Cover Page

Title: Pregabalin Plus Lofexidine for the Outpatient Treatment of Opioid Withdrawal

Clinical Trial Number: NCT04218240

Document Name: Protocol with Analysis Plan

Document Date: 11/2/2022

University of Pennsylvania

Combining Pregabalin (LYRICA®) with Lofexidine (LUCEMYRA™):
Can it Increase the Success of Transition to Naltrexone?

Protocol Number:	**834801**
Regulatory Sponsor:	Kyle M. Kampman M.D. Department of Psychiatry University of Pennsylvania Center for Studies of Addiction 3535 Market Street Suite 500 Philadelphia, PA 19104 215 746 2764
Funding Sponsor:	National Institute on Drug Abuse National Institutes of Health 6001 Executive Boulevard Room 5213 Bethesda Maryland 20892 301 443 1124
Study Product:	Pregabalin Lofexidine
Protocol Number:	9.0
IND Number:	147130

Date November 2, 2022

1.0 SIGNATURE PAGE

By signing below, the University of Pennsylvania indicates approval of this protocol through the University of Pennsylvania's IRB as well as assurance that this study will be conducted according to the procedures described in the protocol, ICH guidelines and Good Clinical Practices, and all applicable regulatory requirements.

_____
Printed Name of Sponsor

_____
Signature of Sponsor

_____
Date

Investigator's Agreement
I have received, read, and understood the information contained in the package insert for LYRICA (Pregabalin) and LUCEMYRA (lofexidine). I have read Protocol (IRB protocol number #) and agree to conduct the study as written in the protocol. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

2.0 STUDY CONTACTS

Study Contact Information

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2.1 TABLE OF CONTENTS

3.0 PROTOCOL SUMMARY

Title	**Combining Pregabalin (LYRICA®) with Lofexidine (LUCEMYRA™): Can it Increase the Success of Transition to Naltrexone?**
Short Title	Pregabalin and Lofexidine for opioid withdrawal
Protocol Version	7.0
Phase	Phase 2
Methodology	Double-blind placebo-controlled parallel group clinical trial
Study Duration	24 months
Study Centers (3)	• University of Pennsylvania Center for Studies of Addiction in Philadelphia Pennsylvania • Columbia University in New York City, New York • Mountain Manor in Baltimore, Maryland
Objective (Primary) Objective (Secondary)	To investigate whether pregabalin-Lyrica® (PGB) combined with Lofexidine-Lucemyra® (LFX) can reduce opioid withdrawal-related subjective effects To investigate, if the PGB/LFX combination can increase the proportion of patients with an opioid use disorder (OUD) who complete detoxification and transition to antagonist treatment with extended- release injectable naltrexone VIVITROL® (XR-NTX)
Number of Subjects	90 subjects. 60 randomized to PGB/LFX; 30 to PGB-PLA/LFX
Inclusion Criteria	• Male and/or female subjects ≥ 18 years of age • Meet DSM-5 criteria for an Opioid Use Disorder with physiologic features. Have 2 or more of the 11 DSM 5 criteria for opioid disorder including tolerance and withdrawal features in the last 12 months • Interested in opioid antagonist treatment • Have used opioids in 20 of the past 30 days • Have a stable address in the local area; not planning to move; have documents for ID check • Absence of medical or psychiatric conditions that are likely to interfere with study participation • Have a 12 lead ECG demonstrating a QTc ≤450 msec and a QRS interval ≤120 msec. The site PI has the final determination for inclusion into the study for ECGs unless there is a question of QT prolongation or other factors (QTc/Fri uses the Fridericia formula (QTc = QT/RR(1/3)). If consultation is needed, the PENN cardiologists and the medical monitor should be contacted. • If female, have a negative pregnancy test, and uses adequate contraception if of childbearing potential
Exclusion Criteria	• Current psychotic disorder (bipolar I, schizophrenia, major depression with psychotic features,) as defined by the MINI • An alcohol, benzodiazepine, or other sedative disorder with physiological features that require medication for detoxification • History of allergy or other serious adverse event due to treatment with pregabalin, XR-NTX, or lofexidine

	• Pending incarceration in the next 30 days • Homicidal or otherwise behaviorally disturbed requiring immediate attention. • High Risk for suicide as determined by answering 'yes' to questions 4 and/or 5 on C-SSRS at screening • Blood pressure <90 mm Hg (systolic) or <60 mm Hg (diastolic). If this value is out of normal range, the investigator and a study clinician will decide subject inclusion or exclusion on a case-by- case basis • Heart rate and/or pulse<50 bpm at screening-sitting • An Estimated Glomerular Filtration Rate eGFR<90 mL/min/1.73m^2 • A history of, or current seizure disorder (excluding childhood febrile seizures) • Inability to read and/or understand English. For example, does not understand the informed consent as demonstrated by failing to answer 9/10 questions correctly on the quiz • Pregnant or breastfeeding • Currently taking sympathomimetic drugs, or a thiazolidinedione antidiabetic • An ALT and/or AST that is at $\geq$ 4X the top limit of normal • A Child-Pugh score >7 • Currently receiving opioids for pain management • In a treatment study where medication was administered in the last 30 days. • Currently using medications that are known to be strong or moderate inhibitors of CYP2D6 such as fluoxetine, paroxetine, mirabegron, bupropion, quinidine, terbinafine, cimetidine, cinacalcet, duloxetine, or fluvoxamine • In a methadone maintenance or buprenorphine treatment program within the last 30 days
Study Product, Dose, Route, Regimen	Pregabalin (PGB) or PGB-PLA given orally at a ***starting*** dose of up to 400 mg on day 1, up to 600 mg daily on Day 2 through Day 4, tapered to 100 mg daily by Day 7; Lofexidine (LFX) starts at 1.62 mg on day 1, 2.16 Day 2 through Day 4, tapering to 0.72 mg by Day 7. After starting dose on Day 1, both study drug doses can be reduced or withheld depending upon patient's clinical observations for Days 1-7. On day 8, subjects are offered an injection of XR-NTX if they provide a urine sample that is negative for opioids, buprenorphine, and fentanyl, and pass a naloxone challenge. All subjects, regardless of whether or not they receive XR-NTX, will be given a list of referrals and help with making an appointment for follow-up treatment when they leave the inpatient detoxification program.
Comfort Medications	The following "comfort" medications are suggested for treatment of withdrawal symptoms that are not suppressed by study medications: ondansetron 4 mg or 8 mg tid PO PRN for nausea and vomiting, trazodone 100 mg HS PRN insomnia, loperamide 2 mg qid PO PRN diarrhea, and a non-steroidal such as Ibuprofen 600 mg qid PO PRN for aches and pains or acetaminophen 650 mg (2 tablets 325 mg) PO qid PO PRN, cyclobenzaprine 5 mg tid PO PRN for muscle aches and pains, and hydroxyzine 25 mg qid PO PRN anxiety. In cases of QTc prolongation that are not >550ms or judged to require stopping study medications, diphenhydramine 50 mg hs PO PRN may be used for insomnia, and trimethobenzamide 300 mg qid PO PRN for nausea.

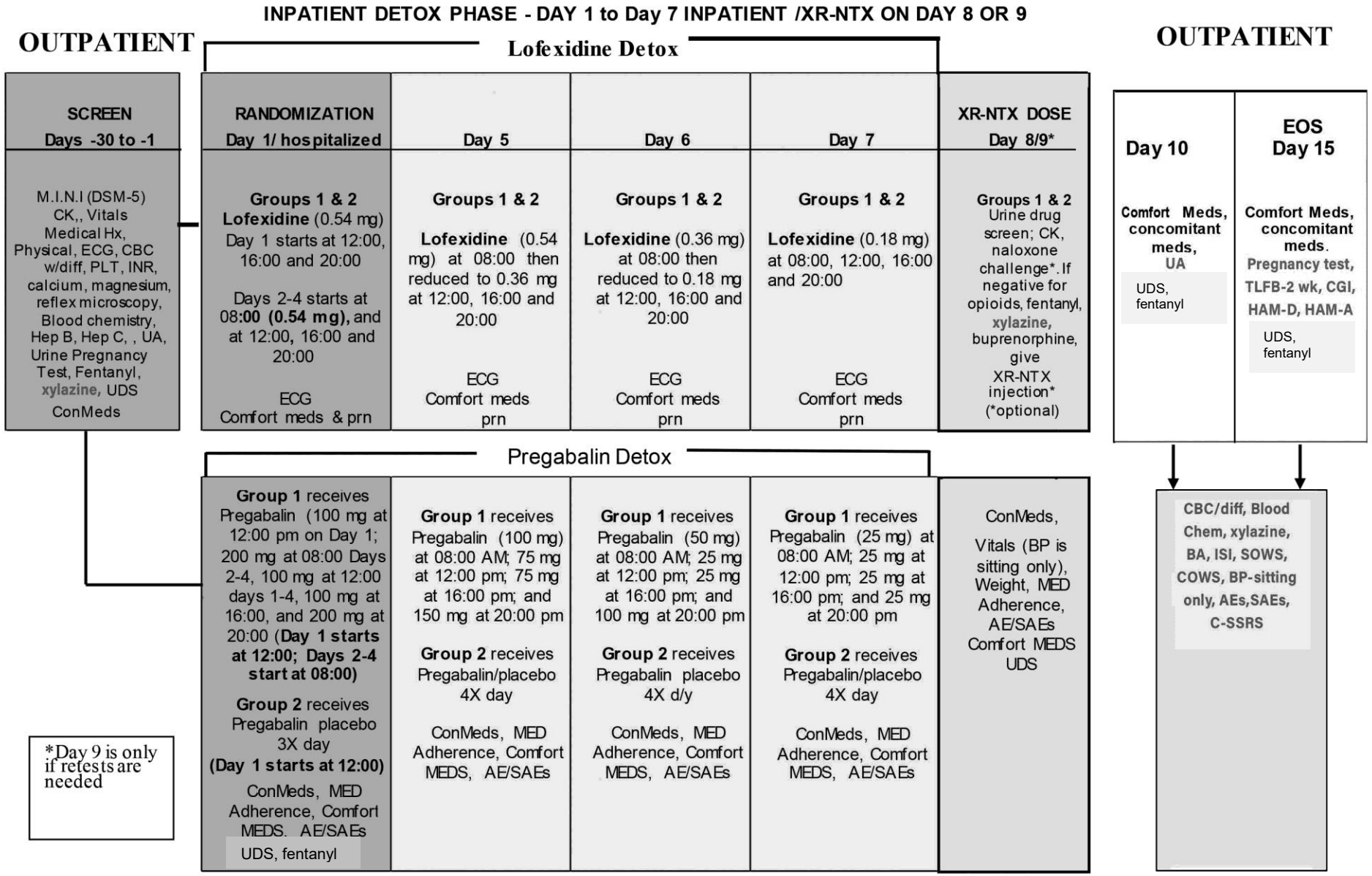
Duration of subject participation and medication administration	Outpatient screening is used to determine eligibility for the study. It will consist of the 30 days prior to inpatient admission for study detoxification and treatment. On day 1 of inpatient treatment subjects will be randomized to PGB/LFX or PGB-PLA/LFX for a 7-day detoxification. On day 8, if the patient completes detoxification, continues to be interested in XR-NTX treatment, provides a urine, and passes a naloxone challenge, he/she will be offered one injection of XR-NTX before hospital discharge. This injection of XR-NTX is optional. If retests must be done, such as a repeat of the naloxone challenge, all subjects are eligible to remain inpatient until Day 9. All subjects, whether they receive XR-NTX or not, will be referred to continuing care and asked to return to the research outpatient clinic on days 10 and 15 for follow-up visits. Subjects who cannot find a provider may be offered an additional XR-NTX injection up to 5 weeks after the Day 8 injection.
Reference therapy	PGB-Placebo plus lofexidine
Statistical Methodology	**The primary outcome** is reduction in subjective withdrawal as measured twice/day using the Short Opiate Withdrawal Scale (SOWS- Gossop). SOWS scores range from zero to 30. Groups will be compared on 10 or more repeated SOWS responses during inpatient treatment using linear mixed-effects regression models. The SOWS total will be regressed on a three-level factor for site, and a two-level factor for pregabalin dose, with random intercept and correlated residuals and a random slope included if necessary for fit. Contrasts between the combined groups will be estimated from this model. **The secondary outcome** is an ordinal response indicating completion of detox and receipt of antagonist treatment, with levels (1) failure to complete detox, (2) completion of detox with failure to receive antagonist treatment, and (3) completion of detox and receipt of antagonist treatment.

Note: Study medication will be provided in blister packs that are prepared by the PENN Investigational Drug Service and shipped to all three study sites. For the University of Pennsylvania, each blister pack will have a patient randomization number and the dosing schedule for each time on each inpatient study day, as summarized in the Study Schematics 4.0 below. For the two external sites, patient randomization will be generated by the site pharmacy or designated unblinded person, who receives the blister packs from the PENN Investigational Drug Service with the dosing schedule for each day.

The doses for each time of each day will be in separate compartments. Lofexidine will be 0.18 mg pink tables; pregabalin or pregabalin placebo will be in capsules. Blue capsules will contain 100 mg pregabalin or placebo; green capsules will contain 25 mg pregabalin or pregabalin placebo. These medications have not been used together and it is likely that doses will need to be held or reduced due to side effects. The most likely side effect from lofexidine is hypotension and/or bradycardia. The most likely side effect from pregabalin is sedation. Thus, in the event of hypotension, the next scheduled dose of lofexidine can be reduced or withheld. A similar adjustment can be made for excessive sedation (POSS score of 3 or 4; difficult to arouse, slurred speech, etc.) For the PENN site, medication counts will be done by the Investigational Drug Service (IDS) pharmacy for each subject. For sites outside PENN, medication counts will be done by the site or site pharmacy.

4.0 STUDY SCHEMATICS

Figure 1. Overview of Study Schematics Pregabalin (LYRICA®) plus Lofexidine (LUCEMYRA™) N= 90



5.0 Table 1. Overview of Study Assessments

Assessment	Outpatient	Inpatient	Inpatient	Inpatient					Inpatient	Outpat	Outpat	EOS/ AMA VISIT (early)
	Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8/9† (all assessments Done both days Unless otherwise Stated)	Day 10 +2 business days	EOSDay 15 +2 business days	
Informed Consent	1X											
Locator Information	1X									1X		
Medical History	1X											
Physical/Weight	1X										1X	1X
CBC* with Diff and PLT, INR	1X									1X INR Not repeated	1X if no D10 No INR	1X No INR
Blood Chemistry, with Magnesium and Calcium	1X									1X Magnesium not repeated	CMP 1X IF No Day 10	1X No magnesium
Creatine Kinase	1X								1X (done at D8-only)			1X
Estimated Glomerular Filtration	1X											
Child Pugh Score	1X											
Urinalysis with Reflex Microscopy	1X									1X		1X
Urine Pregnancy Test - F	1X	1X							1X (if done at D8-do not repeat on D9)		1X	1X
UDS	1X	1X							1X	1X	1X	1X

Assessment	Outpatient	Inpatient	Inpatient	Inpatient					Inpatient	Outpat	Outpat	EOS/ AMA VISIT (early)
	Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8/9† (all assessments Done both days Unless otherwise Stated)	Day 10 +2 business days	EOSDay 15 +2 business days	
Fentanyl	1X	1X							1X	1X	1X	1X
xylazine	1X								1X	1X	1X	1X
Alcohol Breathalyzer Test	1X									1X	1X	
HEP B & C	1X											
ECG	1X	1X	1X	1X	1X	1X	1X	1X				
MINI	1X											
Inclusion/Exclusion	1X											
Randomization Form	1X											
Visual Analog Scale for Craving		2X	2X	2X	2X	2X	2X	2X	1X			
Insomnia Severity Index	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
SOWS-Gossop	1X	2X	2X	2X	2X	2X	2X	2X	1X	1X	1X	
COWS	1X	2X	2X	2X	2X	2X	2X	2X	2X	1X	1X	
POSS		3X	4X	4X	4X	4X	4X	4X	1X			
Naloxone Challenge (optional; only if pt. is interested and detoxed)									1X (if positive on D8- repeat on D9)			1X Can be given to AMA Pts
XR-NTX									1X (if not done D8- do on D9)			1X Can be given to AMA Pts
Vital Signs Cont'd next pg.	1X	8X	8X	8X	8X	8X	8X	8X	1X BP sitting only	1X BP sitting	1X BP sitting only	1X BP sitting

Assessment	Outpatient	Inpatient	Inpatient	Inpatient					Inpatient	Outpat	Outpat	EOS/ AMA VISIT (early)
	Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8/9† (all assessments Done both days Unless otherwise Stated)	Day 10 +2 business days	EOSDay 15 +2 business days	
(BP-sitting & standing); Pulse										only		only
Adverse Events		1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @visit	1X @visit	1X @visit	1X @visit
Serious Adverse Events		1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @visit	1X @visit	1X @visit	1X @visit
Concomitant Medications	1X	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X@each visit	1X @each visit	1X @each visit	1X @visit	1X @visit	1X @visit	1X @visit
Comfort Medications		1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @each visit	1X @visit	1X @visit	1X @visit	
TLFB-90	1X											
TLFB-2-wk											1X	
Clinical Global Impression Scale (CGI)	1X								1X		1X	1X
HAM-D	1X								1X		1X	
HAM-A	1X								1X		1X	
C-SSRS	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
Lofexidine/Pregabalin* * Adherence Pill Count		1X	1X	1X	1X	1X	1X	1X				
XR-NTX Adherence									1X			
End of Study Form (EOS)	EOS only completed 1x when subject completes or drops from study at last study visit											

ECG=electrocardiogram (QT/Fri corrected for heart rate with Fridericia formula (QTc = QT/RR(1/3)); *CBC=complete blood count with diff; PLT, INR (INR at screen only); Chemistry for magnesium need not be done at Day 10; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; COWS=Clinical Opioid Withdrawal Scale; SOWS=Short Opioid Withdrawal Scale; UDS=urine drug screen; BrAC=breath alcohol concentration; TLFB=Timeline Follow-back; CGI=Clinical Global Impression; C-SSRS=Columbia Suicide Severity Rating Scale; HAM- A=Hamilton Anxiety Rating Scale; HAM- D=Hamilton Depression Rating Scale; POSS=Passero Opiate Sedation Scale; MINI=Mini International Neuropsychiatric Interview

The number prior to X refers to the number of times the procedure is done. Vital signs are done 1X sitting and 1X standing Pre-dose and Post-dose at each daily dose scheduled. **Lofexidine/Pregabalin Adherence is done by pharmacy/site collection of bottles per subject and blister packs for all doses. † Day 9 is used for retests if needed, but all assessments are again done as per day 8 unless otherwise noted.

Illicit non-study concomitant meds are covered in TLFB; UDS, Fentanyl and xylazine test are done at screen, and Day 1, Day 8, Day 10, Day 15; and Early termination.

6.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	aspartate aminotransferase
BUP/NAL	Buprenorphine/naloxone
CDC	Centers for Disease Control
CFR	Code of Federal Regulation
CGI	Clinical Global Impression – Rater Version
CK	Creatine Kinase
CMP	Comprehensive Metabolic Panel
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
C-SSRS	Columbia-Suicide Severity Rating Scale
EOS	End of study
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Rating Scale (Ham-D; Hamilton, 1960)
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISI	Insomnia Severity Index
LFX	Lofexidine
MAT	Medication-Assisted Therapy
MINI	Mini-International Neuropsychiatric Interview (M.I.N.I.) For DSM 5 (Sheehan 1998)
OUD	Opioid use disorder
PGB	Pregabalin
POSS	Pasero Opioid-Induced Sedation Scale (POSS; Pasero ,2009)
QTc	QT corrected by heart rate
QTc_{Fri}	QTc Correction using Fridericia formula ($QTc = QT/RR^{(1/3)}$).
SAE	Serious adverse event
SOWS-Gossop	Short Opiate Withdrawal Scale-Gossop (Gossop, 1990)
TLFB	Timeline Follow-Back Interview (TLFB; Sobell & Sobell, 1995)
XR-NTX	Extended-Release Naltrexone

7.0 INTRODUCTION

This document is a protocol for a human research study. The study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312, International Conference on Harmonization guidelines), and applicable government regulations and Institutional research policies and procedures. The Principal Investigator is responsible for assuring good communications with the study co-investigators as well as the monitor and the clinical staff so that each clearly understands and accepts the obligations incurred in undertaking this study. The Principal Investigator ensures that the clinical staff understand the nature of the protocol and the requirements for an adequate and well-controlled study; the obligation to conduct it in accordance with applicable federal and local regulations; obtain informed consent in accordance with 21 CFR Part 50; obtain IRB review and approval before the investigation may be initiated, and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56.

7.1 BACKGROUND

Extended-release injectable naltrexone (XR-NTX; Vivitrol®), an opioid antagonist treatment that was approved by the FDA for the treatment of opioid use disorders (OUDs) in 2010. A single injection of 380 mg provides up to four weeks of blockade and has filled a niche created by situations in which opioid agonist or partial agonist maintenance (e.g. methadone, buprenorphine-naloxone) treatments are unavailable or undesirable due to regulatory or logistical constraints, clinical considerations, or patient preference.

Initially met with skepticism, antagonist treatment has attracted interest from an increasing number of patients. In a recent cohort of 657 community recruited opioid-using patients, more than half, 52.1%, said they would be interested in trying antagonist treatment and possibly extended-release naltrexone (XR-NTX) (Ahamad et al., 2015). The authors cited daily heroin injection (AOR = 1.53; 95% CI = 1.02–2.31) as positively associated with this decision. Satisfaction with agonist treatment and chronic pain were the most common reasons for unwillingness to take XR-NTX. A related study assessed 372 opioid addicted individuals undergoing inpatient detoxification and the degree to which they would be interested in medication-assisted therapy (MAT). Among the 202 that expressed interest, 64 (18.5%) preferred methadone, 98 (28%) buprenorphine, 104 (30%) XR-NTX, and 80 (23%) preferred “NO MAT” at all, due mostly to negative beliefs about all MATs (Uebelacker et al, 2016).

Two recent studies found that XR-NTX treatment was similar in effectiveness to sublingual buprenorphine (BUP/NAL). One study, done in the U.S., compared XR-NTX to BUP/NAL in 570 patients with OUD over 6 months. Though 22% fewer patients started XR-NTX than started BUP/NAL, mainly due to failure to complete detoxification, there was no difference between groups in the percent of subjects who relapsed to opioids, number of opioid negative urine tests, or number of opioid abstinent days among those that started either medication (Lee et al., 2018). In a 12-week trial done in Norway, 159 OUD subjects were randomly assigned to XR-NTX or BUP/NAL, 61% completed the trial with no significant differences between groups in retention or percent opiate negative urine tests (Tanum 2017). A third trial randomized 308 probationers or paroled adult criminal justice offenders with OUD to either a 24-week course of XR-NTX (n=153); or 24 weeks of treatment-as-usual (n=155) consisting of brief counseling and referrals for community treatment programs. At 6 months, XR-NTX patients had a longer time to relapse, lower relapse rate, higher rate of opioid-negative urine samples, and no overdoses compared to subjects in the treatment-as-usual group (Lee et al., 2016). Results showing positive effects of extended-release naltrexone were also found in Russian studies when comparing opioid addicted patients that received oral or implantable naltrexone in St. Petersburg (Krupitsky et al, 2011; 2012; 2019).

7.1.2 Detoxification and Transition to XR-NTX: Although the findings cited above suggest patient interest in XR- NTX and its possible effectiveness in reducing time to relapse and increasing higher rates of opioid negative urines when used as recommended, methods to increase the proportion who complete detoxification and transition from opioid addiction to naltrexone remain understudied.

The usual protocol for opioid detoxification is tapering doses of methadone or buprenorphine, or suppressing autonomic over activity with an alpha 2 adrenergic agonist, such as clonidine or Lofexidine (LFX). The use of αlpha-2 agonists as adjuncts gained popularity when early studies found that withholding a single dose of clonidine prior to anesthesia caused a patient to experience an acute hypertensive crisis (Brodsky and Bravo, 1976) and it was theorized that α-2 agonists reduce withdrawal effects in the central and peripheral nervous systems. Centrally within the locus coeruleus, αlpha-2 agonists were able to produce sedation, analgesia and mild euphoric effects, and partially block the sweating, rhinorrhea and objective signs of withdrawal in chronic opioid users but did not have much effect on the achiness, insomnia, dysphoria and other subjective symptoms.

Opioid tapers with methadone or buprenorphine are better tolerated compared to treatment with alpha 2 adrenergic agonists, but patients interested in XR-NTX treatment need a 7-14-day opioid-free interval to avoid having naltrexone precipitate withdrawal, thus leaving time to relapse. Clonidine avoids this problem (Gold et al, 1980) but does not have FDA approval for this indication, does not decrease the dysphoria and other withdrawal-related subjective effects, and is unpopular with patients and physicians alike. Studies by Ling et al (2005) are an example. They show that only 61% of inpatients randomized to clonidine detoxification remained in treatment and had opioid negative urines at day 13, vs 77% in a buprenorphine detoxified group. Results were even worse in outpatient settings where only 5% of clonidine treated patients completed detoxification vs. 29% of those treated with buprenorphine only.

7.1.3 Detoxification with Buprenorphine. Combining low and decreasing doses of buprenorphine with low and increasing doses of oral naltrexone was also studied as a way to transition to naltrexone and the results were positive in an early study where 56% in the experimental group transitioned to XR-NTX vs 33% in the buprenorphine group (Sullivan et al, 2017). However, a larger trial of 378 patients randomized to one of three regimens: NTX + BUP; NTX + placebo BUP (PBO-B); placebo NTX (PBO-N) + PBO-B found no difference in transition to XR-NTX across groups (41-46%), although for those inducted onto XR-NTX, the management of opioid withdrawal symptoms prior to starting XR-NTX was achieved in a structured outpatient setting using a well-tolerated, fixed-dose ancillary medication regimen common to all three groups. (Bisaga et al, 2018).

7.1.4 Detoxification with Pregabalin. During the time that PGB was available without a prescription in Russia, clinicians observed that opioid addicted patients were using it to suppress withdrawal when their heroin supply ran out. These observations led to a study in which 34 heroin-addicted patients were randomized to detoxification protocols using PGB alone, or clonidine alone (Krupitsky et al, 2017). While groups did not differ on baseline clinical or demographic features, 15 of the 19 PGB subjects completed treatment (79%) compared to 7 of 15 (47%) in the clonidine group ($p = 0.05$, Fisher exact test), and a Kaplan-Meier Survival Analysis confirmed better retention in the PGB group ($p = .001$). There was no significant group difference in reduced severity of withdrawal, however the pregabalin group reported less opioid craving ($p= .05$), less anxiety ($p=0.05$), less depression ($p=0.05$), and higher assessments of general health ($p < 0.05$). Ketorolac was available as needed for pain, and the average dose of symptom-triggered ketorolac in the clonidine group was almost twice that of the PGB group (60.5 ± 8.2mg vs. 36 ± 7.8mg, ($p< 0.05$). In addition, the PGB group reported less fatigue compared to the clonidine group (16% vs. 47%, $p < 0.05$) and there was no significant difference in AR's between groups. These findings were consistent with studies using rodent models that demonstrated PGB attenuates opioid withdrawal (Vashchinkina et al 2017).

PGB has a different mechanism of action than alpha-adrenergic receptor agonists as it potentiates glutamic acid decarboxylase, an enzyme that catalyzes decarboxylation thus increasing the synthesis of GABA, and inhibits calcium influx and release of excitatory neurotransmitters through action at the alpha-2-delta subunit of the NMDA receptor (Kämmerer et al, 2012; Freynhagen et al, 2016). It is rapidly absorbed, reaching a maximum concentration in 10.5 hours that lasts for 8 hours and is excreted by the kidneys and not metabolized by the liver, thus unlikely to alter the metabolism of other drugs. It is approved for neuropathic pain, fibromyalgia, adjunctive therapy for adults with partial onset seizures and, in Europe, for anxiety (Gajraj, 2007). Side effects occurring in >5% of patients are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain and difficulty concentrating. It can increase the PR interval (http://labeling.pfizer.com/showlabeling.aspx?id=561), but only by 3-6 msec and at doses of >300 mg/day. It has a relatively low abuse potential (Schedule V) and available without a prescription in Russia until October 2015 when its status was changed to the equivalent of U.S. Schedule V due to reports of self-administration to experience opioid-like effects or reduce opioid withdrawal (Evoy et al, 2017).

7.1.5 Detoxification with Lofexidine. A third detoxification approach emerged with the approval of LFX, a selective alpha 2 adrenergic agonist. Unlike clonidine, it has reduced potency at the A subtype of the alpha 2 receptor and is associated with less bradycardia and hypotension (Yu et al, 2008; Gowing et al, 2016). Though its effects are similar to clonidine, its better safety profile is an advantage, especially in outpatient settings where hypotension can be a problem (Kahn et al, 1997; Lin et al, 1997; Carnwarth & Hardman, 1998). Like clonidine, it does not target the withdrawal- related subjective effects, thus potentiating a greater likelihood for dropout. An inpatient study randomized OUD inpatients to detoxification using lofexidine or diazepam. Twenty-seven percent (15/55) of the diazepam patients completed 10 days of treatment, vs 46.4% (26/56) of the lofexidine patients, thus more effective than diazepam although with much room for improvement (Guo et al, 2018). In a pivotal study leading to FDA approval, lofexidine showed a small reduction in subjective effects compared to placebo (a 2-point difference on the SOWS-Gossop scale) with significantly greater rates of detoxification completion (41% vs 28%; Fishman et al 2018). Again, showing the need for improvement, particularly for patients transitioning to antagonist therapy.

7.1.6 Detoxification with Pregabalin and Lofexidine. Here we propose to see if PGB can be safely combined with LFX to better reduce the subjective effects of opioid withdrawal and increase the proportion that transition to antagonist treatment. Such an approach could lower the detoxification hurdle for patients who are interested in antagonist treatment or in settings where agonist treatment is unavailable or difficult to access, and reduce overdose risk for those who make the transition. This study, will attempt to identify a PGB/LFX combination that reduces withdrawal- related subjective effects without generating more SAE's than LFX, as a precursor to a larger trial. The combination of PGB and LFX may result in increased drowsiness, lightheadedness and trouble concentrating.

This study is a phase II, double-blind placebo-controlled, study to examine whether: 1) PGB can be combined with LFX and reduce opioid withdrawal-related subjective effects; and, 2) if safe and effective, can the combination increase the proportion of OUD subjects who transition to XR-NTX. To investigate these objectives, preliminary data on the safety and tolerability of PGB/LFX dose sequencing, and the reduction of opioid withdrawal-related subjective effects, will be obtained in the current trial. We will use a two-arm comparison; PGB/LFX versus LFX/PGB-PLA. If the current trial shows that a PGB/LFX combination is likely to be safe effective, and reduces opioid withdrawal related subjective effects, we will conduct a second trial in which we will test the PGB/LFX combination in a larger sample, under well- powered conditions, to evaluate the results of the current trial in relation to the efficacy of the combination to reduce opioid withdrawal-related subjective effects and possibly increase the proportion of patients who complete detoxification and transition to XR-NTX treatment. The first 2-year component will utilize three sites with inpatient units. Each site will recruit around 30 randomized subjects for a total sample size of 90 using DSM-5 criteria to establish

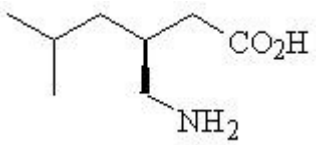
OUD with physiologic features diagnosis.

This trial has 4 distinct phases (see 4.0: Figure 1 schematic): 1) Screening (up to 30 days before inpatient admission and randomization). Patients who were never randomized and who come back after 30 days must be reevaluated and assigned a new screening number; 2) Inpatient Detox (1 – 7) days for medication induction and other assessments, 3) Inpatient administration of XR-NTX (Day 8); and, 4) Outpatient Follow-Up (Day 10 and Day 15). Dosing for lofexidine and pregabalin will begin at 12:00 on day 1 and be tapered starting at day five. This plan will permit dose adjustments for adverse effects, such as BP <90 mmHg systolic or <60 mmHg diastolic, a clinically significant drop in standing vs sitting blood pressure, bradycardia <50 bpm, or excessive sedation. Subjects that need a procedure repeated can continue inpatient treatment through day 9. The Study Schema is seen above in 4.0, Figure 1: Overview of Study Schematics Pregabalin (LYRICA®) plus Lofexidine (LUCEMYRA™)**".** Study assessments are seen in 5.0 Table 1.

7.2 INVESTIGATIONAL AGENT

7.2.1 Pregabalin Structure (LYRICA®): described chemically as (*S*)-3-(aminomethyl)-5- methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure is:

Figure 2. Molecular Structure of Pregabalin



It is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6 that is freely soluble in water as well as in basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is 1.35. LYRICA (pregabalin) is administered orally and supplied as hard gelatin capsules. The study is using the 25 mg strength in green capsules, and 100 mg strength in blue capsules. The capsule shells contain gelatin and titanium dioxide as well as red iron oxide. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

7.2.2 Mechanism of Action. Pregabalin (LYRICA®) binds with high affinity to the $alpha_2$- delta site (a subunit of voltage-gated calcium channels) in central nervous system tissues. Although its mechanism of action has not been fully elucidated, results with genetically modified mice and compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the $alpha_2$-delta subunit may be involved in its anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium- dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting $alpha_2$-delta containing calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest the anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

While pregabalin is a derivative of the inhibitory neurotransmitter gamma• aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors and does not

augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

7.2.3 Pharmacokinetics. PGB is well absorbed after oral administration, eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

7.2.4 Absorption and Distribution. Following oral administration of PGB under fasting conditions, peak plasma concentrations occur within 1.5 hours and oral bioavailability is ≥90% and independent of dose. Following single (25 to 300 mg) and multiple-dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours.

The rate of PGB absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of PGB with food has no clinically relevant effect on its total absorption of PGB and therefore can be taken with or without food. PGB does not bind to plasma proteins. The apparent volume of distribution of PGB following oral administration is approximately 0.5 L/kg. PGB is a substrate for a system that is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, PGB has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, PGB has been shown to cross the placenta in rats and is present in the milk of lactating rats.

7.2.5 Metabolism and Elimination. PGB undergoes negligible metabolism in humans. Following a dose of radiolabeled PGB, approximately 90% of the administered dose was recovered in the urine as unchanged PGB. The N-methylated derivative of PGB, the major metabolite of PGB found in urine, accounted for 0.9% of the dose. In preclinical studies, PGB (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

PGB is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because PGB is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. PGB elimination is nearly proportional to creatinine clearance (CLcr).

7.3 DOSING RATIONALE: RISKS AND BENEFITS

7.3.1 Medication and Blinding US WorldMeds, LLC (Louisville, KY) will provide lofexidine (LFX). Alkermes, Inc. (Waltham, MA) will provide XR- NTX. Each site will have 20 XR-NTX kits before the study begins to endure immediate availability. The Penn Research Pharmacy will prepare blister packs with each day's planed doses in separate a compartment. Each compartment will be labeled with the dosing time on each inpatient study day.

Lofexidine will be provided as pink, 0.18 mg tablets; pregabalin as blue capsules for the 100 mg or placebo doses and as green capsules for the 25 mg or placebo doses. Medical staff will be able to reduce or withhold doses by not removing them from their compartment in the blister pack at their scheduled time of administration, after receiving a physician's order. Such an order is likely to be given after a clinically significant AE that appear to have been study medication-related.

Examples of possible AE's are: clinically-significant prolongation of the QTc or QRS; clinically significant (>20 mm) drop in blood pressure (BP) compared to the last reading; and/or drop in systolic BP of 20 mm or more standing, or 10 mm or more sitting to make it; excessive sedation or dizziness (can use manual blood pressure check if considered necessary). Subjects must exhibit mild to moderate opioid withdrawal prior to receiving the first dose of study medication (COWS >/=6,

SOWS >/= 4), and pass a naloxone challenge to show they are free of physiologic opioid dependence before receiving XT-NTX.

7.3.2 DOSING SCHEDULES

Table 2: LFX Dosing: all tablets are 0.18 mg

	Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
All Groups	0800	0.00	0.54	0.54	0.54	0.54	0.36	0.18
	1200	0.54	0.54	0.54	0.54	0.36	0.18	0.18
	1600	0.54	0.54	0.54	0.54	0.36	0.18	0.18
	2000	0.54	0.54	0.54	0.54	0.36	0.18	0.18
	Total	1.62	2.16	2.16	2.16	1.62	0.90	0.72

Table 3: PGB and PGB-PLA Dosing (in mg)

	Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Group 1	0800	0	200	200	200	100	50	25
(PGB)	1200	100	100	100	100	75	25	25
	1600	100	100	100	100	75	25	25
	2000	200	200	200	200	150	100	25
	Total	400	600	600	600	400	200	100
Group 2	0800	0	PLAC	PLAC	PLAC	PLAC	PLAC	PLAC
(PGB-PLA)	1200	PLAC	PLAC	PLAC	PLAC	PLAC	PLAC	PLAC
	1600	PLAC	PLAC	PLAC	PLAC	PLAC	PLAC	PLAC
	2000	PLAC	PLAC	PLAC	PLAC	PLAC	PLAC	PLAC
	Total	0	0	0	0	0	0	0

7.3.3 Dosing Guidelines:

As stated below investigators may choose to stop or reduce the dose of either Study Medication although BP and pulse changes are more likely to be due to lofexidine and sedation due to pregabalin.

- Patients can be started and continued on Study Medication if the pulse is 50 or above. Medication should be held if the pulse is <50.
- Patients can be started on Study Medications on Day 1 if COWS >/=6 and SOWS >/= 4
- A study physician is required to hold the dose of Study Medication if the systolic BP is < 90 and/or the diastolic is <60. Investigators should hold both lofexidine and pregabalin until the next dosing time when they can be restarted if the vitals return to 90/60 or above.
- Hypotension is a potential side effect of lofexidine; sedation, dizziness, or light-headedness are potential side effect of pregabalin. A drop of 20 mm or more systolic and/or 10 mm or more diastolic; or significant lightheadedness or dizziness, are grounds for holding or reducing a dose of the medication that is the most likely cause. Investigators should use their judgement on which Study Medication to hold or reduce and by how much.

7.3.3.1 The following procedures will minimize risks associated with transient vs. persistent BP changes:

- If the BP reading shows a pre-medication sitting and/or standing drop (orthostatic change) of more than 20mm systolic, and/or more than 10 mm diastolic, wait 2-3 minutes and repeat the sitting and standing BP.

- If the repeat readings are within the acceptable range as defined by the protocol, dosing can be continued as planned.
- If the repeated readings are not within this range as defined by the protocol, hydrate the patient and study medication should be administered at the next scheduled dosing time provided they are in an acceptable range, as defined by the protocol. Retest the BP within an hour. Depending on the results of the BP retest, the physician has the discretion to give full dose, reduced dose, or hold the dose of study medication until the next scheduled dosing time.

Dosing should be given per the protocol scheduled times of 8:00, 12:00, 16:00, and 20:00. However, when dosing cannot be given at the protocol scheduled times, Study Medication can be given up to 1 hour pre or post the scheduled dose time. On day 1, if dosing cannot be given at the 12:00 scheduled time, after 2 hours, wait until the next scheduled 16:00 dose. In case of scheduled dosing changes, medication cannot be scheduled less than a minimum of 3 hours apart.

7.3.4 Potential Risks: These include AEs to PGB, LFX, and XR-NTX (for those who transition to it); potential adverse interactions between PGB and LFX; and a small risk from venipuncture. Clinical trials are conducted under widely varying conditions thus adverse reaction rates in clinical trials cannot be directly compared to rates in clinical trials of another similarly-acting drug, and may not reflect the rates observed in clinical practice.

7.3.5 PGB associated AE's: In controlled and uncontrolled trials across various patient populations during premarketing development more than 10,000 patients received PGB; approximately 5000 for 6 months or more; over 3100 for 1 year or more; and over 1400 for at least 2 years.

7.3.6 Most common AE's leading to discontinuation of PGB. In premarketing trials of all populations combined, 14% of patients treated with PGB and 7% of patients treated with placebo discontinued treatment prematurely due to AEs. AEs most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse reactions that led to discontinuation more frequently in the PGB group compared to placebo were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each).

7.3.7 Most common AE's in all pre-marketing controlled PGB studies. In premarketing controlled trials of all populations, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (mostly difficulty with concentration/attention) were more commonly reported by subjects treated with PGB than placebo (≥5%, twice the placebo rate).

7.3.8 AE's Leading to Discontinuation in controlled PGB trials. For those of neuropathic pain in patients with diabetic neuropathy: 9% of patients treated with PGB and 4% of patients treated with placebo discontinued prematurely due to AEs. In the PGB group, the most common reasons for discontinuation were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation with greater frequency in the PGB than placebo groups were asthenia, confusion, and peripheral edema. Each led to withdrawal in approximately 1% of patients. Table 4 lists AEs, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with diabetic neuropathy in the PGB group for which the incidence was greater than placebo. A majority of PGB patients had AEs with a maximum intensity of "mild" or "moderate".

Table 4: AE'S in trials of Neuropathic Pain Associated with Diabetic Neuropathy in at least 1% of pregabalin-treated patients

Body system - Preferred term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Body as a Whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive System						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and Nutritional						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous System						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal†	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory System						
Dyspnea	3	0	2	2	2	1
Special Senses						
Blurry vision‡	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

* PGB: pregabalin

† Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

7.4 LOFEXIDINE (LFX)

This medication was recently approved by the FDA for opioid detoxification and had been approved for the same purpose in the U.K. It is well-absorbed and reaches a peak plasma concentration 3-5 hours after a single dose. Administration with food does not alter its pharmacokinetics and about 30% of the dose is converted to inactive metabolites during the first pass. Its major metabolites do not influence or inhibit CYP450 isoforms except for a slight inhibition of CYP2D6, thus interactions with CYP substrates are not expected to be clinically significant. However, we are excluding strong or moderate inhibitors of CYP2D6 such as fluoxetine, paroxetine, or mirabegron, bupropion, quinidine, terbinafine, cimetidine, cinacalcet, duloxetine, and fluvoxamine. The major contributor to its metabolism is CYP2D6, though CYP1A2 and CYP2C19 may also be involved. The elimination half-life is about 12 hours. Nearly all of the oral dose is absorbed and accumulation can occur for up to 4 days with repeat dosing. Kidneys are the primary route of elimination, and unchanged drug accounts for 15-20% of the dose.

7.4.1 Safety. Concomitant use of LFX may reduce the efficacy of oral naltrexone, therefore oral naltrexone cannot be given to patients in this study.

7.4.2 Methadone and LFX both prolong the QT interval; therefore, methadone cannot be given to patients in this study.

7.4.3 Most common LFX AEs. The most common AE's (≥10%) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation and dry mouth. LFX can prolong the QT interval and potentiates the sedative effect of benzodiazepines, alcohol and other sedating drugs.

7.4.4 ECG and Vital Signs. ECGs will be reviewed each day before administration of the first dose of study medication. Medication will be withheld if there is clinically significant QTc prolongation. Vital signs will be checked sitting and standing pre-dose and 1-2 hours post dose. Study medication will be withheld if the seated systolic BP is below 90 systolic or below 60 diastolic, and/or if the pulse is <50. A study physician will be contacted for dosing instructions if the seated systolic BP is >20 mm, or >10 mm diastolic below the last reading. Study medications may also be withheld or reduced if there is excessive sedation or other clinically significant AE's that may be caused by study medication. First degree AV block is common and does not indicate a serious problem. Study medication should be stopped and the study cardiologist contacted if there is 2nd degree heart block.

7.5 EXTENDED-RELEASE NALTREXONE (XR-NTX)

XR-NTX will be offered to all patients who complete detoxification, usually on day 8. It is provided in a sealed kit and administered by injection into the gluteal muscle in the upper outer quadrant of the upper outer quadrant of the buttock. Subcutaneous injection may increase the likelihood of severe injection site reactions. To reduce the likelihood of this problem, each needle in the XR-NTX kit is customized and no other needle should be used. Needle length may not be adequate in every patient because of body habitus and as a result, each participant should be assessed prior to injection to assure that needle length is adequate. Patients will be educated to report any injection site reaction and bring it to the attention of a clinician and research staff. A physician will examine patients exhibiting abscess, cellulitis, necrosis, or swelling to determine if referral to a surgeon is warranted. AEs that have been reported in association with XR-NTX treatment are summarized in section 7.5.1 – 7.5.13.

7.5.1 Injection site reactions. These are the most common AEs and were reported in 50% of the placebo group and 69% of the 380 mg XR-NTX group in alcohol treatment studies. Pain, tenderness, induration, swelling, erythema, bruising, or pruritus may follow injections. In some cases, injection site reactions may be very severe. In clinical trials for alcohol dependence, one patient developed an area of induration that continued to enlarge after 4 weeks and required surgical excision. In the post-marketing period, additional cases of injection site reaction with features including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis have been reported. In some cases, these problems required surgical intervention, including debridement of necrotic tissue, with some resulting in significant scarring. The reported cases were possibly due to excess fatty tissue that interfered with

injection into the gluteal muscle. These problems were not observed in the Krupitsky et al study that led to FDA approval for opioid dependence (personal communication, Krupitsky, 2011), and not observed in the study of XR-NTX for preventing relapse to amphetamine dependence (Runarsdottir et al, 2017).

7.5.2 Precipitating Opioid Withdrawal. **XR-NTX** will precipitate or exacerbate withdrawal in opioid dependent patients unless they have been opioid-free for 7-10 days, and this possibility will be explained to study patients**.** The absence of physiologic dependence will be determined by the study clinicians by observation and a COWS scores less than or equal to 10 prior to and 15-20 minutes after a naloxone challenge. If clinically significant withdrawal develops, a study physician will treat it with one or more non-narcotic "comfort" medications. Note: XRNT may be given to patients after a Naloxone challenge in patients about to go AMA from hospital if the naloxone challenge results suggest an absence of physiologic dependence.

7.5.3 Liver Toxicity. The most serious adverse effect of XR-NTX is hepatocellular injury, which has almost always been associated with oral doses of 1400 to 2100 mg per week. These doses result in much greater naltrexone exposure than the 380 mg monthly dose of XR-NTX Data bearing on the safety of this dose was seen in a study of actively drinking alcoholics who received a monthly XR-NTX injections with no evidence of liver toxicity. The study enrolled 624 patients and there were no significant differences in ALT, AST, or bilirubin levels between study groups at any post-baseline assessment, and the GGT in the 380 mg group was lower compared to placebo at weeks 4, 8, 12, and 20. In a subset of patients who were drinking heavily throughout the study, or were obese or taking NSAIDs, there was no increase in the frequency of high liver function tests or hepatic-related adverse events (Lucey et al, 2008). The Physician's Desk Reference (PDR) had a "black box" warning about XR-NTX and liver damage but removed it in 2013.

7.5.4 Liver Impairment. The pharmacokinetics of XR-NTX have not been shown to alter hepatic states in patients with mild to moderate hepatic impairment and dose adjustment is not required in these individuals. XR-NTX pharmacokinetics have not been evaluated in subjects with severe hepatic impairment, therefore participants with severe hepatic impairment will be excluded from the study.

7.5.5 XR-NTX and Gastrointestinal Effects. The most common have been nausea (11% placebo group; 33% XR-NTX), and vomiting (6% placebo; 14% XR-NTX).

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

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

7.5.8 XR-NTX and Drug-Drug Interactions. Studies evaluating drug-drug interactions have not been performed.

7.5.9 XR-NTX and Reversal of Blockade for Pain Management. In an emergency situation, suggestions for pain management are regional anesthesia or non-opioid analgesics. If opioids are required, they must be provided in a setting where establishment and maintenance of a patent airway and assisted ventilation are readily available from persons trained in the use of anesthetic drugs and management of respiratory depression.

7.5.10 Depression and Suicidality. In controlled trials among patients with alcohol dependence, AEs of a suicidal nature (ideation, attempts and completed suicides) were infrequent, but more common in patients treated with XR-NTX than placebo (1%). In some cases, suicidal thoughts or behaviors occurred after study discontinuation but in the context of an episode of depression that began while the patient was on the medication. Two completed suicides occurred in alcohol treatment studies, both in patients treated with XR-NTX, and depression-related events were more common in patients treated with XR-NTX than in those on placebo (1%). However, two studies that have specifically examined the relationship between depression and XR-NTX treatment found that depression and anxiety decrease in association with detoxification and naltrexone treatment (Mysels et al, 2011; Krupitsky et al, 2016)

7.5.11 Naltrexone Contraindications. Patients should not receive XR-NTX if they are taking opioid analgesics; have current opioid dependence; are in opioid withdrawal; failed a naloxone challenge or have a positive urine screen for opioids; exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent; or have acute hepatitis or liver failure.

7.5.12 Opioid Overdose Following an Attempt to Overcome the XR-NTX Blockade. Patients will be told that attempting to overcome the blockade by administering large doses of opioids may result in fatal overdose.

7.5.13 Eosinophilic Pneumonia. There was one diagnosed, and one suspected case of eosinophilic pneumonia in clinical trials. Both required hospitalization and resolved with antibiotics and corticosteroids. Should a person receiving Vivitrol ® develop dyspnea and hypoxemia this diagnosis should be considered.

7.5.14 Data from the Russian XR-NTX Study of Opioid Dependent Patients: Dr. Krupitsky provided the following data from the study that led to FDA approval of XR-NTX for opioid dependence (Krupitsky et al, 2011). In that study, 6 of the 126 subjects (4.8%) randomized to 380 mg XR-NTX reported injection site pain as compared to one of 124 subjects (0.8%) assigned to XR-NTX placebo. ALT in the 380 mg XR-NTX group increased an average of 6.9 IU/L as compared to an increase of 5.6 IU/L in the XR-NTX placebo group; AST increased 3.8 IU/L in the XR-NTX 380 mg group, and 6.7 IU/L in the XR-NTX placebo group; 63 of the 126 (50%) subjects in the XR-NTX 380 mg group reported an AE as compared to 40 of 124 (32%) in the placebo group. Three patients reported 4 SAEs in the XR-NTX 380 mg group (AIDS/HIV or infections); and 4 reported 5 SAEs in the placebo group (2 infections, 1 psychotic disorder, 1 other drug dependence, 1 peptic ulcer). These data suggest that the risks associated with XR-NTX among persons with opioid dependence are no different or more common that those seen among alcoholics.

8.0 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVES

To determine if PGB can be combined with LFX to reduce opioid withdrawal-related subjective effects

8.2 SECONDARY OBJECTIVES

1) To determine if PGB plus LFX will result in more successful opiate detoxifications Successful detoxification is defined as completing the 7-day regimen/dosing of either PBG/LFX or LFX/PGB-PLA without leaving the inpatient unit or otherwise withdrawing from

the study; having a SOWS score of less than 6; a COWS score of less than 9; and a urine drug screen that is negative for opioids, ***excluding buprenorphine, and fentanyl.***

2) To determine whether PGB plus LFX improves rates of completion of detox and receipt of XR-NTX

8.3 ASSESSMENT TOOLS USED TO ACHIEVE OBJECTIVES

The assessment tools used to achieve study objectives are in Table 1. Effectiveness and safety endpoints, based on these assessment tools, are defined in Section 9.2 and 9.4.

9.0 STUDY DESIGN

This study is a phase II, two-part randomized, double-blind placebo-controlled, study to assess the effectiveness of PGB combined with LFX to reduce opioid withdrawal- related subjective effects, and to examine whether a PGB/LFX combination can increase the proportion of opioid use disordered (OUD) subjects who transition to antagonist treatment (XR-NTX).

The study will use three sites, each with inpatient units that provide beds and care from nurses that will be trained in study procedures and dosing requirements. Each site will recruit around 30 randomized subjects, with the Mountain Manor Site and the PENN site possibly recruiting greater than 30 subjects, for a total sample size of 90, using DSM-5 to establish an OUD diagnosis with physiologic features. This trial has 4 distinct phases (see Figure 1 schematic): 1) Outpatient Screening; 2) Inpatient medication induction plus other assessments on Days 1-7; 3) Inpatient XR-NTX administration on Day 8 or 9; and 4) Outpatient Follow-Up (5 days). Total days in study is 15 days plus or minus the time taken to complete the initial outpatient screening assessments. Randomization will occur before inpatient admission.

9.1 GENERAL DESIGN

9.1.1 Phase 1: Outpatient Pre-Screening (Up to 30 days before hospital admission).

Study inclusion and exclusion criteria will be assessed to make sure the subject meets admission requirements. Those who meet requirements will be given information and details of the study including the timeline, potential risks and benefits, inpatient requirements, confidentiality, and told that participation is voluntary. They will be asked to read the informed consent and encouraged to ask questions, then given a quiz in which they must answer 9 of 10 answers correctly (three retries allowed). Potential subjects will then be asked to sign the informed consent and given a copy.

- Once consented, subjects will be screened for up to 30 days to include the following: completion of a locator information form, concomitant medications used in the past 30 days, physical, medical history, complete blood cell count (CBC) with differential and PLT, INR, CMP with magnesium and calcium, urinalysis with reflex microscopy, urine drug screen, a fentanyl urine test, a xylazine urine test, a urine pregnancy test, ECG, creatine kinase test, an eGFR calculation, a Child-Pugh score (liver function), MINI assessment for Opioid Use Disorder with physiologic features (e.g. withdrawal), Insomnia Severity Index (ISI), Clinical Opioid Withdrawal Scale (COWS), Short Opioid Withdrawal Scale (SOWS-G), vital signs (can use manual blood pressure check if considered necessary), Timeline Follow- back (TLFB), Clinical Global Impression Scale (CGI), Hamilton Depression and Anxiety scales (HAM- D, HAM-A), Columbia-Suicide Severity Rating Scale (CSSR-S), an alcohol breathalyzer test, hepatitis B and C tests. Those meeting admission criteria will be asked to report to the inpatient unit on Monday through Friday; randomization will occur at hospital admission. Each collaborating program will enroll around 30 subjects, 20 to receive pregabalin plus lofexidine and 10 to receive placebo pregabalin plus lofexidine. The Pharmacy or designated physician or nurse at each site will receive pre-packaged blinded medications from PENN IDS. All study staff will be blinded.

9.1.2 Phase 2: Inpatient Detoxification (Days 1 thru 7).

Subjects are admitted to the inpatient unit, randomized to one of the two study medication conditions, and will need to demonstrate withdrawal before starting study medications by having *a COWS >/= 6* and a SOWS >/= 4. LFX and PGB dosing will begin at 12:00 on day 1 and a study drug taper will be done from days 5-7. Dose times follow the schedule outlined above and adjustments will be made based on BP changes and/or other AEs. Administration of LFX will be withheld or reduced in cases of dizziness or lightheadedness, clinically significant hypotension and/or the BP changes described above. We will explain to participants the importance for adequate oral hydration during the consenting process and throughout the detox. Similar procedures will be applied to PGB in cases of excessive sedation, dizziness, peripheral edema, or other problematic side effects that appear related that medication.

Dosing schedules are in Tables 2 and 3. Assessments for Day 1 through 7 include:

1) ECG is obtained before the 12:00 dose of study medications on Day 1 and before the 08:00 dose of study medications on Day 2-7
2) VAS is given before the first dose of study medication at 12:00 on Day 1 and before the 16:00 dose on Day 1. On Day 2-7, the VAS is given before the first dose of study medications at 08:00 and before the 16:00 dose of study medications
3) ISI given before the 12:00 dose of study medications on Day 1, and before the 08:00 dose of study medications on Days 2-7
4) COWS is given around 12:00 on Day 1 before the first dose of study medication; and around16:00 before the next dose of study medication. If subject is admitted without the requisite withdrawal (COWS >/= 6 and SOWS >/= 4), subsequent COWS and SOWS can be administered before the first dose of study medication until dosing criteria is met.
5) SOWS-G is given around 12:00 on Day 1 before the first dose of study medication; and around 16:00 before the next dose of study medication
6) POSS is given prior to all doses (08:00, 12:00, 16:00 and 20:00) of study medication
7) Sitting and standing blood pressure and pulse are taken prior to each dose of study medication and 1 to 2 hours after dosing, (can use manual blood pressure check if considered necessary)
8) Weight taken 1x at screen and Day 15 and recorded on the physical form
9) Adverse events/SAEs recorded daily
10) Concomitant medication records reviewed and recorded each day
11) C-SSRS is given at the end of each study day
12) Comfort medications given on a PRN schedule

Successful detoxification is defined as (a) not leaving the inpatient unit before day 8; (b) SOWS of 5 or less and COWS of 8 or less; and, (c) urine drug screen negative for opioids, excluding buprenorphine, and fentanyl.

9.1.3 Phase 3: Inpatient XR-NTX Dosing (Day 8 or 9)

On day 8, subjects will be offered an injection of XR-NTX following naloxone challenge starting with a split dose an option of 0.2 mg first, wait 10-20 minutes, then 0.6 mg (0.8 mg I.M of naloxone total) An injection of Vivitrol is optional, only if the subject is interested in the XR-NTX treatment), and only if the COWS does not rise above 10 (COWS) within 15-30 minutes after the challenge. Subjects will be offered a second XR-NTX dose in the outpatient research clinic 4 to 5 weeks after the Day 8/9 injection if they wish to continue XR-NTX and have been unable to find a community provider. Subjects who fail the naloxone challenge on Day 8 will receive symptomatic treatment, observed until symptoms resolve, and be offered an opportunity for a repeat

challenge and injection on day 9. Note:

Note: XRNT may be given to patients after a Naloxone challenge in Pts about to go AMA from hospital if the naloxone challenge results suggest an absence of physiologic dependence.

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The following assessments will be conducted before the XR-NTX injection:

1) CK test drawn before IM Injection of naloxone (PGB can elevate CK)
2) Vital Signs (blood pressure sitting)
3) Adverse Events Review
4) Urine Pregnancy Test
5) VAS scale
6) ISI
7) SOWS-G
8) POSS
9) UDS
10) Urine Fentanyl test
11) urine xylazine test
12) COWS
13) Naloxone Challenge*
14) Concomitant Medication Review
15) C-SSRS

ADMINISTRATION OF EXTENDED-RELEASE NALTREXONE

The following assessments will be conducted after the XR-NTX injection:

1) CGI
2) HAM-A, HAM-D
3) Inspection of injection site
4) Comfort medication(s) (PRN)

(It is permissible to give comfort medication at visit 8 for Day 8, 9, and at Day 10 for visit 10, 11, 12, 13, 14 and 15. No comfort medication will be given by the study after Day 15. Comfort medication needed after Day 15 will be considered non-study follow-up care. Patients can get comfort medications even if they don't opt for XR-NTX).

* Optional. Subject can opt not to receive this treatment. The Study Physician will discuss with the subject other available options. All assessments for Day 8 except the challenge and XR-NTX will still be collected.

9.1.4 Subjects who remain inpatient. Subjects who remain inpatient for a Day 9 naloxone challenge and XR-NTX administration if they are interested but do not qualify on day 8, will be given the challenge as per the procedures for Day 8. Those who fail a second challenge will be counted as having an unsuccessful detoxification and be referred to the most appropriate and available treatment. Subjects will be discharged after the XR-NTX injection (or failed challenge) and asked to return to the study outpatient clinic for their scheduled Day 10, and Day 15 visits according to the intent-to-treat design.

9.1.5 Phase 4: Outpatient Follow-up Visit Assessments (Days 10 and 15)

Assessments at Day 10: (NO POSS)

1) CBC with diff and PLT, chemistry, calcium, UA with reflex microscopy (Magnesium and INR

need not be repeated).
2) Fentanyl test (urine)
3) Xylazine test (urine)
4) UDS
5) ISI
6) SOWS-Gossop
7) COWS
8) Vital signs
9) Adverse events, concomitant medications
10) C-SSRS
11) Comfort Medication (PRN)

Assessments at Day 15: (NO POSS)
1) Physical/weight
2) Urine Pregnancy test for women
3) Fentanyl test (urine)
4) xylazine test (urine)
5) ISI
6) SOWS-Gossop
7) COWS
8) Vital signs
9) Adverse events, concomitant medications
10) TLFB
11) CGI
12) HAM-D
13) HAM-A
14) C-SSRS
15) Comfort Medication (PRN)
16) UDS

9.1.6 Optional Safety Visit and F/U Day 36 Visit for Second XR-NTX Injection)

Subjects may be asked to come in after the last Day 15 visit for one safety visit, if the PI or study team feels it is necessary, up to 30 days past the end of study visit or 30 days past the F/U Day 36 visit. This safety visit may not be needed for all subjects. The assessments collected will include: CBC, CMP, Ufentanyl, Uxylazine, and a urine drug screen. Compensation will be given for travel.

Subjects may be scheduled to receive a second XR-NTX dose in the outpatient research clinic up to 5 weeks after the Day 8 or 9 injection if they wish to continue XR-NTX and have been unable to find a community provider. Subjects who present for day 36 (+/- 7 days) will undergo the following procedures:

1. A urine drug screen
2. Pregnancy test (women)
3. Naloxone challenge if there is uncertainty about absence of physiologic dependence
4. XR-NTX injection

9.2 PRIMARY OUTCOME ENDPOINT

Reduction in subjective withdrawal as measured by the SOWS-Gossop.

9.3 SECONDARY ENDPOINTS

Completion of detox and receipt of antagonist treatment

10.0 SUBJECT SELECTION AND DISCONTINUATION

All subjects will be recruited at the site level through newspaper and social media advertising, primary care practices and outpatient facilities, and community referrals. For a more detailed description of recruitment procedures, see section 10.3. Once a potential subject has been identified, a CRA or another study staff person will screen him/her for admission/exclusion criteria. For respondents that appear eligible and are interested in participating, an appointment will be made to come to the research facility and review study procedures, expectations, and other information in more detail. The CRA or another study staff person will explain the study and the potential subject will be asked to read the study enrollment consent, and encouraged to ask questions about anything that is unclear. Subjects still interested in participating will be asked to take a 10-item pre-enrollment quiz and correctly answer 9 of 10 true/false questions about the study to be eligible to continue (three additional tries permitted). A study physician, or other designated clinical staff person will do the medical history and physical. A nurse, physician, medical assistant or other designated personnel will draw blood for screening labs, arrange for an ECG whose results will be reviewed by the PI at the site, and if a problem is found, will transmit a copy to the Study Cardiologist, and/or the study Medical Monitor and/or the Lead Study PI to review before a decision is made as to the next step. If Cardiology is used, each site should have a decision sent back to the site within 24 hours. Upon confirmation that all medical and inclusion and no exclusion criteria are met, a study staff person will randomize the subject and make an appointment for admission to the collaborating inpatient unit.

10.1 INCLUSION CRITERIA

1. Male and/or female subjects ≥ 18 years of age
2. Meet DSM-5 criteria for an Opioid Use Disorder with physiologic features. Have 2 or more of the 11 DSM 5 criteria for opioid disorder including tolerance and withdrawal features in the last 12 months
3. Interested in opioid antagonist treatment
4. Have used opioids in 20 or more of the last 30 days
5. Have a stable address in the local area; not planning to move; have documents for ID check
6. Absence of medical or psychiatric conditions that are likely to interfere with study participation
7. Have a 12 lead ECG demonstrating a QTc ≤450 msec and a QRS interval ≤120 msec. The site PI has the final determination for inclusion into the study for ECGs unless there is a question of QT prolongation or other factors (QTc/Fri uses the Fridericia formula (QTc = QT/RR(1/3)). If consultation is needed, the PENN cardiologists and medical monitor should be contacted
8. If female, have a negative pregnancy test and use adequate contraception if of childbearing potential

10.2 EXCLUSION CRITERIA

1. Current psychotic disorder (bipolar I, schizophrenia, major depression with psychotic features,) as defined by the MINI
2. An alcohol, benzodiazepine, or other sedative use disorder with physiological features that require medication for detoxification
3. History of allergy or other serious adverse event due to treatment with pregabalin, XR-NTX, or lofexidine
4. Pending incarceration in the next 30 days
5. Homicidal or otherwise behaviorally disturbed requiring immediate attention
6. High risk for suicide as determined by answering ‘yes’ to questions 4 and/or 5 on C-SSRS at screening
7. Blood pressure <90 mm Hg (systolic) or <60 mm Hg (diastolic). If this value is out of

normal range, the investigator and study Clinician will decide subject inclusion or exclusion on a case-by-case basis, (can use manual blood pressure check if considered necessary)

8. Heart rate and/or pulse<50 bpm at screening-sitting
9. An Estimated Glomerular Filtration Rate eGFR<90 mL/min/1.73m^2
10. A History of, or current Seizure disorder (excluding childhood febrile seizures)
11. Inability to read and/or understand English. For example, unable to understand the informed consent as demonstrated by failing to answer 9/10 questions correctly on the quiz
12. Pregnant or breastfeeding
13. Currently taking sympathomimetic drugs, or a thiazolidinedione antidiabetic
14. An ALT and/or AST test that is ≥4X the upper limit of normal
15. A Child-Pugh score >7
16. Currently receiving opioids for pain management
17. In a treatment study where medication was administered in the last 30 days
18. Currently using medications that are known to be strong or moderate inhibitors of CYP2D6 such as fluoxetine, paroxetine, mirabegron, bupropion, quinidine, terbinafine, cimetidine, cinacalcet, duloxetine, or fluvoxamine
19. In a methadone maintenance or buprenorphine treatment program within the last 30 days

Note: Subjects who fail screening for other than medical or severe psychiatric reasons can be reevaluated by staff at a later date.

10.3 SUBJECT RECRUITMENT AND SCREENING

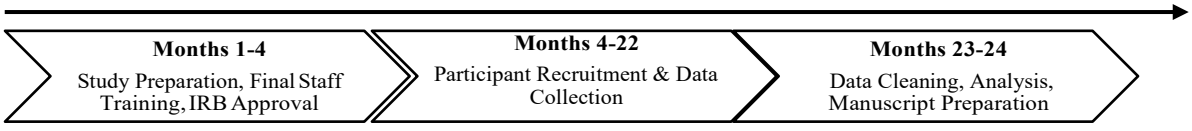
10.3.1 Participating Clinics or Data Collection Centers

1. Penn Presbyterian Medical Center Philadelphia PA
2. New York State Psychiatric Institute, Columbia University New York New York
3. Mountain Manor Treatment Center Baltimore Maryland

Subjects will be recruited from: 1) the community in Philadelphia and other out-patient Clinics in Philadelphia, 2) the surrounding communities of the New York State Psychiatric institute and other outpatient clinic, and, 3) the Mountain Manor area and other clinics through advertising in local media, newspapers, social media, flyers, transit advertising, and word-of-mouth.

10.3.2 Study time Table

Figure 3: Projected Timetable

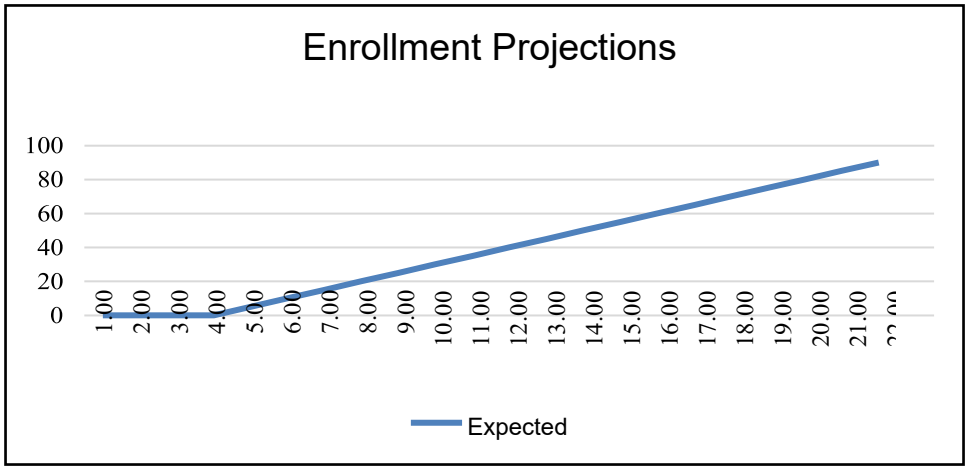


The proposed study will be completed within 2 Years

- Months 1-4: September 2019 – January 2020 – IND receipt, IRB approval, protocol finalization, case report forms finalized, staff hiring and training completed
- Months 4-22: January 2020 - July 2021: Recruitment, study explained and informed consent obtained outpatient follow-up for 90 participants.
- Months 23-24: August 2021: Final data clean-up to ensure accuracy and completeness.

10.3.3 Enrollment Projections

Figure 4 : Enrollment Projections



10.4 TARGET POPULATION DISTRIBUTION (GENDER, RACE, ETC.)

Men and women 18+ years of age. We expect the sample to include 30% women and 30-40% minorities (predominantly African American). Female-focused recruitment strategies include direct appeals to female medical specialties such as OB-GYN offices. Children under the age of 18 will not be included because the safety and effectiveness of XR-NTX extended-release naltrexone has not been established in pediatric patients.

10.5 RECRUITMENT OF FEMALE SUBJECTS

Lactating or pregnant females are an exclusionary factor for this study. For the purpose of guidance, the following methods are considered acceptable means of birth control for this study:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal; transdermal)
2. Progestogen-only hormonal contraception associated with inhibition of ovulation such as Mirena (a progesterone-only IUD) or similarly-acting oral, injectable, or implantable medications; an intrauterine device (IUD) or hormone-releasing system; bilateral tubal occlusion
3. Diaphragm + spermicide; cervical cap; condom; vasectomized partner; sexual abstinence

During the study and for a week after the subject's final study treatment the research staff will explain to the female subject that they will need to take safety measures to prevent pregnancy by not having sex or by using a medically accepted method of birth control such as stated above. Before the study begins, the research staff will be asked which form of birth control the subject is currently using, or if they have had a tubal ligation, bilateral oophorectomy (both ovaries removed), or hysterectomy and thus no longer require hormonal or barrier contraceptives to prevent pregnancy.

If during the 7-day dosing phase of this study we find that a female subject has become pregnant, we will discontinue all medications, make the appropriate treatment referral, and discharge the subject from the medication phase of the study, but ask that she continues to make the 10 and 15-day follow-up visits.

10.6 OBTAINING INFORMED CONSENT

Study procedures will be described by research staff and include the following: Description of the study medication and how it is normally used; rationale for why it is being studied for opioid detoxification; need to begin the study in an inpatient setting; frequency of dosing and length of treatment; potential side effects of pregabalin, lofexidine, and XR-NTX; safeguards and emergency procedures; and option to receive sustained release injectable naltrexone or be referred to another treatment of one's choice upon study completion. Collection of lab specimens (number of venipunctures and urine specimens required) will be reviewed as will eligibility, number and frequency of the research interviews and self-assessments, and payments for participation and completion of follow-up assessments.

Subjects will be assured that participation is voluntary, withdrawal from the study will not jeopardize future treatment, and that if at any time the research or clinical teams feel subjects need another treatment they will be referred to the most available treatment of their choice. All subjects will be informed of the potential risks and benefits including medication side effects, and that their participation may be discontinued at any time because of serious medication side effects, non-compliance with treatment, new information regarding the safety of study medications, or if continued participation is considered to endanger the welfare of subjects or others.

At the end of the consent review session, a 10-item, multiple choice quiz will be given before the subject signs the consent. Subjects scoring below 90% correct will receive additional instructions regarding the study and consent, and the quiz will be administered until they score at least 9/10 questions correctly with a review of the one incorrect question (3 retries allowed). Participants will be given a copy of the consent form with the name and telephone numbers of the investigative team and the Chair of Penn's Institutional Review Board (IRB) along with a 24-hour emergency contact.

10.7 SCREEN FAILURES

Those who screen fail are defined as those who sign a consent to participate but are not randomized because later assessments find that they do not meet study inclusion criteria. An enrolled subject is defined as one for whom written informed consent was obtained, all eligibility criteria are met, and he/she has been randomized to receive study medication. Screen failures will be given referrals to other available treatments. A list of screen failures, not identified by protected health information, will be maintained according to the reason of failure throughout the study. The study will use screening numbers before randomization numbers are assigned.

10.8 EARLY WITHDRAWAL OF SUBJECTS

All randomized subjects are included in the intent-to-treat analysis. After day 15, or at termination for patients who discontinue the trial prematurely, subjects will be asked to complete the following procedures and assessments: physical exam, vital signs, weight, adverse events; concomitant medications; blood samples for chemistry, CK, CBC with diff and PLT, liver function; urinalysis with reflex microscopy, urine drug toxicology screen; a fentanyl urine test, a xylazine urine test, a pregnancy test for females; and the Clinical Global Impression. ECG will be obtained for early terminators. Subjects will be referred to the most appropriate and available treatment and attempts will be made to obtain these data unless the subject requested they not be contacted or cannot be located.

Subjects will be informed at the consent session that medications could be discontinued if (at the discretion of the principal investigator or site physician): 1) Intolerable side effects occur, or 2) Extreme lab values with a repeat test occur, or that he/she may be discontinued from the study due to

development of psychiatric or medical problems that require a more intensive intervention than provided by the study. Examples are psychiatric symptoms that require inpatient treatment (suicidal ideation, acute psychosis, acute mania); clinical deterioration or a change in status that requires admission to an inpatient medical service; or development of behaviors that compromise safety of the subject or staff. Referrals for care will be made and reasons for subject discontinuation from the study medication and/or clinical trial will be documented on the End of Study Final Evaluation Form.

10.9 FOLLOW-UP OF WITHDRAWN SUBJECTS

Standard procedures developed at the treatment sites will be used to locate missing subjects. They include identification and verification of home and work phone numbers, emergency contacts, and persons who might know where they can be reached. A subject's phone number will be called during screening to make sure it is valid and to make further screening appointments if necessary. Subjects who missed an appointment will be re-contacted on the day of the missed appointment by phone, then by letter and finally by registered mail. Contacts will be attempted at least twice a week for a minimum of two weeks, then less frequently by mail. Subjects are not considered lost to follow up until the study has been completed and the database is ready to be closed. All documents regarding phone contacts (attempted and connected) will be noted in a study phone contact form and placed in the individual's study binder.

10.9.1 Follow-up of subjects who need second injections. Subjects who might need to receive a second injection of XR-NTX because they were unable to connect to a community clinic to continue XR-NTX treatment will be offered a second injection up to week 5 at the research clinic. Study staff will again refer them to list of clinics that was given to them at the completion of visits 8 or 9. Subjects will not be paid for a second injection as it is not a formal study visit.

10.10. DATA COLLECTION

10.10.1 Data Handling & Record Keeping. Data will be entered at each site into a REDCap program constructed by the Data Management Unit at the Penn Addiction Treatment and Research Center.

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

10.10.3 Case Report Forms (CRFs). As described in the "assessments" section, they include all primary data collection instruments and are entered and checked through the Penn data management system (REDCap). This includes all concomitant medications as well as records of adverse events. Each site will be responsible for reviewing and maintaining data entry of all case report forms into REDCap data system. All adverse events entries and serious adverse events entries must be reviewed by the study nursing staff and the site PI. If the PI cannot resolve the serious designation of an event, the site should contact the medical monitor (Dr. Woody). All paper sourced assessment documents should be recorded into REDCAP daily. Where ever possible, direct entry into RECAP is requested.

10.11 STUDY MEASURES; SEE TABLES 1 FOR SCHEDULES OF ADMINISTRATION

1. **Medical History:** Done by the appropriate clinical delegated individual at screening
2. **Physical/Weight:** Done at Screen; and at Day 15
3. **Pulse and blood pressure:** done sitting and standing 1X at screen, done Day 1 through Day 7 done before receiving Study Medication and 1 - 2 hours after receiving medication, 1X on Day 8, 1X (sitting only) on Day 10 (sitting only), and 1X on Day 15
4. **ECG:** 1X at Screen, 1X each day for Day 1 through Day 7
5. **Complete Blood Count with diff and PLT:** Done at Screening and Day 10
6. **Chemistry and calcium:** Done at Screening and at Day 10 or Day 15 if not obtained at Day 10
7. **Magnesium Screening** (magnesium need not be repeated at EOS)
8. **Creatine Kinase** at screening and Day 8, and early termination
9. **Hepatitis B and C** done at screening
10. **Urinalysis with reflex microscopy:** Done at Screening and Day 10
11. **Urine Toxicology Drug Screen.** CLIA Waived and FDA approved on-site test with Buprenorphine, or get an additional buprenorphine test, done at screen, day 8/9, day 10, and day 15.
12. **Urine Fentanyl**. Done at Screen, Day 1, Day 8/9, Day 10, and Day 15.
13. Urine Xylazine . Done at Screen, Day 1, Day 8/9, Day 10, and Day 15.
14. **Urine pregnancy test**: Screen and Day 1, Day 8/9 prior to the XR-NTX injection, and at Day 15
15. **Adverse Events**: Collected by research staff at each visit, Day 1 through Day 15
16. **Clinical Global Impression Scale (CGI;** Guy,1976): A brief severity rating of overall health at time of interview using a 7-point Likert scale. Completed by a study staff person and the subject. Administered at day 1, day 8, and EOS
17. **Clinical Opioid Withdrawal Scale** (COWS; Wesson & Ling, 2003): An 11-item, staff administered instrument that measures objective signs of opiate withdrawal. Done 1X at screen, 2X daily Day 1 through Day 7, 2X (naloxone challenge) on Day 8* (optional), and 1X on Day 10, and 1X Day 15
18. **Short Opioid Withdrawal Scale** (SOWS-Gossop; Gossop, 1990): A 10-item, staff administered scale that measures patient's perceptions of opiate withdrawal. Done 1X at screen; 2X daily Days 1 - Day 7; and 1X on Days 8,10, and 15.
19. **CONCOMITANT Medication** (CONMEDS): Any prescribed or non-illicit non-Study Medications used 30 days before screening, and on Day 1 through EOS
20. **COMFORT Medication**: See prescribed medications given for comfort during Day 1 through Day 7, AND Days 8, 10, and 15 by inpatient or outpatient Staff. Only the following comfort medications provided by the study ***are recommended*** to be given as needed: ondansetron 4 mg or 8 mg tid PO PRN for nausea and vomiting, trazodone 100 mg HS PRN insomnia, loperamide 2 mg qid PO PRN diarrhea, and a non-steroidal such as Ibuprofen 600 mg qid PO PRN for aches and pains or acetaminophen 650 mg (2 tablets 325 mg) PO qid PO PRN, cyclobenzaprine 5 mg tid PO PRN for muscle aches and pains, and hydroxyzine 25 mg qid PO PRN anxiety. In cases of QTc prolongation that are not >550ms or judged to require

stopping study medications, diphenhydramine 50 mg hs PO PRN may be used for insomnia, and trimethobenzamide 300 mg qid PO PRN for nausea. These medications will come from the standing inventory at each site. Other comfort medications can be substituted, however the recommended medications should be used first. Any comfort medication that is used must be recorded on the comfort medication CRF on whichever day they are used. All comfort meds ingested on Day 8 (or Day 9) whether ingested when an inpatient or outpatient should be recorded on the comfort medication form for those days. It is permissible to give comfort medication at visit 8 for Day 8, 9, and at Day 10 for visit 10, 11, 12, 13, 14 and 15. Comfort medications on Day 15 are counted as what was taken on the calendar day of day 15. No comfort medication will be given by the study after Day 15. Comfort medications on Day 15 are counted up to and including what was taken at the time of visit on calendar day 15. Comfort medication needed after Day 15 will be considered non-study follow-up care. Patients can get comfort medications even if they don't opt for XR-NTX).

21. **Hamilton Depression Rating Scale** (Ham-D**;** 1960): A 20-minute, 24- item, research staff- administered instrument. Done 1X at screen, 1X Day 8, and 1X Day 15
22. **Hamilton Anxiety Scale (Hamilton A; 1959).** A 5-minute, 14-item, research staff-administered instrument. Done at 1X at screen, 1X Day 8, and 1X Day 15
23. **Insomnia Severity Index** (ISI; Bastien, 2001). 7-item, research staff administered scale; takes about 3 minutes; 1X at screen, 1X Day 1 through Day 7, 1X day 8, 1X Day 10, and 1X Day 15
24. **Mini-International Neuropsychiatric Interview for DSM- 5 (**MINI; Sheehan 1998): Identifies current and lifetime DSM-5 Axis I major psychiatric disorders. Takes about 20 minutes; administered by trained clinician at Screen.
25. **Opioid Craving Visual Analog Scale** (VAS; McMillan & Gilmore-Thomas 1996): Self-administered 100 mm scale. Done 2X daily Day 1 through Day 7, 1X on Day 8
26. **Pasero Opioid-Induced Sedation Scale** (POSS; Pasero, 2009): Brief, study staff or designee administered scale. Done 4X daily (before each dose) Day 1 through Day 7, 1X on Day 8
27. **Timeline Follow-Back Interview** (TLFB; Sobell & Sobell, 1995**):** A semi-structured staff administered interview of self- reported drug use over the past 90 days at screen and EOS (2- weeks).
28. **The Columbia–Suicide Severity Rating Scale (C-SSRS)** is an assessment tool that evaluates suicidal ideation and behavior. It is given at screening and every day from Day 1 through Day 8, and at day 10 and 15.

10.12 SAFETY ASSESSMENTS

Total number of adverse events leading to medication discontinuation (in judgment of study physician), patients reporting at least one adverse event, clinical lab results, ECG, vital signs, weight and evidence of worsening (by urine drug screen results and TLFB results) will be considered in assessing safety.

See Table 5 for the list of laboratory tests to be performed. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. All study-required laboratory assessments will be performed by the site laboratory.

The Site Investigator must review laboratory reports and document this review, and laboratory reports must be filed with source documents. Clinically relevant changes that lead to changes in study

drug, study participation, or use of concomitant treatment will be recorded as AEs on the AE CRF. Clinically significant abnormal laboratory findings are those not associated with the underlying disease unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values that are judged significantly abnormal during study participation should be repeated. If they do not return to normal/baseline within a period of time judged reasonable by the Investigator, the likely cause should be identified, an AE form completed, and the Sponsor notified.

Table 5. Clinical Laboratory Tests to Be Performed for This Study

CBC	**CMP**	**Urinalysis**
Hemoglobin		Urine Color
Hematocrit		Appearance
Red blood cells	Sodium	pH
Mean corpuscular volume	Potassium	Specific gravity (concentration)
Mean corpuscular hemoglobin	Chloride	Protein
Mean corpuscular hemoglobin concentration	Carbon Dioxide	Glucose
Red blood cell distribution width	Glucose	Ketones
White blood cell count	Creatinine	Bilirubin
White blood cell Differentials:	Albumin (ALB)	leukocyte esterase
Neutrophils	Total protein	Nitrite
Lymphocytes	Calcium	Blood
Monocytes	Phosphorus	Urobilinogen
Eosinophils		
Basophils	Aspartate aminotransferase (AST)	
	Alanine aminotransferase (ALT)	**UA Microscopy**
		White blood cell count
Platelet count	Total bilirubin	Red blood cell count
		Epithelial cells
	Alkaline phosphatase	Bacteria
Other:	Blood urea nitrogen	Yeast
INR	Direct Bilirubin	Crystals
CK		Cast
Magnesium		Mucous
HCV Antibody		
HBcAb (core)		
HBsAg (surface antigen)		
HBsAb (surface antibody)		

Subjects who are administratively withdrawn for medical issues will be followed up to document the outcome of the event. Subjects who voluntarily withdraw from the medication phase will be asked to complete the other visits as scheduled. Subjects who voluntarily withdraw from the study and wish no further contact will not be followed up. The reasons for all discontinuations will be documented in a study source document.

10.13 PROTECTION OF SUBJECTS

Potential subjects will be screened for conditions that would preclude use of PGB, LFX or XR-NTX. Adverse events will be monitored by medical and research staff on a daily basis. Subjects will be given a 24-hour emergency number they can call if necessary. If the subject is discontinued from study treatment due to, an AE, he/she will be followed by medical staff until it resolves or becomes stable. Potential subjects will be excluded if they have a history of a severe psychiatric disorder (schizophrenia, bipolar I, depression with suicidal attempts); impairment of renal function; severe liver disease; participated in a medication study within the last 30 days; have an illness which may require hospitalization during the study; history of allergy or other SAE due to treatment with PGB, XR-NTX or LFX, taking sympathomimetic drugs, or a thiazolidinedione antidiabetic; or impending incarceration;. Pregnant females or women who refuse to use acceptable forms of birth control will also be excluded.

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10.13.1 Venipuncture. Venipuncture will be carried out with good aseptic technique by a nurse or physician or qualified designated person.

10.13.2 Risks Associated with Study Procedures

- Behavioral Ratings: Risks are minimal and limited to breach of confidentiality or becoming anxious or embarrassed by some of the questions. Procedures to protect confidentiality and reduce study-related anxieties are described in section 22.0.
- Potential Benefits: Subjects benefit from close medical and psychiatric attention over and above that which they receive in an inpatient detoxification.

10.13.3 Risk Benefit Ratio: The first step for transitioning from opioid addiction to antagonist treatment is detoxification, often using an alpha-adrenergic agonist such as clonidine or LFX. However, patients often drop out due to the dysphoria and other uncomfortable subjective effects of withdrawal and do not transition to naltrexone. The recent studies summarized above provide data to suggest that PGB can reduce these subjective effects, however the risks and benefits of a /LFX combination have not been studied. Both medications are FDA-approved and we have no reason to think they cannot be safely used together, but they have not been tested.

Identifying a dosing combination that improves detoxification success and transition to antagonist treatment has the potential to improve the number of patients that benefit from its relapse and overdose protection effects. For these reasons, we think that the risk/benefit potential of this dosing combination is significant in the likely event that it is safe and effective.

10.13.4 Medical Management of Adverse events. Evaluation and management of AE's may include additional medication, transfer to a medical unit, reduction in study of medication, temporary cessation of study drug, or early termination from the trial if necessary.

11.0 METHODS FOR ASSIGNING SUBJECTS TO TREATMENT GROUPS

11.1 RANDOMIZATION

Dr. Lynch will develop a program using computer-generated, randomly permuted blocks within each site

that are stratified according to male/female. Upon completing screening assessments, research staff will request randomization be performed by the site research pharmacy. The patient will be sequentially assigned to the next treatment based on male/female status. At all sites, patient treatment will correspond to a unique randomization number.

Penn IDS will upload the randomization lists into a Treatment Unmasking Program, per IDS SOP-309. Access to this trial within the program will be provided to authorized Penn users. In the event of an emergency, unmasking can occur at any time using the subject's assigned randomization number. The user will not be unmasked to the treatment of other subjects. For other sites, Dr. Lynch will give the randomization list to PENN IDS who will be responsible for maintaining the randomization blind.

11.2 RANDOMIZATION OF PLACEBO AGENT

The Penn IDS will prepare the placebo medication as matching blinded capsules containing Lactose Monohydrate, Spray-Dried, NF. Blinded placebo capsules will be packaged into blister packs along with lofexidine tablets, in separate compartments that are labeled for dosing times on days 1-7 and ship them to the research sites.

11.3 BLINDING OF STUDY DRUG

Penn IDS will prepare blinded PGB capsules by over-encapsulation of the drug into shells matching the placebo capsules. Blinded PGB capsules will be packaged into blister packs along with LFX tablets, in separate compartments that are labeled for dosing times on days 1-7 and ship them to the research sites.

11.4 RECEIPT OF XR-NTX

The study will use XR-NTX in 380 mg kits supplied by Alkermes, Inc. Alkermes will ship directly to each site a shipment of 20 XR-NTX kits per site. Sites will be responsible for receiving, storage, administration, and accountability for each subject. Sites must use the DIMS system for accountability of dispensed Vivitrol to control product expiration dates. Sites will also be responsible for the destruction and expiration of unused drug (see destruction procedures for XR-NTX). Accountability, expiration, and destruction will be recorded on a XR-NTX accountability log. Each site will administer XR-NTX according to the package insert instructions.

11.5 RECEIPT OF NALOXONE

Subjects will be offered a naloxone challenge on day 8 using 0.8 mg or 1.0 mg I.M. If the COWS scores do not rise above 10 within 15-30 minutes, subjects will receive an injection of XR-NTX* given by a study nurse (or NP, etc.), physician (or PA, etc.) or other licensed and trained health care provider. Each site will acquire their own supply of naloxone and will be responsible for the storage, accountability, and dispensing throughout the trial. (*Naloxone challenge and receipt of XR-NTX is optional. Subject can request guidance on another form of treatment).

11.6 PREPARATION AND ADMINISTRATION OF STUDY DRUG

Study medication will be prepared by the Investigational Drug Service at the Hospital of the University of Pennsylvania (phone: (215-349-8817). It will be sent to the sites and stored and dispensed by their respective research pharmacies/or designated unit at the three sites.

11.7 COMFORT MEDICATIONS

In addition to study medications, subjects can receive, as needed, the following "comfort" medications: ondansetron 4 mg or 8 mg tidPO PRN for nausea and vomiting, trazodone 100 mg HS PRN insomnia, loperamide 2 mg qid PO PRN diarrhea, and a non-steroidal such as Ibuprofen 600 mg qid PO PRN for aches and pains or acetaminophen 650 mg (2 tablets 325 mg) PO qid PO PRN, cyclobenzaprine 5 mg tid PO PRN for muscle aches and pains, and hydroxyzine 25 mg qid PO PRN anxiety. In cases of QTc prolongation that are not >550ms or judged to require stopping study medications, diphenhydramine 50 mg hs PO PRN may be used for insomnia, and trimethobenzamide 300 mg qid PO PRN for nausea. It is permissible to give comfort medication at visit 8 for Day 8, 9, and at Day 10 for visit 10, 11, 12, 13, 14 and 15. No comfort medication will be given by the study after Day 15. Comfort medications on Day 15 are counted up to and including what was taken at the time of visit on calendar day 15. Comfort medication needed after Day 15 will be considered non-study follow-up care. Patients can get comfort medications even if they don't opt for XR-NTX).

Each site will maintain records on use of these medications on the Comfort Medication Log. Comfort medications will be acquired, stored, and dispensed by each site's research pharmacy or designated person. Store according to the information found in the package insert.

11.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications are defined as any medications taken before enrolling in the study that continues into the study and any medication (not comfort medication or study drugs) that are prescribed during the study. They are not the study medications (those provided in the blister packs). They must be recorded on the study concomitant medication form and entered into the database. For example, a diuretic for hypertension medication. All field (start date, dose, times per day, stop date, etc.) must be captured and recorded for the month before the initial screening visit through the follow up assessment.

11.9 RULING OUT CURRENT PHYSIOLOGIC DEPENDENCE BEFORE XR-NTX ADMINISTRATION (NALOXONE CHALLENGE)

The COWS will be performed before administering XR-NTX, to assess the subject's signs/symptoms of withdrawal. Naloxone administration should start with a split dose of 0.2 mg first, wait 10-20 minutes, then 0.6 mg (0.8 mg total). Following in the challenge, the patient should be monitored for 15-30 minutes for the appearance of opioid withdrawal. The absence of physiologic opioid dependence is seen by COWS scores that are < /=10. If clinically significant withdrawal is shown, a study physician will treat it with one or more of the approved non-narcotic "comfort" medications.

1. Signs and Symptoms of a positive naloxone challenge might include:

    - Objective—tearing, sweating, goose bumps, shakes, vomiting, pupillary dilatation, vital sign increases
    - Subjective—feeling of temperature change, joint and/or muscle pain, bone pain, nausea, abdominal cramping, skin crawling

2. If opioid abstinence syndrome is precipitated by naloxone, symptoms will be apparent within a few

minutes and maximal within 20 minutes after administration, but the patient must be observed for 15-30 minutes

If manifestations of opioid withdrawal are evident following the naloxone challenge ***do not*** initiate naltrexone therapy due to potential risk of precipitating more severe and prolonged withdrawal with XR-NTX; the naloxone challenge test may be repeated in 24 hours (inpatient Day 9) in these patients.

If withdrawal symptoms are present, the patient should be treated with withdrawal reducing medication or equivalent and observed until symptoms have resolved (about 20 minutes).

If evidence of withdrawal is absent, naltrexone therapy may be initiated. Please note that even minor and/or transient GI symptoms following naloxone challenge be considered evidence of withdrawal since patients with such symptoms will often develop severe and disturbing GI symptoms if XR-NTX therapy is then initiated.

3. Signs and Symptoms of positive naloxone Challenge might include:

- Objective—tearing, sweating, goose bumps, shakes, vomiting, pupillary dilatation, vital sign increases
- Subjective—feeling of temperature change, joint and/or muscle pain, bone pain, nausea, abdominal cramping, skin crawling

4. If an opioid abstinence syndrome is precipitated by naloxone, symptoms will be apparent within a few minutes and maximal within 20 minutes after administration.

If manifestations of clinically significant opioid withdrawal are evident following the naloxone challenge test, do not initiate naltrexone therapy due to potential risk of precipitating more severe and prolonged withdrawal with naltrexone; naloxone challenge test may be repeated in 24 hours (inpatient Day 9) in these patients.

If withdrawal symptoms are present, the patient should be treated with the clinically most appropriate withdrawal reducing medication and observed until symptoms have resolved (about 20 minutes).

If evidence of withdrawal is absent, naltrexone therapy may be initiated. Please note that even minor and/or transient GI symptoms following naloxone challenge be considered evidence of withdrawal since patients with such symptoms will often develop severe and disturbing GI symptoms if XR-NTX therapy is then initiated.

12.0 RECEIVING, STORAGE, DISPENSING AND RETURN

12.1 RECEIPT OF PGB, LFX, AND XR-NTX

PGB and LFX will be prepared in blister packs and shipped to the research pharmacies or designated persons at each treatment site by the Investigational Drug Service at the University of Pennsylvania. Resupply of packs is requested by email to: PennIDS@pennmedicine.upenn.edu. Upon receipt of study treatment medication, an inventory is to be completed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff count and verify that the shipment contains all items noted in the shipment inventory. Any damaged or unusable study drug in a shipment (active drug or comparator) will be documented in the study files. XR-NTX will be shipped by Alkermes directly to the sites. The sites are responsible for destruction of the study medication per the site's documented procedures and regulations for controlled substances.

12.2 STORAGE OF INVESTIGATIONAL MEDICATION

Study medication will be sent from the Penn Research Pharmacy to the sites and stored at their research

pharmacies or designated research medication storage sites. It must be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C - 30°C (59°F to 86°F). Each site should maintain temperature records throughout the trial and be able to provide them upon request. If sites have a temperature excursion relating to study drugs, please contact the Investigational Drug Service at 215-349-8817.

12.3 DISPENSING OF INVESTIGATIONAL MEDICATION

After randomization, study drug will be dispensed to each subject from an assigned blister pack according to his/her randomization number at the appropriate times by nurses on the inpatient units at the collaborating site. Unused study medication will be collected per site SOP.

12.4 RETURN AND DESTRUCTION OF STUDY DRUG

All unused study medication is to be saved, documented, and returned to the Research Pharmacy or designated person at each site and destroyed at the site according to SOPs for that site. Upon completion of the study, there will be a final reconciliation of study medication that was provided, consumed, and returned. Penn IDS will maintain inventory and subject accountability in Vestigo, an electronic, web-based pharmacy research program. A similar inventory reconciliation will be performed at each site. If electronic recording is not used at the collaborating sites, the research pharmacy or designated person(s) at the site will keep records for the reconciliation of administered, spoiled, expired, and unused drug. Paper logs must be signed and dated and any discrepancies noted will be investigated, resolved, and documented. Unused study drug will be destroyed in a manner consistent with regulations governing Schedule V medications. Medication should not be destroyed until the QA monitor has audited the drug accountability log.

12.5 DISPENSING XR-NTX

On day 8 or 9, a 380 mg injection of XR-NTX will be administered according to subjects' consent and evidence that detoxification has been successful, by a negative naloxone challenge. Dosing will be maintained in a Drug Accountability Log and recorded in RedCap. Subjects who are unable to find an outpatient provider will be offered a second dose of XR-NTX up to 5 weeks after day 8 or 9 (day 36 $\pm$ 7 days).

12.6 STUDY DRUG ACCOUNTABILITY

US WorldMeds LLC will provide LFX and send it to the University of Pennsylvania's IDS pharmacy. Penn IDS will acquire PGB for all sites and the supplies necessary for preparing active and placebo blister-packs. Alkermes, INC. will provide XR-NTX and will send it to each collaborating site. Comfort medications and naloxone will be acquired separately by each site.

All study drug received, dispensed, administered, and returned will be managed by study site personnel and site pharmacies for sites, and the Penn Investigational Drug Service for the PENN site. Medications must be used only as described in the protocol and by the appropriately licensed Investigators named in Form FDA 1572. Study staff will retain the original individual blister-cards, including those empty, partially empty, or full, as well as used and unused XR-NTX kits. Unused medications will be collected and handled as per site SOP. Disposition of any study drug lost or damaged must be documented on the site accountability log or by a report by the site pharmacy. Unused or expired study drug will be retained at the participating site or pharmacies until the site is monitored. After the monitor audit, unused medication can be destroyed according to their usual procedures and documented in the regulatory file.

13.0 STATISTICAL PLAN

13.1 DATA ANALYSES

Kevin Lynch, PhD, the CSA Statistician, and his staff will perform data analyses. Prior to analyses, standard data screening/cleaning procedures will be applied. These procedures will screen the data for data-entry errors, check for outliers, assess the extent and pattern of missing data, and check that appropriate assumptions of normality are met whenever necessary.

13.2 SAMPLE SIZE DETERMINATION

Power Analyses: The primary goal of this study is to determine if the PBG/LFX combination versus LFX/PGB-PLA is safe and effective in OUD individuals, and shows a reduction in opioid–related withdrawal effects greater than lofexidine alone. To assist in this determination, we provide power for the primary comparison of longitudinal subjective withdrawal measures, comparing the groups on rate of decrease across days, using a linear group by time effect for the mixed effects models described above. We have one primary outcome, so use an alpha level of 0.05, and we use two- sided tests. 90 subjects, approximately 30 from each of three sites (MMTC and PENN might have more than 30), who will be randomized into two groups, with 30 assigned to LFX/PGB-PLA, and 60 to LFX plus a starting daily dose of 400 mg of PGB and increasing to 600mg PGB on day 2. Assuming an overall dropout rate of 40%, and within-subjects' correlations of 0.5, the methods of Hedeker et al (Hedeker, Gibbons and Waternaux, 1999) show that this provides 80% power for a group by linear time interaction effect of Cohen's d=0.44 standard deviations between the two groups.

13.3 STATISTICAL METHODS

13.3.1 Primary Outcome - Reduction in SOWS-Gossop criterion. The primary outcome will be reduction in subjective withdrawal as measured by the SOWS - Gossop (scores range from zero to 30). The groups will be compared on the 14 repeated SOWS-Gossop responses obtained during the seven-day detoxification period, using linear mixed-effects regression models; the SOWS-Gossop total will be regressed on a three-level factor for site, and a two-level factor for medication group, with time and group by time effects. The covariance structure will include a random intercept and correlated residuals, with a random slope included if necessary for fit. Contrasts between the PGB group and the PGB-PLA group will be estimated from the model. Exploratory analyses of heterogeneity of dose effects across sites will be performed including a site by dose interaction term in the main model.

These models will provide valid estimates and tests if any missing data is statistically ignorable (Laird, 1998). Dropout may be associated with reports of subjective withdrawal, and will be ignorable if available subjective scores prior to dropout are predictive of dropout. To assess possible effects of non-ignorability on inference, we will perform sensitivity analyses using pattern- mixture models and selection models. For pattern mixture models, subjects are grouped on the basis of their pattern of missing data. Usually, rarely occurring patterns are grouped, so as to keep the number of pattern-groups at a manageable level. This grouping defines a nominal variable, which is then used as a predictor in the analyses, although a covariate representing missingness on a continuous scale can also be used. The regression coefficients associated with this variable, and its interactions with the other predictors, quantify how response-predictor relationships differ across the different patterns of missingness. Overall predictor effects may be found by averaging over the patterns (Little, 1993). For longitudinal data, subjects are usually stratified according to the visit after which they dropped out. Hedeker and Gibbons (1997), and Hedeker and Rose (2000), apply these methods to mixed effects models in longitudinal data. Selection models (Little, 1995; Kenward, 1998; Verbeke and Molenberghs, 2000) take a different approach, by explicitly modeling the probability of drop out, and incorporating the predicted probabilities

into the main longitudinal analysis. Heuristically, this can be thought of as a two-stage process, but usually the two steps are performed as part of a single model. Any approach to non-ignorability requires us to make assumptions on the variables associated with missing data, and on the form of the relationship between the variables and dropout. Comparisons between the predictions of the primary analyses, and each set of pattern mixture and selection models, provides some evidence for assessing the sensitivity of results to missing data.

13.3.2 Secondary Outcomes. Completion of and receipt of antagonist treatment: Our completion threshold criterion is based on the study of Fishman et al (2019), where completion of detoxification was defined as "proportion of participants completing the study, defined as having received at least 1 dose of study medication on day 7 and completing the 3.5- hour post dose SOWS-Gossop assessment on day 7. Receipt of antagonist treatment will be defined as completion of the process to receive antagonist treatment and receipt of the first dose.

We will define a three-category ordinal response: (1) failure to complete detoxification, (2) completion with failure to start antagonist treatment, (3) completion and receipt of antagonist treatment. We will compare these groups using ordinal logistic regression models, with a three-level factor for site, and a two-level factor for medication group, as the explanatory variables.

13.4 SAFETY OUTCOMES

13.4.1 Suicidality. We will compare the groups on presence of active suicidal ideation on the basis of the C-SSRS, which will be administered daily. We define Active Suicidal Ideation to be an endorsement of either Question 4 (active ideation without plan) or 5 (active ideation with plan). If there is sufficient variability in these repeated binary outcomes, we will compare the groups using a mixed effects logistic regression model, similar to the linear mixed effects models described above for the primary outcome; if variability is too low, we will use a (non-mixed-effects) logistic regression model to compare the groups on proportion of participants reporting active ideation at any time in the period

13.4.2 Sedation. The POSS will be administered four times a day on dose days, yielding a set of repeated measures on the POSS score for each participant. We will compare the groups on this score, using linear mixed effects models similar to those described above for the primary outcome.

13.4.3 Elevated Creatine Kinase. On day 8 of detoxification, participants will be classified as having elevated creatine kinase if their level is more than three times their screening level. We will compare groups on this response using a logistic regression model with site and group as explanatory variables.

13.4.4 Edema. We will compare groups on the proportion of participants whose study medications were discontinued due to peripheral edema, using a logistic regression model with site and group as the explanatory variables.

13.5 TOLERABILITY OUTCOMES

13.5.1 Achiness. The SOWS-Gossop scale will be administered twice a day. Item 10 yields an ordinal measure of achiness. We will use mixed effects ordinal logistic regression models, with site and group as the main explanatory variables, to compare the groups on their probabilities of the different ordinal levels.

13.5.2 Anxiety. Item 1 of the SOWS-Gossop yields an ordinal measure of anxiety, and we will compare the groups using mixed effects logistic regression models as for the Achiness item above.

13.5.3 Insomnia. The Insomnia Severity Index will be administered daily during detoxification, and yields a total score. We will compare the groups on the score using linear mixed effects models similar to those described for the primary outcome.

13.6 SUBJECT POPULATION FOR ANALYSIS

All subjects who are randomized will be analyzed according to the Intent-to-Treat study design.

13.7 ADVERSE EVENT RECORDING AND REDCAP SYSTEM ENTRY

AE names will be recorded based on the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms found in the REDCap Database. Information regarding adverse events (AEs) will be recorded in REDCap and on an adverse event log and will include the following:

- AE Description
- AE Code
- Expectedness
- Date of Onset/ Change in Severity
- Continuous or Intermittent
- Severity
- Seriousness
- Study Drug Relatedness
- Action Taken Regarding Study Drug
- Other Actions Taken
- Outcome

Coding will be from a list of terms provided to each site formulated using MedDRA medical terminology.

13.8 VITAL SIGNS

Vital sign data (HR and BP) will be presented as summary statistics of maximum (max) absolute values, max change from baseline, and time to max value during the 1-hour period after each dose of study medication. Data will be compared between groups and within groups by study day by Wilcoxon rank sum statistic. Effects will be considered statistically significant at a two-sided $p < 0.05$.

14.0 DATA MANAGEMENT

14.1 DATA ACQUISITION AND TRANSMISSION

14.1.1 Data Entry Methods. This study will use the University of Pennsylvania REDCap (Research Electronic Data Capture) data system for data entry capture. REDCap is a widely-used, secure web application that can be used to build and manage surveys and databases online. It provides audit trails for tracking data manipulation and user activity, and provides Data Queries options for documenting and controlling the process of resolving data issues using a data resolution workflow option.

Data will be collected by trained study staff using standardized forms with a study number to identify the participant. A code linking the participant to the study group will be kept confidential in a password protected database. The Physician, nurse practitioner, clinical research coordinator and Clinical Research assistants (CRAs) at each site will be responsible for collecting and checking clinical data at their site. All data entered will be cross-checked by an independent research monitor assigned to the project ensuring that all fields are completed appropriately, the database is complete and accurate, and corrections are done according to GCP requirement. Any inconsistencies/deviations will be documented and reviewed by the PI and reported to the required oversight departments IRBs etc.).

15.0 SAFETY AND ADVERSE EVENTS

15.1 DEFINITION OF ADVERSE EVENT (AE)

Any symptom, sign, illness, or experience that develops or worsens during the course of the study. Abnormal results of diagnostic procedures are considered AEs if they result in study withdrawal, are associated with a serious adverse event, lead to additional treatment or further diagnostic tests, and/or are considered by the investigator to be of clinical significance. Normal withdrawal events are not recorded as AEs unless extreme or exacerbated.

15.2 ADVERSE EVENT REPORTING PERIOD

The period during which AEs must be reported begins at study screening and ends at the last follow-up.

15.3 POST-STUDY AEs

At the last scheduled follow-up, the investigator and /or clinical staff will instruct each subject to report any subsequent event(s) that the subject or the subject's physician or treatment staff believes might reasonably be related to study participation. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated participation that may reasonably be related to the study. The sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a subject that has participated in the study. Patients who become pregnant during the study should be followed up to determine if there was any evidence of fetal harm or an abnormality.

15.4 ABNORMAL LABORATORY VALUES

A laboratory abnormality should be documented as an AE if any of the following conditions are met: 1) A repeat test confirms it; 2) It suggests a previously undetected disease and/or organ toxicity; 3) It requires active management; e.g. discontinuation of medication, more frequent follow-up assessments, further diagnostic investigation, etc.

15.5 HOSPITALIZATION, PROLONGED HOSPITALIZATION & SURGERY

Any AE that results in hospitalization or prolonged hospitalization will be reported as a SAE unless it involves detoxification for relapse to opioid dependence since they are common and expected in studies involving opioid addicted individuals. Any condition that requires surgery should be documented as an AE or SAE, depending on the need and length of hospitalization. However, neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization is for diagnostic or elective surgical procedures for a preexisting condition.
- Hospitalization or prolonged hospitalization is required for the study.
- Hospitalization or prolonged hospitalization for treatment of the disease addressed by the study unless it is a worsening or increase in the expected frequency of admissions.

15.6 RECORDING AE's

At each patient contact the research team will seek information on AEs by questioning and, as appropriate, by examination. Information on AEs will be recorded in a source document and the appropriate CRF. The course of each event will be followed until resolution, stabilization, or it has been determined that study treatment or participation is not the cause. SAEs that are ongoing at the end of the study will be followed up to determine their outcome. Any SAE that occurs after the study and is considered possibly related to it is to be recorded and reported.

15.7 REPORTING SAE's

The Penn IRB considers disability, hospitalization or prolongation of hospitalization, congenital defects, and life-threatening events to be SAEs that must be reported (orally, e-mail, fax) to the Penn IRB when they are identified if judged related or possibly related to the study, or unexpected. In such cases, a report to the Penn IRB and NIDA is to be filed within 5 working days. When additional information is available, a follow-up and/or final SAE report is to be filed. If the report is a narrative, the minimum necessary information at the time of the initial report should include: identifier, subject number, description of event, date of onset, current status, if study treatment was discontinued, reason why the event was serious, and whether it was related to study treatment or procedures. Copies of each report and documentation of IRB notification and receipt will be kept in the study file.

15.8 STUDY SPONSOR NOTIFICATION BY INVESTIGATOR

A serious adverse event must be reported to the study sponsor (Penn) by fax, email or telephone within 72 hours of when the event is reported to any of the study staff. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed or emailed to the study sponsor within 72 hours. The investigator will keep a copy of this SAE form on file at the studysite. Report serious adverse events by phone and facsimile to the study sponsor:

Kyle M. Kampman, M.D. kampman@upenn.edu (Sponsor)	215-506-3799 beeper	215-746-2988 fax
George E. Woody, M.D. woodyg@upenn.edu (Medical Monitor)	215-746-7702	215-746-2988 fax

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following **48 hours,** the investigator must provide further information on the serious

adverse event in the form of a written narrative if such information has been received. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

15.9 REPORTING DEATHS

The Penn IRB requires that investigators report a death within **24 hours** of staff becoming aware of it, if it was unexpected or indicates that participants or others are at increased risk of harm. Other deaths are to be reported within 72 hours regardless of whether they were related to study participation.

15.10 OTHER REPORTABLE EVENTS

The following are also reportable to the Penn IRB:

- Any AE that, even without detailed analysis, represents a SAE that is rare in the absence of drug exposure (i.e. agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any AE that would cause a change in the product information, protocol or informed consent, orwould prompt IRB action to assure protection of human subjects.
- Information that indicates a change to the risks or benefits of the research, in terms of severity or frequency as, for example: safety monitoring indicates that a side effect is more severe or morefrequent than expected; new information shows that an arm of the study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a study medication.
- Breach of confidentiality
- Protocol change that was taken to eliminate an apparent immediate hazard.
- The research team cannot resolve a participant complaint indicating unexpected risks.
- Protocol violation (an accidental or unintentional deviation from the protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects their rights or welfare.
- Reporting results: After final data are analyzed, the team will prepare reports for scientific, peer-reviewed journals describing the clinical outcomes. Thedata will be made available, after publication, to other scientists who wish to perform additional analyses.

15.11 IRB NOTIFICATION BY INVESTIGATOR

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB based on the IRBs current AE/SAE reporting requirements and timeline for reporting (e.g. 5 business days). Copies of each report and documentation of IRB notification and receipt will be kept in the study regulatory binder.

15.12 FDA NOTIFICATION BY SPONSOR

The study sponsor (Penn) shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible based on the FDAs current SAE reporting requirements and timeline for reporting (e.g. no later than 7 calendar days from the sponsor's original receipt of the information).

If a previous adverse event not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor (Penn) will submit the adverse event in a written report to the FDA as soon as possible based on the requirements and timeline (e.g. but no later than 15 calendar days from the time the determination is made).

16.0 STUDY MONITORING/AUDITING/AND INSPECTION

A research monitor will be selected by the sponsor and assigned to this trial and be responsible for completing the monitoring process. A CV for the monitor will be obtained, updated bi-annually, and kept in the regulatory binder to document the monitor's qualifications. Monitors will meet with the sponsor and review the protocol, CRF and the monitoring checklists that are completed by study staff.

On-site or remote monitoring will include:

- compliance with ICH and GCP(R2) oversight
- regulatory and protocol compliance
- data quality
- participant safety
- source data verification
- review and analysis of eligibility requirements
- informed consent procedures
- adverse events and all associated documentation
- review of study drug administration/treatment
- regulatory files, protocol departures reporting
- pharmacy records
- response assessments
- data management (data entry timelines for assessments as defined by the protocol)

16.1 STUDY INITIATION VISIT

The Principal Investigator will be responsible for assuring via personal contact with co-investigators, the monitor, and clinical staff that the research team understands and accepts the obligations incurred in the undertaking of this clinical trial.

The Principal Investigator and monitor will meet with the clinical staff (research nurses and study technician) to ensure they understand and accept the following: the nature of the protocol and the requirements for an adequate and well-controlled study; obligation to conduct the investigation in accord with 21 CFR Parts 312, 511, 812, 813 and any other applicable regulations; obligation to obtain informed consent in accord with 21 CFR Part 50; obligation to obtain IRB review and approval of a clinical investigation before the investigation is initiated and ensure continuing review of the study by the IRB in accord with 21 CFR Part 56; and keep the sponsor informed of IRB approvals and subsequent actions concerning the study.

Training will consist of an explanation of the protocol and review of the CRF. In addition, the duties of each member of the staff outlined in all applicable regulations will be reviewed. All questions will be answered.

A report of the Study Initiation will be written by the monitor detailing the visit, specifically noting the information reviewed with the clinical staff and any questions generated during the training. The report will be filed in the regulatory binder. A copy of the Study Initiation Report will be sent to the Office of Human Research, University of Pennsylvania School of Medicine, Room 150 Anatomy-Chemistry Building, Philadelphia, PA 19104-6061.

16.2 MONITORING VISITS

Monitoring will be conducted in accord with University of Pennsylvania Sponsor-Investigator Standard Operating Procedure PM 504. Enrollment will be complete when 90 patients are randomized into the trial. Approximately 2 patients/site will be randomized per month and monitoring visits conducted periodically throughout the study. The first visit will occur no more than two weeks after the first patient is entered. Subsequent visits will be conducted quarterly, as described below.

- Visit 1: Initiation Visit
- Visit 2: Approximately 25% of subjects to be randomized have completed the trial and 100% Source Document Verification for the first two randomized subjects
- Visit 3: Approximately 50% of subjects to be randomized have completed the trial.
- Visit 4: Approximately 100% of subjects to be randomized have completed the trial. This visit serves as the closeout-monitoring visit.

If a greater than 10% error rate is noted during the data review, the monitor will source data verify 100% of the data on a larger sample at the following monitoring visit

16.3 MONITORING LOG

At the beginning of each monitoring visit, the monitor and any representative of the Sponsor participating in monitoring must sign and date the monitoring log.

16.4 MONITORING REPORT

All monitoring visits will be documented on the Monitor's Report and Visit Checklist. The original report for each visit will be filed in the regulatory binder and copies of the report will be sent to the Data Safety Monitoring Board (DSMB) and the Office of Human Research at the aforementioned address**.**

16.5 VISIT 4: CLOSE-OUT VISIT

Monitoring visits can be documented on the Visit Report form located on the Penn Office of Human Research (OHR) website. The monitor and investigator will review the report and file it in the Monitoring Binder. In addition to the Monitoring Visit Report, the monitor will write a letter to the PI addressing each component of the visit and queries will be given to the study staff to complete within the next month.

17.0 MEDICAL MONITORING

17.1 SAFETY AND MEDICAL MONITORING

The Site Principal Investigator will oversee the safety of the study at his/her site. The Study PI and the Medical Monitor will oversee safety procedures at each site. Safety monitoring will include assessment and reporting of adverse events as noted above, as well as construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events. The Medical Monitor for this study is Dr. George Woody.

18.0 ETHICAL CONSIDERATIONS AND SAFETY

18.1 GOOD CLINICAL PRACTICE (GCP)

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312; International Conference on Harmonization guidelines) and all applicable governmental regulations and institutional policies and procedures. The protocol and any amendments will be submitted to NIDA, and the Penn IRB for approval before procedures are changed unless they require immediate action to protect participants' safety. All subjects will be given a copy of the informed consent describing the study with sufficient information for them to make an informed decision about participation. Any information obtained in connection with the study that can be used to identify participants will be kept confidential. An informed consent will be written and submitted along with the protocol for review by the Penn IRB if this study is funded. No procedures will be done unless the participant has reviewed and been given the opportunity to ask questions about the purpose and procedures used in the study and understand its risks and benefits. All participants must sign the informed consent in order to participate in the study.

18.2 MEDICAL EMERGENCIES

Patients that have a medical emergency during the study will be told to consult a study physician, their primary care provider, or go to the nearest emergency room and tell them when they last received study medication. Patients will be given a wallet card that identifies them as participating in a medication study and possibly receiving PGB, LFX, or XR-NTX. The subject can ask them to call the telephone numbers listed on the wallet card for further instructions or information. In the event that a patient is hurt or injured as a result of participation in the study, he/she is to contact the investigator listed on the consent form. In the event of physical injury resulting from research procedures, treatment will be provided without cost to the patient, but financial compensation is not otherwise offered from the University of Pennsylvania or the participating site. If the patient has an illness or injury that is not directly related to study participation, the patient's insurance or will be responsible for the cost of medical care.

18.3 UNBLINDING PROCEDURES

All research staff will be blind to the medication status until the end of the study. An off-site statistician will work with the Penn research pharmacist in setting up the randomization sequences. The patient will be sequentially assigned to the next treatment based on male/female status. At Penn IDS, the treatment will correspond to a unique randomization number.

Penn IDS will upload the randomization lists into a Treatment Unmasking Program, per IDS SOP-309. Access to this trial within the program will be provided to authorized Penn users. In the event of an emergency, unmasking can occur at any time using the subject's assigned randomization number. The user will not be unmasked to the treatment of other subjects. The subject, or treating physician can call the site PI to notify him or her of the medical emergency and request a release of authorization of medical information for the non-study treating physician. Study personnel will follow-up with an attempt to secure written authorization from the subject, if possible, for the authorization to release medical information to the stated non-study physician.

19.0 STOPPING RULES

19.1 STUDY STOPPING CRITERIA

In addition to oversight by the University of Pennsylvania IRB and Office of Human Research,

the trial will be conducted under the supervision of a Data Safety and Monitoring Board, as outlined below in section 8.6.1. This independent board will review the study every 6 months. The DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies either when significant benefits or risks have been uncovered or when it appears that a clinical trial cannot be concluded successfully. The DSMB will review all adverse events and will have access to unblinded data in order to determine the association between adverse events and study medication. If a pattern of significant adverse events is uncovered that suggests that the risks of continuing the trial outweigh the expected benefits of the trial then the DSMB will recommend that the study be stopped.

19.2 MEDICATION DISCONTINUATION CRITERIA

All randomized subjects are included in the intent-to-treat analysis. All subjects who prematurely discontinue treatment will be scheduled for a final evaluation and end-of trial visit (unless these two fall within 2 weeks of each other), and the follow up visit. Subjects are not dropped from all study activity unless they request to not be contacted or cannot be located for assessment.

Subjects will be informed at the consent session that medications may be held or discontinued due to intolerable side effects, hypotension or other problematic cardiovascular effects, or extreme lab values confirmed by a repeat test. (AST or ALT levels greater than 4 times upper limit of normal; elevated BUN, creatine kinase, or other evidence of renal damage). Subjects will also be informed at the consent session that he or she may be discontinued from study treatment due to: 1) Development or exacerbation of significant psychiatric or medical symptoms which necessitate admission to a medical unit or an intervention different from that provided by the protocol; 2) Clinical deterioration for any reason or a clinical status which necessitates inpatient admission; 3) Prolonged QTc after repeat ECG; 4) Blood pressure is less than 90 mm Hg (systolic) or less than 60 mm Hg (diastolic). For sitting to standing blood pressure (orthostatic change), if there is a change in systolic blood pressure of more than 20mm or diastolic blood pressure more than 10mm HG, the dosing nurse or physician may hold the lofexidine or pregabalin dose until the next dose and then recheck (can use manual blood pressure check if considered necessary). If at any point blood pressure is less than 90/60 the nurse or physician should also hold the lofexidine or pregabalin dose and consult a study physician. If for any dose, the blood pressure results remain below the previously stated minimum mmHg by the next scheduled dose, the next dose may be reduced or withheld. Dosing discontinuations can be discussed with the Lead PI and the medical monitor if it impacts subject continuation in the dosing part of the study. The reason the subjects misses their next dose of Study Medication or discontinues from Study Medication must be documented in the subject's casebook

20.0 SUBJECT STIPEND AND REIMBURSEMENTS

Each site will reimburse subjects as per the procedures below:

TABLE 6: PENN SUBJECT STIPENDS AND REIMBURSEMENTS

Screen	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day15
	InPatient Admission	InPt	InPt	InPt	InPt	InPt	InPt	InPt VIVITROL	InPt optional	F/up	F/up
50.00	125	125	125	125	125	125	125	125	125	50	50
10.00	10.00							10.00*	10.00*	10.00	10.00
Total											
60.00	135.00	125	125	125	125	125	125	135.00	135.00	60.00	60.00

This study will use Greenphire ClinCard as the payment method. The patient's social security number will be collected but not used or stored in any data records kept by the research study

staff. Subjects will receive $50 for completing screening assessments and a maximum of $10.00 total for travel reimbursement for screening. During this inpatient phase of the study, patients will be reimbursed $125.00 per day for completing assessment for a possible total of up to $1000.00, plus $20.00 for travel on days 1 and 8 (admission and discharge) for a total of $1200. If subjects are inpatient for 9 days, however, as seen in Table 8 above, the maximum reimbursement for completing all assessments for screening and the 9 inpatient days will be $1175, plus a total of $20.00 for travel reimbursement for Screening on Days 1 and 9 for a maximum total for completing all assessments of $1205.00. For the follow-up visits-Day 10 and Day 15, subjects will receive $50.00 for completing all outpatient assessment for a total of up to $100.00, plus a total of $20.00 for travel reimbursement for a total of $120.00. The maximum that a subject can receive for screening, a 9-day inpatient stay completing all assessments, plus outpatient visits and travel reimbursement is $1325.00 for the study. The maximum that a subject can receive for the 8-day inpatient stay, completing all assessments plus travel reimbursement is $1200.00.

TABLE 7: MOUNTAIN MANOR SITE SUBJECT STIPENDS AND REIMBURSEMENTS

	Screen	Day1 InPt Admt	Day 2 InPt	Day 3 InPt	Day 4 InPt	Day 5 InPt	Day6 InPt	Day7 InPt	Day 8 InPt VIVITROL	Day 9 Possible) InPt VIVITROL	Day 10 F/up	Day 15 F/up
Assessments Total	**50**	**125**	**125**	**125**	**125**	**125**	**125**	**125**	**125**	**125**	**50**	**50**
Travel	**10**	**10**							**10***	**10***	**10***	**10***
Total	**60**	**135**	**125**	**125**	**125**	**125**	**125**	**125**	**135**	**135**	**60**	**60**

This study will use Clinical Trials Payer (CT Payer) gift cards as the method of payment.

- Subjects will receive $50 for completing assessments during the screening visit.
- During the inpatient phase of the study, upon completion of all assessments on each inpatient day, patients will be compensated $125.00 (Days 1-8; possibly including day 9).

- For the follow-up visits-Day 10 and Day 15, subjects will receive $50.00 for completing all assessments. In addition, subjects will receive $10.00 reimbursement for travel for the screening visit, for travel on the day of inpatient admission and discharge*, and travel for the day 10 and day 15 follow-up visits. The maximum that a subject can receive for a 9-day inpatient stay plus outpatient visits, and travel reimbursement is $1325.00. The maximum that a subject can receive for the average 8-day inpatient stay and completing assessments plus travel reimbursement is $1200.00. You will only receive reimbursement for travel if you are traveling to or from the treatment center for study related reasons. You will receive your CT Payer Card and be reimbursed during screening but will not be reimbursed for other study procedures until you are released from inpatient care.

Please note: In order to be compensated for participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

TABLE 8: COLUMBIA SITE SUBJECT STIPENDS AND REIMBURSEMENTS

Screen	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day 9	Day10	Day 15
	InPt Admt	InPt	InPt	InPt	InPt	InPt	InPt	InPt	optional	OutPt	OutPt

								VIVITROL		F/up	F/up
50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
10.00	10.00							10.00	10.00*	10.00	10.00
Total											
60.00	60.00	50.00	50.00	50.00	50.00	50.00	50.00	60.00	60.00	60.00	60.00

You will be paid during the study. The study involves time-consuming assessments that are not included in usual treatment and you will be paid for the time and travel needed to complete assessments. You will receive $50 for completing assessments during the screening visit. During the inpatient phase of the study, upon completion of all assessments on each inpatient day, you will be compensated $50 for a possible total of up to $450 if you are inpatient for 9 days, however as seen above, the expected average inpatient stay is 8 days. For the follow-up visits-Day 10 and Day 15, you will receive $50 for completing each outpatient assessment for a total of up to $100. In addition, you will receive $10 reimbursement for travel for the screening visit, travel on inpatient admission day and discharge from inpatient, and $50 for the day 10 and day 15 follow-up visits. The maximum that you can receive for a 9 day inpatient stay plus outpatient visits, and travel reimbursement is $650.00 for the study. The maximum that you can receive for the average 8-day inpatient stay and completing assessments plus travel reimbursement is $600.00.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. For compensation of $600 or more, we are required by law to reports your earning to the IRB. Therefore, your Social Security Number and amount earned will be reported, and you will receive the appropriate IRS form at the end of the year in which you were paid. Please not that payments for this study may affect your eligibility for Medicaid and other city and state support services. No information about which study you participated in will be provided to the IRS.

21.0 POTENTIAL BENEFITS

This study is designed to identify a non-opioid detoxification medication protocol that is easy to use, does not require special licensing, and can increase the chances that opioid addicted patients are able to transition to naltrexone. If hypotheses are confirmed the study will have identified a medication that is more effective than current options for detoxifying opioid addicted patients.

22.0 CONFIDENTIALITY

22.1 HIPAA COMPLIANCE

All research staff have HIPAA training, support the privacy of clinical and research data collected as part of any study, and follow NIH policy in use and disclosure of protected health information in a manner that respects privacy in accord with the “Privacy Rule” under the Health Insurance Portability and Accountability Act (HIPAA) and other applicable laws. All subjects sign a HIPAA-authorization form, receive a copy of this form, and receive a notice of the site’s privacy practice. HIPAA signed forms are retained in locked file cabinets with patients’ source documents.

Information about study subjects will be kept confidential and managed according to requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

No information about subjects will be disclosed to others without the subject's prior written permission, except as stated in the informed consent, or if necessary to protect the rights or welfare of a subject in accordance with the law. Names or unique identifying information are never used in the publication of research data. Procedures designed to maintain confidentiality include: (1) formal training for all research staff on the importance of confidentiality; (2) procedures to protect a patient's confidentiality; and (3) formal mechanisms limiting access to information that can link data to individual patients. Data forms that include identifying information are kept in locked cabinets. Only the unique identification (ID) number, assigned at the time of initial contact represents patients during data entry, data transfer, analyses, or other file management procedures. To facilitate tracking, a password-protected computer file on a secure server is maintained containing the identity of patients, ID numbers, and information about how they can be reached. This file, however, contains no clinical data. All data are stored in a securely locked area accessible only to authorized research personnel. The Principal Investigator (PI) is required to allow trial-related monitoring, audits, IRB review, and regulatory inspection by providing direct access to source documents. The FDA, IRB, and other regulatory authorities will also have access to source documents. We inform subjects of this access in the informed consent. HIPAA regulations are followed.

23.0 INDEPENDENT DATA AND SAFETY MONITORING BOARD

23.1 DESCRIPTION

A safety monitoring board has been established at the Center for the Studies of Addiction with the following purpose (according to NIDA guidelines): to assure that the safety of study subjects is protected while the scientific goals of the ongoing studies are being met. The DSMB is charged with monitoring safety of participants and quality of the data, as well as the appropriate termination of studies when significant benefits or risks have been uncovered or a clinical trial cannot be concluded successfully.

23.2 BOARD MEMBER QUALIFICATIONS

All board members will meet NIDA requirements regarding background and experience, and none will have ethical conflicts, including financial interest related to study outcome. Individuals invited to serve on the board will disclose any potential conflicts in writing. The board will meet every six months (unless more frequent meetings are deemed necessary) and will be chaired by James McKay, M.D., a faculty member within the Department of Psychiatry at the University of Pennsylvania. Other members of the board include faculty of the University of Pennsylvania School of Medicine, Department of Psychiatry.

When the current study is reviewed, Dr. Kampman will prepare and submit a summary report on the trial status, followed by a closed session under the direction of Dr. McKay. Issues related to recruitment, subject safety and efficacy, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues) will be assessed. Following each DSM Board meeting, Dr. McKay will make recommendations to Dr. Kampman, and a final report (edited by all Board members) will be prepared and submitted to NIDA, the Penn IRB, and (if required) the FDA. In addition to semiannual reviews, at the occurrence of

the second medication associated serious adverse event or after the first fatal medication associated adverse event the protocol will be reviewed by the DSMB the DSMB to consider modifications to the protocol or discontinuation.

24.0 DSMP STUDY MONITORING PLAN

This study has a monitoring plan on file with NIDA. The investigator will allocate adequate time for such monitoring activities and also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

25.0 COVID SAFETY PLAN

a. Risk for COVID Procedures:

1. COVID PRECAUTIONS – University of Pennsylvania

I. When you bring your study subjects in for their visit to 3535 for their screening visit, you should perform a nasal swab for ROUTINE SARS-CoV-2 testing. This should be ordered and sent to the Presby lab. The results will be back within 24 hours.
II. The Director of Infection Control at PPMC, and the Infection Control team will provide guidance to the 4WS and 5 WS units on best practices for screening and managing the patients. The Infection Preventionist staff person is tasked with oversight for IC related topics for Behavioral Health.
III. Through the Infection Preventionist staff person, the infection Control team will alert WS 4 team that a test within 24-48 hours is acceptable within the context of your planned study admissions.
IV. Once the patient is admitted, they will be quarantined for 72 hours in a single room, re-tested, and if negative, will then be released from quarantine into a semi private room.

2. COVID PRECAUTIONS – MOUNTAIN MANOR Treatment Center

I. Outpatient Screening
Standard Covid screening questions and Covid testing will be incorporated into the screening visit. Study staff will follow standard infection control procedures including wearing masks and distancing, during consent and assessments.
II. Treatment center admission
Patients receive Covid screening questions and Covid testing on the day of admission. Admitted patients are admitted in cohorts, separated from the general treatment population until Covid results are known. Patients who test Covid negative are integrated into the general treatment population. Patients who test positive are placed in medical isolation until an appropriate disposition can be arranged. Study staff and usual care clinical staff follow standard infection control procedures including wearing masks, use of other PPE as appropriate, and distancing.
III. Post discharge follow-up
Any post discharge study assessments may be obtained remotely by telehealth platform as appropriate.

3. COVID Precautions – Columbia University

There are risks of exposure to coronavirus 2019 (COVID-19). At this time, there is still a significant risk of infection from COVID-19 whenever entering a public setting or interacting with others.

Participation in this research study also carries additional risks. We will discuss additional risks due to COVID-19 with participants prior to beginning the study. NYSPI will test for COVID-19 prior to any participant entering the unit and also on the first day when a participant enters the unit. Please see COVID-19 test SOP. Below are additional precautions we are taking due to COVID-19.

I. **All research at NYSPI has been modified to reduce in-person visits and procedures.**
   - We now use technology (telephone and computer) to perform all possible research procedures (such as obtaining consent, clinical interviews, symptom scales, and other tests) remotely.
   - We are recommending that only tests and procedures that cannot be performed remotely should take place in-person. If the participant prefers an in-person meeting for a specific visit or procedure, we encourage him/her to discuss this possibility with the study team.

II. **We are monitoring research participants and staff for signs and symptoms of COVID-19.**
   - The participant will be contacted by study staff on the day prior to your visits and asked whether they have any symptoms consistent with COVID-19. Upon their arrival to NYSPI, we will again ask the participant questions about any possible COVID-19 symptoms and take their temperature.
   - If they are having any symptoms of COVID-19, we will postpone the visit and recommend that they see a medical professional for evaluation.
   - All staff are required to self-monitor themselves for any possible symptoms of COVID-19 and are instructed to stay home and not come to work if they are sick in any way.

III. **We are taking extra precautions at NYSPI to reduce the risk of COVID-19 infection.**
   - When the participant enters NYSPI, he/she will be required to wear a face covering. If they do not have one, they will be given a surgical face mask.
   - Staff will wear masks and other personal protective equipment as appropriate to the procedure (e.g., gowns, gloves).
   - The participant will be asked to maintain physical distancing (at least 6 feet space between them and other people) while at NYSPI where possible unless specific research procedures require temporarily being closer to study staff.
   - Alcohol-based hand sanitizer will be provided at the building entrance and many other areas.
   - We are restricting visitor access to only those who are essential for our participants' care.
   - Visitors will be screened for fever and symptoms of COVID-19 prior to entry and will be asked to wear face coverings and limit their movement within NYSPI.

IV. **We have increased our routine cleaning and disinfection procedures in order to further protect research participants and staff from COVID-19 at NYSPI.**
   - All equipment used by participants (e.g., blood pressure cuffs, EKG machine) will continue to be thoroughly disinfected before and after each participant's use.

V. **<u>Procedures for admission to the inpatient unit:</u>**
   - All participant must present to the unit with evidence of a negative COVID test. On the day of admission the participant will be brought directly to the back of the dorm area. The participant must be wearing a mask and will be assigned to a single room. The participant will remain in this room for at least the first 24 hours. All meals will be brought to them by unit staff, any assessments will be done in their room with staff wearing PPE, and they can have their telephone during that time so they can call family/friends and play games. Of note, the telephone will not be available after the first 24 hours. There will be no smoking breaks escorted by research staff until after the 24 hour isolation period is complete. After the first 24 hours staff will provide a new mask to them daily which they are encouraged to wear at all times while in public places.
   - Upon admission, the unit staff will send off a COVID nasal swab to New York Presbyterian for analysis. Once that returns negative and 24 hours has elapsed the participant can enter

the day area. If the COVID test is positive 1) research procedures will be halted, and 2) a clinical decision involving the Clinical Director will be made regarding appropriate next steps.
The participant will be made aware that they will also have a COVID antibody (serum) test drawn soon after admission. They will have an additional nasal swab COVID test prior to discharge from the unit.

26.0 AUDITING AND INSPECTING

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

27.0 FUNDING SOURCE

This study is sponsored through a grant from the US National Institute on Drug Abuse.

28.0 DISCLOSURE OF CONFLICT OF INTEREST IN THE DSM

All University of Pennsylvania investigators conducting clinical trials are required to submit a Financial Disclosure Form. This form is submitted either in connection with submission of a grant application or proposal transmittal form to the Office for Research Services (ORS), or with submission of a protocol to the Institutional Review Board (IRB) for approval. The IRB or the ORS review disclosures to determine if it appears that the investigator has a Significant Financial Interest related to the conduct of the study. Significant Financial Interests are referred to the University Conflict of Interest Standing Committee (CISC). There are currently no conflicts of interest for the Principal Investigators.

29.0 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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30. APPENDICES