Drug Education (DE) group will participate in session(s) designed to provide a presentation and discussion of drug-related issues. Following release from jail, all participants will receive phone calls from the study team to facilitate scheduling of appointments to occur twice monthly for the first 3 months after release then monthly for the last 3 months of the intervention phase for medical management and to complete assessments. The study nurse will also contact study participants to assess well-being and adverse events.

5.2 Duration of Study and Clinic Visit Schedule

The duration of this study will include a projected 2-4 weeks for screening/baseline assessments and medication induction, and a 24-week intervention phase to include, specific to assigned condition, medication, PN, DE, assessments, and medical management. The screening phase will differ in the length of time needed to complete eligibility assessments, random assignment, and to complete medication induction in the VI and PNV conditions. Induction will be scheduled to occur within 4 weeks of discharge. Screening assessments will include the collection of laboratory samples and medical assessments to ensure participant safety. Confirmation of opioid-free status (UDS and naloxone challenge) before medication induction will take approximately two hours. Assessment visits at 1, 3, 6, 7, and 12-months will take about 30-60 minutes depending on the scheduled assessments. Medical management visits will last from 20–60 minutes and will include collection of UDS and other short measures of status and well-being. PN sessions are expected to take about 60 minutes. DE sessions will take about 20 minutes.

5.3 Study Population

Participants will be 150 individuals meeting DSM-5 criteria for opioid use disorders who are 18 years and older, have been detoxified from opioids in the Bernalillo County Metropolitan Detention Center and meet eligibility criteria.

5.3.1 Inclusion Criteria

Study participants *must*:

1. Be at least 18 years of age or older,
2. Meet criteria for DSM-5 opioid use disorders,
3. Be detained for at least 48 hours,
4. Have an expected release date within one year,
5. Plan to reside in area after release,
6. Have at least one instance of relapse to opioid use after a period of abstinence.

5.3.2 Exclusion Criteria

Study participants *must not*:

1. Have a medical (e.g., liver failure, congestive heart failure) or psychiatric condition (e.g., suicidal ideation, psychosis) that would make participation unsafe in the judgment of the medical staff or the PI,
2. Have current or chronic pain or have plans to undergo pain treatment/therapy,
3. Have known sensitivity to naltrexone or naloxone,
4. Have participated in an investigational drug study within the past 30 days prior to screening,
5. Be a nursing or pregnant female, or not agree to use a medically acceptable form of birth control such as oral contraceptives, barrier (diaphragm or condom), levonorgestrel implant, intra-uterine progesterone contraceptives system, medroxyprogesterone acetate contraceptive injection, or complete abstinence. Females who become pregnant during the course of the study will be withdrawn from the study and, if requested, will be provided with referrals for drug treatment and/or medical care,
6. Have any pending legal action that could prohibit continued participation for the 24-week intervention period of the study, such as legal proceedings that could possibly result in incarceration,
7. Have a current pattern of alcohol, benzodiazepine, or other depressant or sedative hypnotic use, as determined by the study physician which would preclude safe participation in the study.

5.4 Participant Recruitment

Recruitment through a close collaboration with the Bernalillo County Metropolitan Detention Center (BCMDC) staff, combined with IRB-approved presentations and posted announcements in the jail facilities will proceed until 150 participants are recruited, consented, and randomized. Given the potential recruitment pool of more than 80 individuals per month, it is expected that an average of 6-8 individuals will be randomized per month across the 20-month enrollment period. Based on prior evidence in similar trials, refusals and early (pre-randomization) dropouts will account for approximately 20% of individuals presenting for screening.

Recruitment plans include hypervigilence to the issue of voluntariness. All BCMDC and study staff will be extensively trained on this issue to ensure that their actions and words do not convey any level of coercion. Training will include a discussion of the fact that treatment and study compliance are optimized when participants have the opportunity to consider the study, ask questions, and provide voluntary consent to participate. Furthermore, all recruitment documents and the ICF will emphasize that decisions whether or not to participate are solely up to the individuals, that the decision will not affect the treatment or possible treatment to which the individual is eligible, that participation/non-participation will not affect the sentence, release, probation, or any other aspect of the individual's incarceration.

The main method of recruitment will be announcements of the study made to inmates in the Bernalillo County Metropolitan Detention Center (BCMDC). An informational flyer will be provided to arrestees who are within 4 weeks of release and have been detoxified from opioid use. Individuals who convey interest in this study to jail staff will be referred to study staff. If still interested after receiving a description of this study, study candidates will complete a consent process that includes an detailed explanation of the study, risks and benefits, and that study

participation is voluntary and will have no effect on a participant's sentence, jail term, probation, parole, or release.

Treatment procedures for jail inmates: Offenders are detoxified (if necessary) under physician supervision within the jail setting. After this, they are moved to the general inmate population but have follow-up visits with the jail physicians. While in custody, they may opt to pursue participation in available onsite treatment programs.

Prior to release, a case worker from Inmate Services meets with the inmate and may make a referral to a community-based program, which can be either drug-free residential or outpatient, depending on inmates' needs and preferences. Show-up rates in the community tend to be quite low, but transportation directly from the jail to treatment programs has resulted in improved admission rates.

5.5 Study Sites

UCLA Integrated Substance Abuse Program (ISAP). The leadership, data management, and analysis portions of the proposed project will occur at UCLA ISAP in Los Angeles.

Walter Ling, MD, will be the physician PI for this study. He has extensive experience in both the use of Vivitrol and behavioral treatments. He will be involved in supervision of the medical aspects of this study, randomization, and will meet regularly with other study personnel. He has conducted over a dozen clinical trials using MAT and will be responsible for medical team training. More recently, he has conducted research using Vivitrol and has been instrumental in the training of other ISAP medical personnel on the Vivitrol injection.

For this project, the primary sites for recruitment, data collection, and treatment services are the Bernalillo County Metropolitan Detention Center and the University of New Mexico, Department of Psychiatry.

Bernalillo County Metropolitan Detention Center (BCMDC). Recruitment and induction will occur at the jail sites in the BCMDC System. The jail facility houses sentenced and unsentenced inmates. The types of inmates housed here are general population, violent/assaultive offenders, psychiatric, and inmates needing medical services. This facility is staffed with Sheriff Service Technicians, intake and release specialists, medical service staff contracted by the County Behavioral Health Department, and clerical support staff. Bernalillo County opened the MDC facility in 2003. Currently, the MDC averages about 40,000 bookings per year, with an average daily population of 2,636. Males account for 87% of the inmate population. With regard to race/ethnicity, 54% are Hispanic, 23% White-Non-Hispanic, 12% American Indian, 9% African-American, 0.4% Asian, and 1.7% are categorized as "Other." Currently the MDC detoxifies an average of 758 individuals monthly—412 from alcohol and 346 from opiates.

The University of New Mexico Addiction Substance Abuse Program (ASAP), The University of New Mexico Center on Alcoholism, Substance Abuse, and Addictions (CASAA); These programs will be the locations for post-release assessment and medical management visits. ASAP and CASAA offer a range of treatment services designed to help individuals coping with substance use disorders. Services include screening, crisis intervention, individual, group, and family counseling, HIV/Hep education, assessment, and evaluation, referrals to community-based services, and outreach to the community. Outpatient treatment programs providing psychosocial interventions are located throughout the county. In the community, the MATS program provides comprehensive detoxification, treatment, and transitional housing services for medically indigent

populations in the Albuquerque area. Operated by Bernalillo County, the MATS program has extensive partnerships with other community medical, mental health, alcohol/drug and homeless service agencies. The Addictions and Substance Abuse Program (ASAP) is operated by the UNM Department of Psychiatry and is conveniently located adjacent to the UNM CASAA facility.

6.0 OUTCOME MEASURES

The project emphasizes evaluation of the clinical utility of the Vivitrol pharmacotherapy with and without a PN condition (VI, PNV), as compared to a drug education (DE) condition. Descriptive statistics will provide an overall assessment of the implementation of the protocol.

6.1 Primary Outcome Measure

The primary outcomes will be opioid use and a DSM-5 diagnosis of opioid use disorder 6 months after randomization.

6.2 Secondary Outcome Measures

(1) HIV risk behaviors (compared using repeated measures procedures to evaluate possible change in sexual and drug-related behaviors that may inhibit or promote HIV infection) measured by the HIV-GAIN;

(2) Self-reported number of days incarcerated during the intervention and follow-up phases;

(3) Self-reported number of days of opioid and other drug use measured by TLFB, and objective measures of drug use by urine drug screens (UDS) at the 6-month post-release assessment (end of the intervention phase);

(4) Self-reported days in drug abuse treatment;

(5) Self-reported number of arrests;

(6) Self-reported craving for opioids;

(7) Self-reported number of overdoses; and

(8) Self-reported motivation for treatment.

7.0 STUDY PROCEDURES

7.1 The Consent Process

This study will be reviewed and approved by the Medical Institutional Review Board (M-IRB) of the University of California, Los Angeles, and the Institutional Review Board of the University of New Mexico.

All participants will voluntarily sign an informed consent prior to study participation. The informed consent process involves a detailed verbal description of the study and the data collection procedures. The participant will be encouraged to ask questions about the study procedures throughout the process. The risks of participating in this study will be detailed in the consent form. Staff will emphasize that participation is voluntary and that participants may withdraw consent at any time without prejudice, and will be given referrals to other local treatment programs.

After discussing the study procedures, potential risks and benefits, the voluntary nature of study participation, and that participation will have no effect on a participant's sentence, jail term, probation, parole, or release, study candidates will answer a brief quiz to verify and document a thorough understanding of the research prior to signing the consent form. The study candidate will sign the consent form as witnessed by a study investigator or physician. Research staff will receive extensive training in the informed consent process. A copy of the signed consent form will be given to all participants

7.2 Screening

The study team will provide a basic description of the study to interested individuals who respond to IRB-approved flyers and announcements at BCMDC. Study staff will verify pre-eligibility status of each study candidate with jail staff (e.g., has completed opioid detoxification, jail term and expected release date). Individuals determined as pre-eligible will be scheduled for a consent/screening appointment. Screening will begin with the informed consent process. A complete medical history and physical exam will occur after consent. Participants will be randomized to study condition when results of all assessments, including blood chemistries and ECG, are obtained and eligibility is confirmed. Screening will take ~4 hours, excluding review of lab results. This process may occur over multiple days.

7.3 Random Assignment

Eligible participants will be randomly assigned to study condition (VI, PNV, DE) in a 1:1:1 strategy using an urn randomization procedure (Stout et al., 1994) to provide multivariate balance across two characteristics correlated with outcomes in addiction treatment trials: type of opioid (heroin or prescription drug) and gender.

Individuals who terminate participation before induction onto the assigned medication (or similar time-point for behavioral assignments) will be replaced. Those terminating after VI induction or provision of the first DE session will not be replaced and will be counted as "treatment failures" (in an intent-to-treat scenario).

7.4 Medication Pre-Induction

7.4.1 Vivitrol Pre-Induction

Vivitrol Pre-administration and Injection Procedures. Individuals must be free from opioids for at least 7 days before receiving the Vivitrol injection, which is confirmed via self-report and facility records. To ensure opioid abstinence at time of induction, a naloxone challenge will occur followed by one day of oral naltrexone before Vivitrol injection, adhering to NIDA-approved and IRB-approved procedures. Subsequent Vivitrol injections administered every four weeks will require confirmation of opioid abstinence by either naloxone challenge or administration of oral naltrexone, as determined appropriate and necessary by the Study Physician and/or Nurse Practitioner (NOTE: In New Mexico, a Nurse Practitioner [NP] has virtually all the same medical privileges as a Physician and can function as an Physician).

The pre-induction strategy includes:

- *Step 1.* Participants must self-report no clinically significant opioid use (i.e., at any level that could constitute a potential risk of precipitating opioid withdrawal upon naloxone administration in the next step) in the previous seven days.

- *Step 2.* A urine drug screen will be administered shortly before the naloxone challenge and must be negative for opioids. Individuals who are opioid-negative will continue in the pre-induction process. Individuals may have an additional urine drug screen on a subsequent day if the study medical clinician determines that a second screen is appropriate.

- *Step 3.* Completion of all pertinent psychosocial and medical screening and eligibility assessments.

- *Step 4.* Absence of opioids in a urine screen is not absolute proof that a patient is entirely opioid-free; As such a naloxone challenge will be administered. Prior to subsequent Vivitrol injections every four weeks, the naloxone challenge can be performed at the discretion of the study physician to ensure continued suitability for the Vivitrol injection. An example of a naloxone challenge procedure may begin with I.V., I.M., or subcutaneous delivery of 0.1mg naloxone. If no significant opioid withdrawal symptoms appear after a few minutes, a second dose of 0.3mg would then be administered followed by a brief observation period. With no observed discomfort, 0.8mg naloxone would then be administered as the final dose, followed by an observation period. A minimum 0.8mg bolus must be given before determining the outcome of the challenge. An alternative is to challenge with a single 0.8mg bolus. The determination as to whether the participant is eligible to continue on to VI induction will be made by the study medical clinician based on clinical judgment, including both objective and subjective assessments. Attention to individual symptoms and symptom changes should guide determination of eligibility. Signs of discomfort or an increase in withdrawal symptoms following naloxone administration should be taken as a positive result of the challenge, with induction delayed until a negative challenge result is achieved.

Participants who experience withdrawal symptoms following the naloxone challenge can be treated with ancillary medications if appropriate, observed until symptoms resolve, and given the opportunity to be re-challenged on a future date. Participants who are not interested in continuing to participate, or who fail a repeat naloxone challenge, will not be eligible to participate.

7.5 Pharmacotherapy

7.5.1 Extended-release Naltrexone (VI)

Depot Naltrexone as Vivitrol. Vivitrol is a combination of naltrexone-containing microspheres that are delivered by injection every four weeks into the muscles of the buttock. Plasma concentrations of naltrexone and 6-beta naltrexol (its main metabolite) after a single Vivitrol injection are detectable for at least 30 days and must be re-administered to maintain its effect. Continued use of naltrexone is not associated with tolerance or addiction. The most common AE has been reaction at the injection site, reported in 50% of the placebo group and 69% of the 380mg Vivitrol group *Physician's Desk Reference* (PDR). The most common gastrointestinal AEs are nausea (11% in placebo group; 33% in Vivitrol group) and vomiting (6% in placebo group; 14% in Vivitrol group). For pain management in an emergency situation, regional anesthesia or non-opioid analgesics are advised.

Extended-release Naltrexone **(**VI) will be provided to participants as a gluteal intramuscular injection (380 mg) administered every four weeks. The VI injection shall be administered following the guidelines provided in the package insert, including the pre-induction procedures described above.

Well-developed precautionary procedures will be followed to avoid adverse events associated with induction. For example, body habitus will be assessed during the physical exam at screening to assure that needle length is adequate for intramuscular administration as an inadvertent subcutaneous injection of VI may increase the likelihood of injection site reactions. The needle provided in the VI package is a customized needle required for injection of medication. Individuals whose body habitus precludes a gluteal intramuscular injection of naltrexone using the required needle will be excluded from the study.

7.6 Behavioral Treatment

7.6.1 Drug Education (DE)

This condition is intended as an enhanced treatment-as-usual condition. Enhancements will include standardized materials for drug education and overdose prevention education.

7.6.2 Patient Navigators (PN)

In addition to receiving Vivitrol, participants in the PNV condition will be assigned a Patient Navigator (PN). A PN provides one-on-one assistance to surmount barriers to entry and adherence with medical care for chronic disease. Originally designed to improve outcomes in oncology for disadvantaged female patients, the PN conceptual foundation is a strengths-based case management perspective to help patients keep their appointments (through scheduling, reminders, and accompanying the patients), improve communication between the patient and their providers, offer health education, provide assistance with personal barriers to treatment (e.g., transportation, health insurance, childcare), and offer emotional support. Clinical trials have found that PN increased cancer screening and follow-up rates, improved entry and adherence to HIV treatment, and increased adherence to medical appointments and greater likelihood of achieving an undetectable viral load compared to controls.

Addictions treatment studies have also found positive outcomes in randomized trials for services comparable to PN to increase the likelihood of treatment entry from: a central drug treatment intake; receiving medical care at a hospital; and community outreach. Although a case

management approach was not found effective in linking drug users newly-released from prison to community treatment, that study's sample was heterogeneous in terms of its drug use (only 10% were opioid-dependent) and did not receive pharmacotherapy. PN has not been studied in re-entry into the community with treatment initiated in jail. It is our hypothesis that PN has the potential to assist newly-released detainees to overcome barriers to successful community treatment entry.

In this study, the Patient Navigator (PN) will meet with PN participants to discuss barriers to treatment, facilitate referrals to community outpatient behavioral drug abuse treatment, and provide assistance with other social support-related needs.

7.7 Study Team Training

Research staff will be certified in good clinical practices and will continue to receive regular boosters in clinical research procedures, including protection of privacy and well-being of human research participants.

The PI and Study Physician/Nurse Practitioner and other clinical personnel will receive training in the medication procedures (i.e., preparation for the Vivitrol injection and its administration). The Study Physician will provide on-site training at BCMDC and BCMDC clinical staff may also travel to UCLA to observe medication procedures.

7.8 Medical Management

At each clinic visit, participants will meet with study physicians and other study personnel such as nurses, research assistants, and counselors, to review urine results, discuss adverse events, consider the study medication effects and side effects, and discuss other pertinent issues in keeping with sound medical practice. Participants' engagement in self-help groups such as 12-step is permitted. Medical Management visits will occur twice-monthly during months 1-3, and monthly during months 4-6, and Vivitrol injections will be provided monthly to participants in the VI and PNV conditions.

7.9 "Rescue" Protocol

Participants who develop significant problems, who cannot tolerate naltrexone, or whose pre-existing condition worsens during the study may receive increased levels of care deemed necessary by the Study Physician, and they will be referred to other treatment resources.

7.10 Discharge, Early Termination, Taper, and Post-study Procedures

Participants withdrawn early from the study will be referred to appropriate services. Participants in the VI and PNV conditions will not require any medication taper.

7.11 Ancillary Medications

Ancillary medications may be provided by the study medical team for study medication-related side effects as clinically indicated. A range of prescription and over-the-counter ancillary medications may be used for anxiety, nausea, vomiting, diarrhea, muscle pain, and insomnia.

7.12 Concomitant Medications

Participants will be instructed to contact the study medical clinician before taking any non-study medications, including prescription drugs, over-the-counter preparations, and herbal supplements, during the course of the study. Participants reporting use of medications that may interact with naltrexone will be excluded or withdrawn based on clinical judgment.

Management of Study Medications

Appropriately qualified and trained medical personnel will maintain an accurate and current accounting of all study medication, which will be available for verification by study monitors. Drug-accountability records including perpetual inventory, will include the amount of study medication ordered, received, transferred between areas of the study site, and those dispensed to individual participants.

7.12.1 Study Medication Storage

Study medication will be stored in compliance with federal, state, and local laws and institutional policy. Study medication will be stored in a locked, secure, limited-access location under the conditions specified by the package insert; Vivitrol will be stored in a locked refrigerator.

7.12.2 Unused Medication

Unused expired study medication will be logged into an inventory of unused medication, and all medications not used by the end of the study intervention phase will be logged and returned to NIDA (or as directed) for destruction. Unused medications will be accurately labeled, securely stored, and kept separately until sent for destruction. Damaged, expired, or unused study medication will be accounted for by the NIDA contract monitor before being returned for destruction. Expired naloxone and other ancillary medications obtained for this study will be destroyed on site or sent for destruction per local institutional policies.

7.12.3 Dispensing of Study Medications

All study medications shall be dispensed by an appropriate licensed physician/nurse practitioner appropriately trained and authorized to dispense study medications. Vivitrol injections will be administered in Week 1, and every four weeks for 24 weeks (total of 6 injections).

7.12.4 Drug Packaging

Vivitrol will be supplied in single use packages. Each package will contain one 380 mg vial of Vivitrol® microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of Vivitrol®, one 5 mL prepackaged syringe, one 1-inch 20 gauge needle, two 1.5-inch 20 gauge needles, and two 2-inch 20 gauge needles with needle protection devices. Lot number and medication expiration date will be included on the package labels supplied by the manufacturer.

7.13 Participant Withdrawal

There are no formal criteria for investigator withdrawal of a participant, however, any participant for whom study participation is deemed potentially unsafe as determined by the medical clinician will be withdrawn from participation, even if the participant would like to continue. Also, participants who have difficulty complying with the study procedures may be withdrawn.

Participants will be withdrawn from medication if it is clinically determined that continuation may be unsafe. For example, participants who develop uncontrolled hypertension will be discontinued and instructed to see their private physician, or will be provided with referrals for medical care. Women who are assigned to one of the VI conditions and become pregnant during the intervention period will be withdrawn from study medication, referred for medical care, and the pregnancy will be followed until an outcome is known. Participants who experience intolerable side effects or other physical or psychiatric conditions regardless of relationship to the study medication will also be withdrawn from further study medication administration.

The medical clinician may determine that a participant's clinical condition has deteriorated during the course of the study. Examples of clinical deterioration that might trigger a decision to withdraw the participant from medication include the following:

- The initiation or recurrence of risky behaviors that make further participation unsafe;
- Overdose;
- Emergence of psychosis, suicidal ideation, severe cognitive impairment or dangerous criminal behaviors;
- Evidence of general medical deterioration; or
- New onset of psychiatric or medical conditions that would require intervention that would preclude continued participation in the study protocol.

In the event the participant is withdrawn from further medication administration, referrals to treatment programs or recommendations for medical care will be provided. The study medical clinician, in collaboration with the principal investigator may consult with the study medical monitor in making this decision. At any time, participants may decide that they no longer wish to continue to receive medication or to participate in the study. Those who opt out of medication will be allowed to continue to make clinic visits and complete assessments and will complete post-intervention and follow-up assessments.

7.14 Blinding

This is an open-label, non-blinded trial.

7.15 Participant Reimbursement

Study participants will receive gift cards or cash as compensation for time, travel, parking, and other costs borne by the participant. Participants will be provided with medical management at no cost, and those in the VI and PNV conditions will receive no-cost medication.

Incentives will be provided for participating in screening, twice-monthly medical management visits in months 1-3 and monthly visits in months 4-6 during the intervention phase, and assessment visits at months 1, 3, 6, and 12. A $25 incentive will be provided for screening; $20 for each of 9 medical management visits ($180), $40 for each of 3 post-release assessment visits ($120), and $80 for a final visit at month 12. Each participant will be eligible to receive $405.

8.0 STUDY ASSESSMENTS

Measures and instruments will be used to ensure a comprehensive assessment of status and functioning variables. These data, along with the DATCAP, will also be used to support the economic analysis. (The DATCAP will be administered during Year 2.) On average, screening and eligibility assessments will be completed in 4-6 hours (specific to treatment group). Post-release assessments will be completed in approximately 30- 60 minutes. Medication Management visits are expected to take approximately 30-60 minutes.

Table 1. Data Collection Time and Event Schedule

Timepoints	**Screening**	**Pre-release**	**Post-release**	
Clinic Visits			**Medical Mgmt**	**Assessments**
				Months 1, 3, 6, 7, 12
Measures				
Safety & Med. Measures				
Physical Exam / Med History	X			
Injection site inspection	X		X	
Vitals	X		X	
12-lead ECG	X			
Clinical Lab Tests	X			
HIV Test	X			
Pregnancy Test	X		X	
Prior/Concomitant Meds	X		X	
AEs			X	X
Drug Use Measures				
DSM-5 Checklist	X			
COWS (Withdrawal)	X			
SOWS (Withdrawal)	X			
Urine Drug Screen (UDS)	X	X	X	X
Substance Use Report (TLFB)	X	X	X	X
VAS (Craving)	X	X	X	X
Crime and Recidivism				
Self-Report Arrest/Tx History			X	X
Arrest Records				X
CJ-DATS Crime Grid	X			
HIV Risk Measure				
HIV-GAIN	X			X
Cost				
Form 90				

8.1 Safety and Medical Measures

8.1.1 Medical and Psychiatric History

The participants' medical and psychiatric history will document past and present health conditions at screening to help determine eligibility and to provide baseline information.

8.1.2 Physical Examination

A physical examination will be completed at screening to ensure that there are no exclusionary medical conditions and to gather baseline information. An examination of the participant's body habitus will address appropriateness for VI gluteal intramuscular injection.

8.1.3 Injection Site Examination

Appropriate medical personnel will examine the injection site on the visit following each injection procedures. Additional monitoring may be required. Participants will be asked to immediately report any site reactions to allow evaluation, monitoring, and possible referral, as needed. Injection site examinations will be documented.

8.1.4 Electrocardiogram (ECG)

A 12-lead ECG will be administered at screening.

8.1.5 Clinical Laboratory Tests

A comprehensive blood chemistry including liver function, hematology panel, and a standard urinalysis will help determine eligibility at screening. An accredited laboratory (College of American Pathologists or equivalent), that meets CLIA guidelines, will provide lab results, normal values, and proof of lab certifications.

8.1.6 HIV Testing

On-site HIV testing will use the FDA-rapid test (INSTI™ HIV-1 Antibody Test Kit; bioLytical Labs, Inc.), providing results within one minute to ensure participant awareness of HIV status.

8.1.7 Pregnancy and Birth Control Assessment

Pregnancy test information will be collected for female participants and include test results, and self-reports of birth control method(s).

8.1.8 Vital Signs

Vital signs (e.g., body temperature, blood pressure, pulse, respiration rate) will be collected at screening, at each medical management visit throughout the intervention phase, before and after naloxone administration, at Vivitrol injections.

8.1.6 Prior and Concomitant Medications

Information about prescription, over-the-counter medications, and herbal supplements used by participants will be collected at screening for medications taken in the previous 4-week period. At other medical management visits, the form will document medications taken since the previous data collection visit.

8.1.7 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Medical or psychiatric adverse events (AEs) will be collected by inquiring of participants: "How have you been feeling since your last visit?" AEs will be recorded at each visit after consent according to the adverse event reporting definitions and procedures. If a reported AE suggests medical or psychological deterioration, it will be brought to the attention of the study medical clinician for further evaluation, and seizures will also be reported to the DSMB as they occur. SAEs will be medically managed, reported, and followed in accordance with applicable regulatory requirements.

8.2 Drug Use Measures and Psychological Measures

8.2.1 Substance Use Report: Timeline Follow-Back (TLFB)

The TLFB will be used to elicit participants' self-reported use of alcohol and illicit substances. At screening, substance use reported by the participant for the prior 30-day period will be assessed. The TLFB will be administered at each study visit throughout the medication phase, at the post-medication visit, and at follow-up to document the participant's self-reported use of substances for each day since the previous assessment.

8.2.2 Urine Drug Screen (UDS)

Urine samples will be collected at every clinic visit using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. The UDS will test for the presence of opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, MA, marijuana, methadone, and Ecstasy (MDMA). A validity check may be performed using a commercially available adulterant test strip that indicates normal ranges for creatinine, pH (at minimum), nitrate, glutaraldehyde, specific gravity, bleach and pyridinium chloromate. Study staff may observe the collection of UDS. In the event of suspected tampering, the study team will request a second sample and may observe the urine collection process according to clinic standard operating procedures.

8.2.3 Visual Analog Craving Scale (VAS)

Participants' opioid craving will be documented on a visual analog scale (VAS) that ranges from 0 (no craving) to 100 (most intense craving possible). The VAS will be completed at screening and at each Medical Management and assessment visit.

8.2.4 DSM-5 Checklist/Modified CIDI

The DSM-5 Checklist is a semi-structured interviewer administered instrument that provides current diagnoses for substance use disorders based on DSM-5 diagnostic criteria. The CIDI will be modified for use in this study. Either/both measures will be completed at screening to determine presence and severity of opioid use disorder, and at 6 months as the primary outcome.

8.2.5 HIV-Gain

The HIV-Gain will be used to assess HIV risk. It will be administered at screening and at assessment visits.

8.3 Crime and Recidivism

8.3.1 Arrest Records

Arrest records will be accessed to compile information on participants' arrests, convictions, sentences, and incarcerations.

8.3.2 CJ-DATS Crime Grid

Criminal Justice history will be documented including information about criminal activity, arrests, convictions, and incarcerations with this 24-item section of the CJ-DATS intake instrument.

8.4 Data Collection and Management

Study measures will be collected using electronic data entry, and managed by ISAP's Data Management Center (DMC) to manage large amounts of data. This process performs range checks and other verification procedures during and immediately after completion of data entry, thus ensuring the reliability of de-identified data transmitted to our DMC via a secure server at the end of each day. Upon study completion, each participant's data record is saved to disk and securely stored.

8.5 Data Sharing

The project will comply with NIH regulations regarding provision of access to the data set (in non-identifiable form) after study completion. As approved by the PI, the ISAP DMC will respond to requests for data. Articles from the project will be made available via submittal to PubMedCentral after publication.

9.0 TRAINING

The study staff will be trained and certified as specified in the study Training Plan. Training will cover standard human subject training (e.g., Good Clinical Practices), as well as protocol-specific training as needed (e.g., assessments, study interventions, fidelity to the protocol and safety procedures, data management and collection, research procedures including understanding reliability and validity, and problem solving). Study Medical staff will be trained on all aspects of medication induction and delivery.

10.0 STATISTICAL ANALYSES

The project emphasizes evaluation of the clinical utility of Vivitrol in jail inmates as compared with a Drug Education condition (DE), while descriptive statistics will provide an overall assessment of the implementation of the protocol.

Analyses will include an Intent-to-treat (ITT) design such that all randomized participants who received at least one dose of medication (VI, PNV), or received at least one session of drug education (DE) will be included who did not violate the protocol in a way that could potentially affect the efficacy results. Participants will be excluded from the Protocol Population (PP) if:

1. concomitant medication that is known to have significant clinical effect on primary or secondary endpoints was administered.

2. Violations of the inclusion or exclusion criteria are judged to affect the efficacy evaluations.

Subjects in the PP population will be allocated to treatment groups in the analysis based on the actual treatment they received. If there is substantial difference between the ITT population and the PP population, all analyses described below will be performed using only subjects in this group.

All statistical tests will be performed using two-sided .05 significance levels, unless otherwise stated. All comparisons between treatments will be reported with parameter estimates and 95% confidence intervals. For parameters measured at baseline and subsequently, the variables of interest are changes from baseline.

Post-baseline variables will not be imputed; estimates can be obtained using the hierarchical models specified below under the assumption of missing at random. For the primary outcome measure, diagnosis at six months, subjects who have dropped out for whatever reason will be considered to retain the diagnosis. Other outcome measures for which data are missing will be imputed using multiple imputation methods. Sensitivity analyses will repeat specific analyses using permutation tests of at least 1000 samples.

10.1 Primary Outcome

The primary outcomes of opioid use and a DSM-5 diagnosis of opiate use disorder 6 months after randomization.

10.2 Secondary Outcomes

Analyses will include descriptive, binomial and multinomial methods to address secondary outcomes:

(1) HIV risk behaviors (compared using repeated measures procedures to evaluate possible change in sexual and drug-related behaviors that may inhibit or promote HIV infection) measured by the HIV-GAIN;

(2) Self-reported number of days incarcerated during the intervention and follow-up phases;

(3) Self-reported number of days of opioid and other drug use measured by TLFB, and

objective measures of drug use by urine drug screens (UDS) at the 6-month post-release assessment (end of the intervention phase);

(4) Self-reported days in drug abuse treatment;

(5) Self-reported number of arrests;

(6) Self-reported craving for opioids;

(7) Self-reported number of overdoses; and

(8) Self-reported motivation for treatment.

10.3 Power and Sample Size

With the primary focus of this study on the feasibility and clinical utility of the two pharmacotherapies, the study is not powered to be an exhaustive comparison but to parsimoniously enable preliminary characterization of outcomes that will be needed to inform a future, larger scale multi-site trial. We expect that a baseline sample of 150 participants with 50 participants per condition will yield a final aggregate sample of approximately 120 participants, assuming 10-20% dropout. (Our similar studies have had 85-90% follow-up rates.) Thus, a final evaluable sample size of 120 participants would permit detection of a medium-large effect size (~*.60*) between conditions for some of the outcome variables (at ~.70 power) and .5 effect size (at .80 power) for others. For example, we expect that the measure “time to first opioid use” will be markedly different among the three groups, given the difference given the expected relapse among the no-medication group. Over time, the total number of opioid-free urine results is expected be greater among the VI participants, who are likely to show less dropout and better long-term retention compared to the DE group. Our selection of the effect size is based on effects found in the literature for Vivitrol when compared against placebo, and is consistent with both Cohen (1988) and with more recent guidance; for example, Lipsey and Wilson (1993) did a meta analysis of 302 meta-analyses that included over 10,000 studies and found that the average effect size was .5, adding support to Cohen's recommendation that selection of the effect size of .5 is appropriate (Bausell & Li, 2002).

10.4 Analysis Approach

Analyses will employ modeling approaches that are less sensitive to biases from missing data, using a technique that conceptualizes missing data in two ways: intermittent missing data for participants active in the trial and dropouts (Shoptaw et al., 2002). Analysis of urine drug screen results are conducted using aggregates such as the Treatment Effectiveness Score (Ling et al., 1997), which is tested by condition using GLM and non-parametric strategies, where appropriate. Retention differences between conditions will be tested using an appropriate survival analysis model. Counts and composites of scores on drug craving and psychological measures will also be analyzed by treatment condition using t-tests and ANOVAs. Secondary analyses may include use of longitudinal models (Diggle et al., 1994), including normal mixed-effects models (Littell et al., 1996; SAS Institute, 1996; Singer, 1998; MIXED; PROC MIXED, SAS Institute Inc, Cary, NC) for continuous measures and generalized linear mixed models (Littell et al., 1996; GLMM; GLIMMIX macro, SAS Institute, Inc) for categorical measures. A six-step analysis approach is described below.

10.4.1 Data Screening

Typical data screening activities will be conducted; univariate analyses will determine cell frequencies, normality, linearity, and homoscedasticity of continuous variables, and missing values. Variables with non-normal distributions will be transformed, when appropriate, using procedures recommended by Mosteller and Tukey (1977). Missing values will be handled using conventional case elimination, mean substitution, or estimation procedures (e.g. Cohen & Cohen, 1983). Preliminary analyses will address baseline characteristics of the two medication conditions using univariate techniques to determine the adequacy of the random assignment procedures, and whether these procedures result in groups similar in pertinent characteristics. Any variables determined to differ significantly between conditions will be used as covariates. We will also conduct attrition analyses to determine whether participants who failed post-consent screening differ from those randomized.

Baseline Characteristics and Treatment Group Differences

To appraise differences in baseline characteristics of the treatment groups, continuous variables will utilize analysis of variance, ordinal variables will utilize the Cochran Mantel Haenszel test, and dichotomous variables will utilize the chi-square (χ^2) test or Barnard's test. As appropriate, transformation such as log, square root or inverse may be utilized to accomplish the twin goals of variance stabilization across levels of the predictor variables and normal distribution of the outcome variable, if necessary.

For continuous variables, the number of non-missing and missing values and the median, mean, standard deviation, minimum, and maximum will be obtained for each treatment group. For categorical variables, the counts and proportions of each value will be tabulated.

Differences between participants who were considered but not randomized (screen fails) will be compared with randomized participants on selected demographic characteristics. Summary tables for continuous variables include mean, standard deviation, median, min and max will be prepared. Outcome measures will be summarized by treatment group and by visit when applicable.

Treatment group differences at the 0.10 level of significance in baseline variables may be included as stratification variables or covariates in efficacy analyses.

10.4.2 Primary Statistical Analysis of the First Primary Outcome Measure

A mixed effects logistic regression will used to model the binary primary outcome measure; the diagnosis of opioid use disorder at six months post treatment. are modeled as a linear combination of predictor variables. A logit link function will be used to link subject covariates to the probability of success There will be two levels in the model: within sites and between sites. The model will included treatment, cluster (site) and baseline covariates as fixed effects and subject as a random effect. Indicator variables will identify whether a subject has received XR-NTX, methadone and a behavioral intervention (PN.) Site by treatment interactions will be included in the model. Interactions that are statistically significant at the 10% level will be investigated and may imply that analyses of individual sites is required. In this case, relevant contrasts will be performed within the sites.

Additional covariates will include age, gender, whether a subject had prior methadone maintenance treatment and baseline self-reported cocaine use. Other possibilities mediating

factors include opioid dependence severity at baseline, concurrent cocaine or alcohol and/or benzodiazepine misuse, and homelessness.

SAS PROC Mixed will be used to perform the analysis. The coefficients in the model will be estimated by generalized least squares (GLS), with covariance parameters estimated by restricted maximum likelihood (REML). Standard errors of the parameter estimates will be computed using the model. This procedure assumes that missing observations are ignorably missing or missing at random (MAR).
The primary contrast is a comparison of the probability of a DSM-5 Opioid Use Disorder Diagnosis at 6 months for those on medication versus those receiving enhanced treatment as usual (etau.) The contrast will utilize XR NTX data from both the NYU and UCLA and Interim Methadone data from FRI; the medication plus PN treatment arm will not be included.

Descriptive statistics will examine feasibility issues of the pharmacotherapy, analyzing AEs, side effects, and patient and clinician acceptance, and reasons for early termination or post-randomization refusal of assigned condition. Single-point, between-group comparisons of these measures can be tested using t-tests or ANOVAs for continuous variables and chi-square for binary measures.

10.4.3 Economic Analysis (Aim 3)

The costs of the Vivitrol will be estimated using the Drug Abuse Treatment Cost Analysis Program (DATCAP[d1]; French, 2003b). The DATCAP is a data collection instrument and interview guide designed to estimate the costs of substance abuse treatment and related interventions. Because the DATCAP organizes cost data across standard categories of resources (e.g., personnel, buildings and facilities, supplies and materials, and miscellaneous), it can be used for other types of interventions including pharmacotherapies. Cost data will be obtained to calculate the total annual cost of Vivitrol and the average per-client cost. We will not include any costs specific to research conducted under this study. To ascertain the full economic impact of Vivitrol, cost data will be compared to changes in key clinical measures of effectiveness (e.g., time to relapse, days of abstinence, re-arrest) to estimate cost-effectiveness ratios. Cost-effectiveness analysis (CEA) is inherently an incremental analysis that compares doing a little more or a little less of something to capture marginal variations in costs and effectiveness across interventions (Gold et al., 1996). Differences in program cost are divided by differences in program effectiveness to calculate incremental cost-effectiveness ratios (ICERs). One can then compare the ratios of cost to outcome for two or more alternative programs (in this case Vivitrol) to determine which programs are relatively more cost-effective (i.e., have a lower cost-effectiveness ratio). The more expensive pharmacotherapy will be directly assessed to see if the additional cost generates greater effectiveness across the key outcomes of interest. As an alternative approach to examining the full economic impact of this pharmacotherapy, we will estimate the economic benefits associated with reductions in criminal activity and criminal justice system costs, improved employment, and reduced health care use. The difference between economic benefits and intervention costs represents the net economic benefits of the interventions. The primary objectives of the benefit analysis are to identify important economic outcomes for Vivitrol, convert these outcomes into dollar equivalents, and estimate the therapy's total and domain-specific economic benefits. Decreases in some measures between baseline and follow-up, such as number of arrests, represent improvement while other measures, such as hours worked, show improvement with increases. Benefit-cost analysis (BCA) expresses results as a benefit-cost ratio (benefit divided by cost) or a net benefit estimate (benefit minus cost) and considers an intervention cost-beneficial if the benefit-cost ratio exceeds unity or if the net benefit estimate is positive. In

summary, we will be able to describe the economic impact of Vivitrol in terms of both cost-effectiveness and net economic benefits.

11.0 REGULATORY COMPLIANCE AND SAFETY MONITORING

11.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, consistent with the International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements.

11.2 Institutional Review Board Approval

Prior to initiating the study, written UCLA and UNM IRB approval will be obtained to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, the UCLA and UNM IRBs will approve all consent forms, recruitment materials, and any materials given to the participant. Annual reports and progress reports will be submitted to the IRBs annually or as requested.

11.3 Informed Consent

All potential candidates for the study will be given a current local IRB-approved copy of the Informed Consent Form to read in English. Appropriately qualified and trained study personnel will explain all aspects of the study in lay language and answer all of the study candidate's questions. Participants who remain interested after receiving an explanation of the study will be given a short quiz to test his/her understanding of the project, the purpose and procedures involved, and the voluntary nature of his/her participation. Those who cannot successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form. Participants will not be administered any assessments or study procedures prior to signing informed consent.

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a study participant's consideration for participation in the trial. Every study participant will be given a copy of the signed consent form to keep for reference. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

11.4 Drug Accountability

Upon receipt, the investigator, pharmacist, or authorized designee is responsible for maintaining written inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent shall be accounted for.

11.5 Quality Assurance and Safety Monitoring

Protection of the rights and welfare of study participants will be a vigilant process conducted by the research team and by the sponsors of the research. In addition to the data and safety monitoring procedures described in this protocol, additional safety monitoring through the Data and Safety Monitoring Board will be conducted regularly throughout the duration of the study.

11.6 Data and Safety Monitoring Board (DSMB)

This study will utilize a DSMB to oversee ongoing trial progress. The purpose of this board is to determine whether risks emerge during the conduct of the trial that make continuation unethical (e.g., clear and significant superiority of one condition over another). This process is intended to assure the IRBs, the sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in research trials. Safety monitoring begins with the initial review of the protocol during the study development process. Reports of participant serious adverse events (SAE) will be provided to the DSMB as they occur. The DSMB will meet as necessary over the study duration.

11.7 Medical Monitor

A Medical Safety Monitor will be responsible for overseeing safety and for evaluating all Adverse Events (AEs). He/She will review all Serious Adverse Events (SAEs) within five days of their occurrence and all other Adverse Events on a regular basis. It is the responsibility of the Principal Investigator to provide this information to the medical safety monitor. It is also the Principal Investigators' responsibility to inform the IRB of any reportable AE/SAE.

11.8 Quality Assurance Monitor

The monitoring of the study will be conducted on a regular basis using a local quality assurance monitor. Investigators will host periodic visits by local QA monitors. The purpose of these visits is to encourage and assess compliance with GCP requirements and to document the integrity of the trial progress.

Monitors will assure that submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and Principal Investigator supervision and involvement in the trial. Reports will be prepared following the visit and forwarded to the Principal Investigator.

11.9 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements.

11.10 Confidentiality

By signing the protocol signature page, the investigators affirm that study information will be maintained in confidence and such information will be divulged to the IRBs, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use). The Department of Health and Human Services (HHS) office that issues the CoC will be advised of changes in the CoC application information. Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations.

Participant records will be kept confidential by the use of study codes for identifying participants on CRFs, secure separate storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

11.11 Health Insurance Portability Accountability Act (HIPAA)

Written authorization from participants for use of protected health information will be obtained. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

11.12 Investigator Assurances

UCLA ISAP will maintain a Federal Wide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects. Prior to initiating the study, the Principal Investigator and sub-investigators will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

11.13 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. It is the responsibility of the investigator to maintain appropriate disclosure to their individual institution according to their requirements.

11.14 Inclusion of Women and Minorities

This study should attract a diverse study population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed and plans implemented to increase representation by all sex and racial/ethnic groups.

11.15 Description of Plans to Conduct Valid Analyses of Study Results by Gender and Race/Ethnicity

The association between specific demographic characteristics and outcome will be studied. The demographic characteristics of potential importance include: age, gender, race, and ethnicity.

11.16 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

11.17 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with local IRB, State and Federal requirements, whichever is longest. The sponsor must be notified in writing and acknowledgment must be received prior to the destruction or relocation of research records.

11.18 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Investigator; the National Institute on Drug Abuse (the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the sites' Institutional Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

11.19 Reporting to Sponsor

The Principal Investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event reporting and Serious Adverse Event reporting will occur as previously described. At the completion of the trial, the PI will provide a final report to the Sponsor.

11.20 Study Documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved current and previous consent forms and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. The original recording of an observation should be retained as the source document.

11.21 Protocol Deviations, Violations, and Reporting and Management

Any departure from procedures and requirements outlined in the protocol will be classified as either a protocol deviation or protocol violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that performance does not compromise the integrity of the trial.

Additionally, the study team is responsible for reporting Protocol Violations to the IRB as required.

11.22 Safety Monitoring

11.22.1 Adverse Events (AEs)

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the Principal Investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix A. The occurrence of AEs will be assessed at each study visit starting at the time that informed consent is signed through the post-medication assessment, and study staff will follow-up on the status of any AEs that remain at the post-medication assessment.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered investigational product-related or clinically significant**.** For this study, AEs will include events reported by the participant, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE Form. The AE Form is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a study physician or investigator must review the AE Form completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution.

A Medical Clinician will review or provide consultation for each serious event as needed. These reviews will include an assessment of the severity and causality to the study drug or study procedures. The Medical Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. The medical monitor will determine which safety events require expedited reporting to the IRBs, NIDA, the DSMB, and other regulatory authorities as appropriate.

This will include all suspected adverse reactions that are serious and unexpected. The study staff will be trained to monitor for and report adverse events and serious events.

The BCMDC has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Study medical clinicians will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

11.22.2 Definitions of Adverse Events and Serious Adverse Events

Full definitions of adverse events and serious adverse events, their identification, characterization regarding severity and relationship to therapy and processing are described in Appendix A.

11.22.3 Reportable Adverse Events and Serious Adverse Events

Reporting of AEs and SAEs is described in Appendix A. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA.

Adverse Events

For the purpose of this study, the following AE will not require reporting in the data system but will be captured in the source documentation as medically indicated:

- Grade 1 (mild) unrelated adverse events

This would typically include mild physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Other adverse events that are deemed moderate, severe or serious, regardless of the relationship to the study medications, will be captured and reported in the data system.

Serious Adverse Events

All SAEs will be documented in the source documentation as medically indicated and reported through the data system.

11.23 Possible Risks of Study Medications

The most serious adverse effect of naltrexone is hepatocellular injury, which has almost always been associated with oral doses of 1400 to 2100 mg per week. Recent study findings show that no evidence of liver toxicity was found in those receiving monthly Vivitrol® injections such as provided in this study. Participants will not be allowed to participate if there is any indication or report of acute symptomatic hepatitis or liver failure.

Vivitrol® injections may be followed by pain, tenderness, induration, swelling, redness, bruising, or itching. Injection site reactions have been the most common adverse events associated with Vivitrol®, but the injection site will be monitored after each injections. Any participant exhibiting adverse events will be evaluated by the study physician for possible referral to a surgeon if warranted. Other side effects may include nausea and vomiting. Continued use of naltrexone is not associated with tolerance or addiction, but naltrexone will precipitate withdrawal if given to a person who is physiologically dependent on opioids. To eliminate this risk, a naloxone challenge will be administered to each participant in this condition before administration of each Vivitrol injection.

12.0 DATA MANAGEMENT AND PROCEDURES

This protocol will utilize the UCLA ISAP Data Management Center (DMC). A web-based distributed data entry model will be implemented. This electronic data capture (EDC) system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld.

12.1 Operations Manual

An Operations Manual or Standard Operating Procedure documents will be provided for this study that incorporates procedures from this protocol with those procedures in more detail as necessary for the day-to-day conduct of the trial. The Operations Manual will be used to train study staff, to provide reference for study procedures, and to support quality management activities.

12.2 Data and Statistics Center Responsibilities

The DMC will 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of EDC system and for the completion of eCRFs, 5) perform data cleaning activities prior to any interim analyses and prior to the final study database lock.

12.3 Data Collection and Entry

Data will be collected on source documents and entered by the site into eCRFs or in the EDC, or will be collected via direct entry into the eCRF. In the event that the EDC is not available, the DMC will provide paper source documents and completion instructions. Data will be entered into the EDC in accordance with the instructions provided during project-specific training and guidelines established by the DMC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

The investigator is responsible for maintaining accurate, complete and up-to-date research records. In addition, the investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

12.3.1 Data Monitoring, Cleaning, and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in the EDC. These reports will be monitored regularly by the DMC. In addition, the DMC will identify inconsistencies within eCRFs and between eCRFs and post queries in the EDC on a scheduled basis. Data inconsistencies and errors by will be corrected by entering all corrections and changes directly into the EDC.

12.4 Study Documentation and Records Retention

Study documentation includes all data correction forms, workbooks, source documents, monitoring logs and appointment schedules, Sponsor correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and

signed participant consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records, among others).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, participant diaries, biopsy reports, ultrasound photographs, participant progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

12.5 Data Transfer and Lock

At the conclusion of data collection for the study, the DMC will perform final cleaning activities and will “lock” the study database from further modification. The final data will be provided to the PI for analyses.

12.6 Confidentiality

12.6.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration (FDA) under the Freedom of Information Act providing, in part, that proprietary information furnished to investigators and Institutional Review Boards will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and Institutional Review Board (IRB).

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

13.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date

INVESTIGATOR(S)

- I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only deviate from the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of participants.
- I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 45 CFR 46 and 21 CRF Part 56 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46 and 21 CFR 312.64.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 45 CFR 46 and 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 45 CFR 46 and 21 CRF Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without sponsor, lead investigator, and IRB approval, except where necessary to eliminate apparent immediate hazards to human participants.
- I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.
- I agree to comply with all the applicable federal, state, local, and institutional regulations regarding the obligations of clinical investigators and other pertinent requirements in 21 CRF 312.

Typed Name	Signature	Date
Principal Investigator		
Principal Investigator (*if applicable*)		
Sub-Investigator		
Sub-Investigator		

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15.0 APPENDICES

APPENDIX A

Adverse Event Reporting Definitions and Procedures

The Principal Investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

Definition of Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related, which occurs during the conduct of a clinical trial. Any change from a baseline pre-existing condition based on clinical status, ECGs, lab results, x-rays, physical examinations, etc., that is considered clinically significant by the study medical clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered "**serious**" (i.e. a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study medical clinician or sponsor, it:

1. Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study drug/intervention, must be reported.
2. Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Is a congenital abnormality or birth defect.
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the investigator brochure or the package insert or is not listed at the specificity or severity that has been observed. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy

Any pregnancies that occur to a participant enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Women who become pregnant during the

medication period will be discontinued from further medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

Medical and Psychiatric History

A thorough medical and psychiatric history during the screening phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Eliciting and Reporting Adverse Events

Appropriately qualified and trained medical personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Medical personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to their IRB, per their IRB's guidelines.

Sites are required to enter reportable AEs and SAEs in the EDC system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate serious adverse events and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained medical personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event.

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)

Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.

Guidelines for Determining Causality

The study medical clinician will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction:
Is there a reasonable possibility that the study drug/intervention caused the event?

Monitoring Adverse Events

Local quality assurance monitors will review study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

Safety Management Procedures of AEs/SAEs

A Medical Monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Medical Monitor. All SAEs will be reviewed by the Medical Monitor and, if needed, additional information will be requested. The medical monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the Medical Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the medical monitor in writing for review by the sponsor and DSMB. Subsequent review by the Medical Monitor, DSMB, and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment. The study sponsor, DSMB and FDA retain the authority to suspend additional enrollment and intervention for the entire study as applicable.

Reporting to the Data and Safety Monitoring Board: The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Regulatory Reporting for an IND study

All serious and unexpected suspected adverse reactions are reported by the medical monitor on behalf of the sponsor to the FDA in writing within 15 calendar days of notification. Suspected adverse reactions that are unexpected and meet the criteria for death or immediately life-threatening also require notification of the FDA as soon as possible but no later than 7 calendar days of notification of the event, with a follow-up written report within 15 calendar days of notification of the event. The medical monitor will prepare an expedited report (MedWatch Form 3500A or similar) for the FDA and other regulatory authorities, DSMB and copies will be distributed to all sites. Expedited reports will be placed in the site regulatory files upon receipt. A copy of all expedited reports will be forwarded to the site's local IRB, as required.

Participant Withdrawal

The study medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant is withdrawn from further study medication administration. The study medical clinician should consult with the site principal investigator, the lead investigator and/or Medical Monitor as needed. If necessary, a study medical clinician may suspend the interventions and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end-of-medication visit to assure safety and to document end-of-medication outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.