CLINICAL RESEARCH PROTOCOL

STUDY NUMBER(S):	**843403**
PROTOCOL(S) TITLE:	**Open label comparison of injectable buprenorphine (CAM2038, Brixadi®) and naltrexone (Vivitrol®) for opioid use disorder**
IND NUMBER:	151811
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FUNDING SPONSOR(S):	National Institute on Drug Abuse
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Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
MP	Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization

ITT	Intention-To-Treat
LSMEANS	Least-Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
DSMC	Data Safety Monitoring Committee
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
US	United States

1 STUDY SUMMARY

1.1 Synopsis

Title:	**Open label comparison of injectable extended release buprenorphine (CAM2038, Brixadi®) and naltrexone (Vivitrol®) for the treatment of opioid use disorder**
Short Title:	Brixadi and Vivitrol
Study Description:	This study will elucidate the cognitive mechanisms of response to opioid agonists and antagonists used to prevent relapse in OUD through investigation of the underlying neural circuits. We shall use previously validated cognitive probes, functional Magnetic Resonance Imaging (fMRI), and extended-release injectable preparations of opioid partial agonist buprenorphine (XRBUP, Brixadi) and opioid antagonist naltrexone (XRNTX, Vivitrol), in OUD patients. Using two medications with opposing mu opioid receptor action will allow a comprehensive evaluation of the mechanisms of response to relapse prevention pharmacotherapy in OUD. The study will determine the presence of treatment effects in the domains of executive function, incentive salience, and resting functional connectivity and the interaction that will indicate a difference between the two medications. Then we will evaluate the ability of the brain fMRI signal to explain relapse defined by % of opioid-positive urine tests and adherence to the study interventions. Participants will be recently detoxified treatment-seeking patients with OUD who will receive 3 monthly injections of XR-NTX or XR-BUP and have weekly urine toxicology monitoring. The project will enroll 200 participants over 6 years. The proposal would be the first neural systems' level investigation of the cognitive effects of the next generation extended release preparation of buprenorphine and naltrexone to explain the individual heterogeneity of OUD treatment response and failure. This project has the potential to advance the theory and personalized treatment of OUD by elucidating the brain mechanisms of vulnerability to relapse in OUD and in SUD in general. The proposal is similar to an existing UPenn IRB protocol 814234 and Biomarkers of disease and response to treatment in opioid addiction in all aspects except the addition of XRBUP, Brixadi.
Objectives:	Compare brain fMRI response to injectable extended-release buprenorphine (Brixadi, XR-BUP) and naltrexone (XR-NTX, Vivitrol)

Medications and Interventions	**XRBUP (CAM2038, Brixadi)** is a subcutaneous (SC) injectable extended-release formulation of buprenorphine that has been developed by Camurus AB (Sweden) and licensed in the US by Braeburn Pharmaceuticals. Brixadi is available in a range of weekly and monthly doses (8,16,24 and 32 mg weekly and 64 and 96 mg monthly) (Lofwall et al 2018). CAM2038 was approved under brand name Buvidal for OUD by the European Medicines Agency and approved as Brixadi by the FDA.This creates a unique window of opportunity for research. Braeburn, the US licensee of Brixadi has agreed to provide the study medication at no cost (See Letter of support). **XRNTX (Vivitrol):** is a monthly extended-release intramuscular injection of 380 mg of naltrexone manufactured by Alkermes Inc, that has been approved by the FDA for OUD since 2010 (Lee et al 2017) XRNTX maintains therapeutic levels of naltrexone and its active metabolites for approximately 4 weeks after each injection. **Functional magnetic resonance imaging (fMRI):** is an established method of clinical medical imaging**.** Combined with **neurocognitive testing**, standard clinical MRI scanner can be used as an accurate and robust means of evaluation of brain response to medications such as opioid agonists and antagonists, that modulate cognitive and motivational processes in addiction (Davis et al 2017, Moningka et al 2019). **Neurocognitive testing:** Psychological tasks are a well-established means to evaluate a particular cognitive or emotional domain. We shall use established tasks probing four domains: motivation, response inhibition, emotional controls and awake rest during the fMRI sessions, to simultaneously assess domain-specific behavioral performance and brain activity.
Primary Endpoint:	Group (XRNTX, XRBUP) by Session (PRE, ON) **interaction** in the brain fMRI signal in 4 cognitive domains
Secondary Endpoints:	Domain-specific cognitive performance, Urine toxicology, Adherence to follow up and treatment visits.
Study Population:	200 individuals between the ages of 18 and 65 who have a diagnosis of Opioid Use Disorder (OUD).
Phase:	Phase 2a/b
Description of Sites/Facilities	UPenn Department of Psychiatry, Center for the Study of Addictions, 3535 Market St., Suite 500, Philadelphia, PA 19104
Enrolling Participants:	UPenn Center for the Study of Addictions

Description of Study Intervention:	XRBUP (CAM2038) or XRNTX (Vivitrol)
Study Duration:	Six years (72 months)
Participant Duration:	20 weeks

2 INTRODUCTION AND RATIONALE

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures**.** This proposal brings four main innovations**: I**t would be the first neural systems' level investigation of the cognitive effects of extended-release preparations of a partial opioid agonist (XRBUP) and an antagonist (XRNTX). These formulations remove the pharmacokinetic and motivational imbalance between the monthly injectable naltrexone and daily sublingual buprenorphine that were compared in prior research (Wang et al 2015). In addition to differences in pharmacokinetics, long acting formulations are likely to have a different effect on patients' expectations of possible reward, which directly impacts dopaminergic signaling that regulates salience of drug and non-drug stimuli. Second, it would be one of the first comprehensive investigations of the cognitive effects of buprenorphine in OUD. Third, it would apply machine-learning algorithms to the integrated brain-behavior models to explain the individual heterogeneity of treatment response to MAT. Last, this would be the 1st study of the next generation injectable buprenorphine (Brixadi) that is expected to appear on the US market by September 2023 but is already approved by the FDA in terms of safety and efficacy. The significance of this project is in its potential to advance OUD theory and treatment by elucidating the brain mechanisms of vulnerability to relapse. Further, the results of this study could lay the foundation for improving treatment outcomes in OUD and in SUD in general. Project goals also directly address national public health priorities recently outlined by the directors of NIDA and the NIH: finding novel and increasing the effectiveness of available OUD treatment strategies (Volkow et al 2017).

2.1 Study Rationale

Investigation of brain and behavioral mechanisms of the effects of the two injectable extended release preparations for the treatment of opioid use disorder with the ultimate goal of improving treatment outcomes in opioid use disorder. Both of these preparations are FDA-approved. One is opioid antagonist (Vivitrol, XRNTX), and other is a partial opioid agonist (Brixadi, XRBUP).

2.2 Background

Opioid use disorder (OUD) has reached epidemic proportions in the US, with devastating public health consequences (Compton et al 2016, Hedegaard et al 2017, Jiang et al 2017). Since 1999, the number of deaths due to opioid overdose has more than quadrupled (Jones 2013), and it is now among the leading causes of death in adolescents and young adults (Jones et al 2015). Treatment of OUD has three distinct targets: (i) prevention of opioid overdose in users of illicit drugs, (ii) detoxification from physiological dependence, and (iii) prevention of relapse. Of these, relapse presents the greatest treatment challenge because it persists after protracted abstinence and even a brief relapse can be fatal. There are two efficacious classes of medication-assisted therapies (MAT) for OUD: opioid agonists (e.g. methadone and

buprenorphine) and antagonists (e.g. naltrexone). Both have high affinity for the mu-opioid receptor (MOR) with antagonists lacking inherent opioid-like activity. Both MAT agonists and antagonists are well tolerated and highly effective at preventing relapse and withdrawal when taken (Lee et al 2017, Tanum et al 2017, Latif et al 2018). Nevertheless, in the clinic, MAT is associated with significant rates of continued illicit use that is on a continuum with non-adherence to MAT and relapse (Soyka et al 2008, Tkacz et al 2012, Hser et al 2014, Schuman-Olivier et al 2014). Vulnerability to relapse is a multidimensional phenotype comprised of pre-treatment characteristics and treatment response. Understanding the individual variability in treatment response is critical for elucidating the mechanisms of relapse. Although motivational and cognitive factors are ultimately responsible for relapse, cognitive assessments have not provided robust explanation of MAT effects (Nunes et al 2015). fMRI allows probing the cognitive mechanisms of MAT by studying the underlying neural circuitry. Studies indicate that incentive salience and executive functioning are key cognitive-behavioral domains that exhibit abnormalities in established OUD (Kwako et al 2016). Our preliminary studies have identified probes of executive function and incentive salience with well-established normative brain fMRI signatures that are sensitive to oral methadone or extended-release naltrexone (XRNTX) (Langleben et al 2014, Wang et al 2015, Shi et al 2018, Wang et al 2018). Comparable data on sublingual (transmucosal) buprenorphine/naloxone (Suboxone) is extremely limited and is lacking entirely on the recently approved extended-release injectable buprenorphine (XRBUP) preparations (Becerra et al 2013, Pujol et al 2018). comparisons between buprenorphine and naltrexone introduced by the differences in routes of administration (Lee et al 2017, Tanum et al 2017).

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

For the present proposal, we will use injectable extended release naltrexone Vivitrol (XRNTX) that has been FDA approved since 2010 for the treatment of OUD and CAM2038 or Brixadi, manufactured by Camurus AB (Sweden) and Braeburn Pharmaceuticals (USA) (Lofwall et al 2018). XRNTX is a monthly IM injection of naltrexone. XRBUP is a weekly or monthly injection of buprenorphine. The active ingredients of Vivitrol and Brixadi are naltrexone and buprenorphine, both of which have been in clinical FDA-approved use for over 30 years. Brixadi and Vivitrol are injectable extended release preparations of these two well known drugs. Complete PK, PD and Toxicology profile for Vivitrol is available from attached package insert and at https://www.vivitrol.com/. Complete PK, PD and Toxicology profile for Brixadi is available from Braeburn Website:
https://braeburnrx.com/braeburns-brixadi-buprenorphine-extended-release-subcutaneous-injection-ciii-receives-fda-approval-for-moderate-to-severe-opioid-use-disorder/

Opioid receptor actions of buprenorphine include analgesia, alleviation of withdrawal-like symptoms, and antidepressant effects. Opioid receptor actions of naltrexone include opioid receptor blockade. The main potential side effect of both medications is precipitated opioid withdrawal when administered to an individual who has not been sufficiently detoxified from opioids. Buprenorphine may rarely lead to over-sedation and respiratory depression in overdose, although because of its mixed agonist/antagonist properties, it is very unlikely. Other important side effects of naltrexone include prevention of action of opioid analgesics and hepatotoxicity when given to patients with compromised liver function. This is avoided by testing liver function prior to and during treatment.

Urine drug screen (UDS) and self-report of past use have long been the two main outcomes variables in SUD treatment studies. XRNTX and XRBUP differ from the traditional pharmacotherapies because once administered, the patient cannot terminate their effect for approximately one month (Dunbar et al 2007). During this time, continued illicit opioid use has more psychological that pharmacological significance (Sullivan et al 2013). Moreover, receiving an injection is 100% verifiable and not subject to interpretation. Thus, adherence is an additional valid measure of treatment response to injectable extended-release medications. Concurrent use of non-opioid medications, which XR MAT does not prevent, has been shown to be associated with unfavorable outcomes (Grella et al 2011, Wang et al 2015). This justifies its inclusion as an exploratory outcome variable in the clinical-behavioral model.

2.2.2 Dosing Rationale

Dosing will be in the range approved by the FDA. For Vivitrol only one dose strength of 380 mg of naltrexone is available. For Brixadi, a combination of weekly (8mg, 16mg, and 24mg) and monthly doses of 64mg, 96mg, or 128mg will be used in the range and manner approved in accordance with the FDA and EMA]

2.2.3 Clinical Adverse Event Profile

Vivitrol® (XRNTX) is naltrexone for extended-release injectable suspension. Vivitrol is approved by the FDA for the treatment of opioid use disorder. It is manufactured and marketed in the US by Alkermes plc. Full prescribing information is available at https://www.vivitrol.com/

Brixadi® (CAM 2038, XRBUP), is prolonged-release buprenorphine solution for injection. On May 23, 2023, the U.S. FDA granted approval of Brixadi to Braeburn Inc for the treatment of Opioid Use Disorder . . Information on safety and adverse events profile for Brixadi is available at https://braeburnrx.com/braeburns-brixadi-buprenorphine-extended-release-subcutaneous-injection-ciii-receives-fda-approval-for-moderate-to-severe-opioid-use-disorder/

2.2.4 Dosing Rationale

Dosing will be in the range approved by the FDA. For Vivitrol only one dose strength of 380 mg of naltrexone is available. For Brixadi, a combination of weekly doses (8mg, 16mg, and 24mg) and monthly doses of 64mg, 96mg, or 128mg mg will be used in the range and manner approved in accordance with the FDA and EMA]

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Medications (please see Sections **2.2.1** and **2.2.2**):

Participants who are opioid-positive upon screening will undergo office-based treatment using FDA-approved generic medications to alleviate opioid withdrawal symptoms as determined by the study physicians, following symptom-triggered approach that includes clonidine 0.1 mg tid, dicyclomine 20 mg qid, clonazepam 0.5 mg q12 hrs PRN, diphenhydramine PRN, non-steroidal

anti-inflammatory drugs (NSAID's) PRN, trazodone 50 mg qhs and oral hydration solutions. Common side effects of these medications include over sedation and hypotension. These will be prevented by proper patient education and communication, and frequent medical monitoring.

***Investigational Agent*:**

XRBUP (Brixadi) is an extended-release formulation of buprenorphine. It is known as CAM 2038 and brand name Buvidal (EU) and Brixadi (US). CAM 2038 has been approved as Buvidal for opioid use disorder by the European Medicines Agency (MEA) and on May 23, 2023, The U.S. Food and Drug Administration granted approval of Brixadi to Braeburn Inc. It is administered by subcutaneous (SC) injection. It is available in multiple concentration and duration of action. For the present proposal we will use either the 64mg, 96mg, or the 128mg monthly dose. Braeburn, the US manufacturer of CAM 2038, has agreed to provide the study medication at no cost (See letter of support).

The most important and nevertheless rare side effects of buprenorphine are (1) precipitated opioid withdrawal; (2) anxiety; (3) pain and infection at the injection side, (4) liver toxicity in cases of compromised liver function. These will be minimized by the following steps:

Although complete lack of physiological dependence is not required for buprenorphine induction in the clinic, in order to avoid selection bias between XRNTX and XRBUP, all participants will undergo complete detoxification from opioids. This will be confirmed by an opioid-negative urine test or self-report of no opioid use in the last 5-7 days. Naloxone challenge test would not be necessary for CAM 2038 induction.

Anxiety is usually self-limited and will be treated symptomatically, initially with the weekly psychotherapy and if necessary, with medications indicated for this purpose.

Daytime sedation is uncommon and usually temporary. If it persists, patient will be interviewed again about concomitant sedative medications or alcohol. If these or other unrelated causes such as insomnia are not identified, the PI will determine whether it is necessary to exclude the participants from the study.

Meticulous injection technique: our experienced personnel who has administered thousands of Vivitrol injections without ANY complications over a decade, psychoeducation

Applying the exclusion criterion regarding elevated liver function tests labs described in the Exclusion Criteria section above.

Opioid overdose is a feared complication of OUD in general. In the context of the present study, overdose needs to be considered in two settings: during treatment and after participation ended. Individuals receiving buprenorphine or naltrexone are unlikely to experience opioid overdose during treatment, because buprenorphine is a partial agonist whose antagonist properties increase in a dose-dependent fashion and naltrexone is an antagonist that blocks the effects of illicit opioids. Buprenorphine treatment discontinuation does not lead to precipitous increase in sensitivity to illicit opioids. Individuals formerly treated with XRNTX do lose their tolerance to opioids and are therefore at an increased risk of opioid overdose if they discontinue MAT

treatment abruptly and usually against medical advice. Nevertheless, studies found that the rate of opioid overdoses after XRNTX discontinuation is actually lower than in the control groups. However, to minimize the risk of overdose, participants completing the study will be referred to the clinical program of their choice using a "warm-handoff" procedure that will include (1) beginning to make arrangements for post-study referral before the effects of XRNTX or XRBUP wear off allowing one month for the project coordinator and the participant to establish clinical treatment (2) monitoring and assisting participants in making their follow up appointment and escorting them to their first appointment as needed (3) Providing psycho-education about opioid overdose risk and provide prescriptions for the nasal Naloxone spray used as a rescue in case of an overdose.

XRNTX (Vivitrol) is an FDA-approved medication for opioid relapse prevention (https://www.vivitrol.com/content/pdfs/prescribing-information.pdf.) It is a suspension of 380 mg of naltrexone in a nanoparticle slow release vehicle, for intramuscular injection. The most important and nevertheless rare side effects are (1) precipitated opioid withdrawal; (2) anxiety; (3) pain and infection at the injection side, (4) liver toxicity in cases of compromised liver function and (5) loss of opioid tolerance and therefore greater risk of opioid overdose after study completion or in case of drop out. These will be minimized by the following measures:

Ensuring that the participant is not physiologically opioid dependent, by obtaining an opioid-negative urine test, self-report of no opioid use in the last 5 days (7 days for buprenorphine and methadone) and a negative naloxone challenge test (Langleben et al Addiction Biology 2014).

Anxiety is usually self-limited and will be treated symptomatically, initially with the weekly psychotherapy and if necessary, with medications indicated for this purpose.

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Applying the exclusion criterion regarding elevated liver function tests labs described in the Exclusion Criteria section above.

Risks of the study unrelated to the investigational product:

1) Exposure to high magnetic fields: The Siemens Magnetom Prisma 3 Tesla MRI scanner we will use in the study is a clinical MRI system approved by the FDA. Information about this scanner is available on manufacturers website: https://www.siemens-healthineers.com/en-us/magnetic-resonance-imaging/3t-mri-scanner/magnetom-prisma

2) FDA guidelines and the IRB committees consider this scanner to be a minimal risk device. Specific Absorption Rates (SAR) of electromagnetic energy by the body is controlled by a directional coupler that serves as a circuit breaker that switches the magnet off, if the local SAR exceeds the FDA limit of 8 watt/kg in any gram of tissue. The exposure characteristics are kept on file with a copy of the consent form at the University of Pennsylvania Center for MRI and Spectroscopy (CAMRIS). Although pregnancy is not a contraindication for MRI, pregnant women will not be eligible for XRNTX and therefore, screened out prior to them being considered for our study.

3) Participants who successfully complete detoxification, will undergo a neuroimaging session immediately followed by induction to XRNTX or XRBUP over a period of up to 14 days, which will include oral Naltrexone 50 mg for the XRNTX group followed by the 1st injection of XRNTX, or by injection of one or more weekly XRBUP in 8mg, 16mg or 24 mg strength with the total weekly dose not to exceed 32mg, followed by an injection of monthly XRBUP in 64, mg, 96mg, or 128mg strength (**Figure 1**). If deemed clinically necessary, induction to XRBUP may be extended by up to one week, using the same weekly Brixadi schedule. Buprenorphine/naloxone (Suboxone) is an FDA-approved sublingual form of buprenorphine that may be used during the induction if clinically indicated. Total duration of induction onto XRBUP will not exceed 14 days. Participants who are unable to complete the detoxification or induction will be excluded from the study and referred to a clinical addiction program for continuation of treatment as indicated. Suspected adverse reactions to any of the medications used in the study will be reported appropriately to the IRB, FDA at 1-800-FDA-1088 or www.fda.gov/medwatch, Alkermes, plc at 1-800-VIVITROL (1-800-848-4876) or email: usmedinfo@alkermes.com or both or Braeburn Inc at 1-833-274-9234 .

4) Emotional discomfort and drug craving: Viewing drug-related images (cues) can sometimes trigger drug-related craving in participants with a drug-use history. This craving may cause some emotional and physiological arousal, but it does not pose a medical risk. Our standard practice is to have a trained clinician available in the event that the participant is still experiencing continued arousal or discomfort, either from the images or for any other reason, at the end of the imaging session. If the participant is still aroused, the clinician has a number of psychological strategies (deep relaxation, imagery, distraction, consequences tools, etc.) that can quickly help the subject inhibit craving and feel more comfortable and in control of her/his feelings. Taking these precautions increases the participant's level of comfort and safety. After testing hundreds of participants over more than a decade, none has ever dropped out as a consequence of drug-related images exposure session. We have demonstrated sessions handled with these precautions do not lead to an increase in drug use. There is a small chance that participants may become upset when discussing their history of drug use or other behaviors. We will discontinue administration of research instruments if a subject shows discomfort. If necessary, the investigators who are clinicians with expertise in addictions, will work with the participant to alleviate any concerns.

5) Confidentiality: There is a potential risk of a loss of confidentiality in any research participation. As our subjects carry a substance abuse diagnosis, this is a risk we take especially seriously. Following completion of an imaging session, raw data will immediately be transferred to electronic storage by the MR technician for later processing. This storage is in a locked room with access limited to the investigators and data processors. Subjective and physiological data are likewise kept in a locked area accessible only to the investigators/data processors. No published or presented materials will identify subjects by names, initials, or any other means that could be used to identify the participant. As part of consent procedures, patients will be advised of precautions taken to preserve confidentiality. Further, all participants in the data collection procedures have been instructed to not divulge any information concerning subjects to any person or agency without the written and explicit consent of the subject.

These procedures have been effective in completely protecting patient information in past studies. All study staff receive Good Clinical Practice and Human Subjects Protection training as well as HIPAA privacy training before working with any subjects. All medical records and research information will be kept confidential.

2.3.2 Known Potential Benefits

The study offers significant benefits to participants and to society, both of which have enabled highly successful recruitment into our prior similar studies. The direct benefits from participation in the study is undergoing opioid detoxification, receiving relapse prevention treatment for OUD, referral for continued treatment of OUD and incidental clinically relevant findings identified from the psychiatric, neuropsychological, and/or brain MRI procedures conducted during the study. There is also a strong benefit to society from understanding mechanisms that could potentially alter the way we treat opioid dependence and overdose.

Participant Retention: Participants will have numerous motives to remain in the study. First are the significant benefits of participation described in the previous section. Second, they will receive significant monetary compensation for their time. Third, the study team includes experiences clinicians who will make all efforts to create rapport with participants that will help them maintain contact even if they decided to end their pharmacotherapy. Last, the study coordinator and technician have been specially trained to maintain ongoing contact with OUD patients.

Protection of Participants: All medical records and research information will be kept confidential. Medical records, and research data may only be accessed by staff engaged in the research project or clinical care of the subjects, or by representatives of the National Institute on Drug Abuse, the Food and Drug Administration, or other government agencies as required and permitted by law. Prior to every session subjects will be reminded that should they become uncomfortable for any reason, the study can be terminated with no penalties. Participation will not have any effect on subject's legal status or medical care.

2.3.3 Assessment of Potential Risks and Benefits

Rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the study design: The project involves two medications that have been FDA approved for OUD in USand are in active clinical use in the US (Vivitrol, XRNTX) and Brixadi will be available on market by September 2023. . Active ingredients of both medications are off patent medications that have been used for OUD for over 30 years in the US. Dosages, risks and benefits of both medications are well known in the literature and have been described in detail in Sections **2.2.1, 2.2.2, and 2.2.3**. They are both among the safest medications in their class and their use clearly outweighs the risks entailed in not providing these treatments to patients with OUD, first and foremost fatal opioid overdose, spread of infections such as HIV and Hepatitis C and criminal activity. Risks are minimized by inclusion and exclusion criteria that ensure enrollment of only participants with OUD and excluding all categories of patients at above usual risk of AE from either medication.

Justification as to why the benefits of participation in the study outweigh the risks of the information to be gained: Participation in the study benefits the participant directly as follows:

Directly to the participant: Free expert evaluation and initiation of state-of-the-art treatment for OUD and monitoring of its effects. Both medications are among the safest medications in their class and their use clearly outweighs the risks entailed in not providing these treatments to patients with OUD, first and foremost fatal opioid overdose, spread of infections such as HIV and Hepatitis C and criminal activity.

Benefit to society: as detailed in section 2.1 (Study Rationale), investigation of brain and behavioral mechanisms of the effects of the two injectable extended release preparations for the treatment of opioid use disorder with the ultimate goal of improving treatment outcomes in opioid use disorder.

3 STUDY OBJECTIVES AND ENDPOINTS

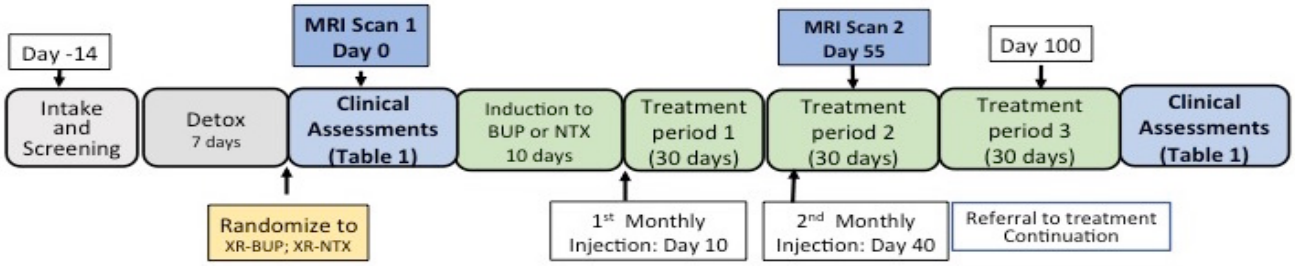
3.1 General Design

Study Design: The proposed study is a prospective open label 2-group study to compare the brain and behavioral responses of individuals with OUD receiving XRBUP and XRNTX treatments. The study will be conducted in two phases – Phase 1 = feasibility and Phase 2 = confirmation. Study interventions (XRNTX and XRBUP) and their duration will be same in both phases. Phase 1 (2 years) will have more cognitive and behavioral probes, some of which may not survive into Phase 2 (3 years) if found to not yield significant discrimination between the study interventions (groups). Participants will be men and women with current DSM-5 diagnoses of opioid use disorder (OUD) who will be randomized to XRBUP or XRNTX. Phase 1 will recruit 60 participants and Phase 2 will recruit 200 participants. The study length for each participant is comprised of up to 30 days of screening and baseline evaluations (called "week 1"), a 12-week open label trial (medication phase), and one follow-up visit 4 weeks after end of medication phase. The overall duration of the project will be 5 years (60 months). We intend to recruit 4 subjects per month for 40 months.

Table 1. Study timeline

Year/Phase	Year 1 (Phase 1)				Year 2 (Phase 1)				Year 3 (Phase 2)				Year 4 (Phase 2)				Year 5 (Phase 2)			
Quarter	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Preparation	x	x	x	x					x	x										
Recruitment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Data Collection		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Data Analysis/QC			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Publication				x	x			x	x			x	x			x	x	x	x	x

Figure 1: Outline of study interventions



3.2 Primary Study Endpoints (see Table in the Schedule of Activities (SoA), Appendix Section 12.1.

Clinical:

1) percent of the urine drug screen (UDS) tests positive for opioids during the last month of participation.

2) The number of study interventions (1,2 or 3) participant adhered to.

Surrogate: Brain fMRI response in three cognitive domains:

1) Response inhibition (Go-NoGo task)

2) Drug cue reactivity (Opioid Cues task)

3) Emotional identification (IDemo Task)

4)

Primary Hypothesis:

Aim 1 (Phase 1): Estimate the differential brain fMRI response between XRNTX and XRBUP in OUD treatment groups. We hypothesize that **(H1)** XRBUP and XRNTX will modulate the regional brain activity in the two-key cognitive-behavioral domains and measures of brain connectivity from pre-treatment (PRE) to on-treatment (ON) and this response will differ between the two medications. Milestone for transition to Phase 2: The MAT group (XRNTX, XRBUP) by Session (PRE, ON) **interaction** will have at least small (d' =/> 0.2) effect size in all brain measures.

H1a: Incentive salience (opioid cue-reactivity task): The decrease in the brain response to drug related stimuli (ON minus PRE) in the medial prefrontal cortex (mPFC) and the ventral striatum (VS) will be **greater** in the XRNTX than in the XRBUP group.

H1b: Executive function (Go-NoGo task): XRNTX will improve the efficiency of response inhibition more than XRBUP, leading to a greater **decrease** in the brain signal (ON vs PRE) during the NoGo trials in the inferior frontal cortex in the XRNTX group (see A.2.b).

H1c: Resting state functional connectivity (rsFC): change (ON vs PRE) in the rsFC between the VS and the right inferior frontal gyrus (rtIFG) and the mPFC will be **greater** in the XRNTX (vs. XRBUP group).

Aim 2 (Phase 2): Confirm in the full sample (n=200), the significance of MAT (XRNTX, XRBUP) by Session (PRE, ON) interaction in all domains from Aim 1. Test the explanatory value of integrated brain-behavior models of relapse vulnerability, identify differences in variable loading between MAT group, and explore potential mechanism of individual variability in treatment outcome.

H2a: Using logistic regression, we will test the explanatory value of brain signal in modeling treatment failure (Section **C.5.c**) and identify specific variables that differentiate MAT groups (interaction).

H2b (Exploratory): Test if the models that include brain response better explain treatment success or failure when compared to those fitted solely with demographic and clinical measures: demographic + clinical measures vs. demographic + clinical measures + brain response).

3.3 Secondary Study Endpoints (abbreviations spelled out on Page 27, "STUDY MEASURES"):

Depression (HAM-D2); Anxiety (HAM-A); Opioid Withdrawal (COWS); Opioid Craving (Opioid Craving Scale); TLFB interview; Percent UDS positive for cocaine (Ten-drug urine screen)

3.4 Primary Safety Endpoints

Brixadi adverse events: Brixadi has been shown to be safe and well tolerated in a number of Phase I, II and III trials, involving approximately 120 subjects. The most common side effects of **Brixadi** noted in clinical trials include: Adverse reactions most frequently reported for buprenorphine are headache, nausea, hyperhidrosis, insomnia, drug withdrawal syndrome and pain. Uncommon (between 1 and 0.01%) adverse events reported include Infection, Influenza, Pharyngitis, Rhinitis, injection site cellulitis, Lymphadenopathy, Hypersensitivity and Decreased appetite.
There were no medication-related Serious Adverse Events in any of the clinical trials conducted thus far. . In the proposed trial, patients will be monitored remotely twice a week for adverse events and weekly in person by a nurse or trained research staff for presence of adverse events or clinical deterioration.

Clinical deterioration and/or suicide risk management: All of the investigators have had experience managing and referring subjects under these conditions. The TRC follows standing emergency policy when managing clinical deterioration related to addiction or psychiatric symptomatology for all of our subjects. At the weekly visit, subjects are evaluated for the presence or persistence of any symptoms, indicative of clinical deterioration due to a rapidly increasing problem with cocaine use, alcohol use, and/or psychiatric symptoms, including suicidality. Between visits, subjects are instructed to contact the study physician or an authorized research staff member in the event that disturbing symptoms become evident. In all cases, these subjects are immediately evaluated, and if deemed appropriate, are referred to clinical treatment. If possible, they will be maintained in the trial as long as it is deemed safe to do so. Also, any additional treatment is recorded for data analysis purposes. At any time, subjects who are severely suicidal or at high risk of medical or physical harm will be immediately discontinued from the trial and appropriate medical treatment instituted. All subjects who are discontinued from the trial are still encouraged to attend the follow-up visits.

4 STUDY PLAN

4.1 Study Design:

Single-blind, prospective study with Phase 1 (N = 60) to show feasibility and Phase 2 (N = 200) to confirm Phase 1 findings if they meet the milestones of effect size. This is to comply with the structure of the two-phase R61/R33 NIH funding mechanism. Both Phases will use the same sequence of data collection (Section 3.1, Figure 2).

Rationale for the study duration: Early medication effects are considered to be strong predictors of long term effectiveness both at the clinical (e.g. tolerability and symptom relief) and at the neural systems and pharmacodynamic levels (McDermott et al 2015). XRNTX exhibits high drop-out rate in the first 2 months of treatment, with 50% to 75% retention at the 3rd XRNTX injection (Wang et al 2015, Lee et al 2017). In a trial of sublingual buprenorphine, retention at 3 months was approximately 75% and relapse rates defined as repeated opioid positive urines were almost unchanged between 3 and 6 months time points (Lee et al 2017). Thus, a 70-day follow up period provided by two monthly XRNTX or XRBUP injections is a necessary and sufficient time window for a neurobiological evaluation of the mechanisms of relapse vulnerability while minimizing the effect of unrelated variables such as change in family, employment or medical status, on the outcome variable. We optimize the two-phase design by designing experiments that would generate data that could serve two purposes: the initial Phase 1 exploratory and milestone target and then part of the Phase 2 sample that would address confirmatory questions that require a sample size that neither phase could reach separately.

Summary of preliminary findings as rationale for primary hypotheses: Our preliminary and published data show that the proposed neurocognitive measures (e.g. neural response) have the potential to provide a neural systems level mechanistic explanation for the effects and the differences between agonist and antagonists MAT as presented in Aim 1. Our preliminary data also suggest that the proposed fMRI probes could explain early treatment failure which in this context is a close approximation of relapse, independently from demographic and clinical-behavioral predictors. In addition, each of the three sets of neural measures increased the AUC of the best demographics + clinical measures model (**Figure 3**). Examining the different sets of variables gives information on the brain mechanisms underlying treatment outcome. Combining all available neural measures yields a substantial increase in AUC, from 0.76 to 0.92, relative to the best non-neural model. While the preliminary dataset was too small to provide definitive results, these results suggest that combining variables from the behavioral and neural domains may further improve their value in explaining the mechanisms of individual variability in treatment response and relapse vulnerability in OUD.

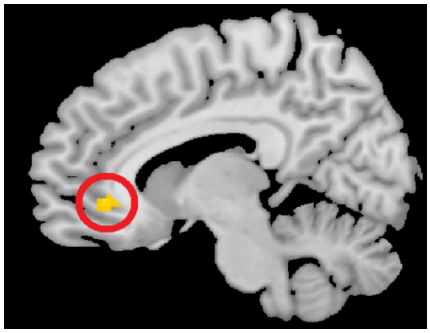


Fig 2. *Response to drug minus non-drug stimuli. PFC/ACC activation greater in adherent vs. non-adherent patients (N=14)*

4.2 Scientific Rationale for Study Design

OVERVIEW OF DESIGN AND PROCEDURES:

Design: This is a prospective, open-label, randomized study in individuals with OUD (**Figure 1**). The goals of the study are

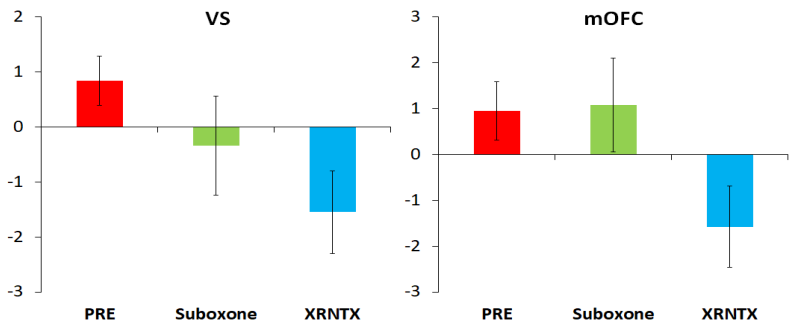


Fig 3. *Brain response to drug vs. non-drug stimuli in the VS (left) and mOFC (right) among patients not on MAT (PRE), on Suboxone, and on*

to confirm hypotheses about neural mechanisms of response to MAT in OUD and to evaluate their association with MAT treatment outcomes **(**at 2 months.
Overview of Procedures: Recruitment, screening, consent, demographics, detoxification, and recurring assessments and post-participation referrals will be performed at the UPenn Center for Studies of Addiction (3535 Market Street, Philadelphia, PA 19104). Screening and initial intake measures may be conducted at participant's treatment facilities. Neuroimaging will be performed at the UPenn Center for MRI and Spectroscopy (CAMRIS) equipped with a Siemens 3 Tesla whole-body Prisma MRI system (See Resources section). The team will maintain phone contact with participants via the coordinators to address any clinical or other issues that may arise during participation. Refer to Section 2.1 for Study Design.

4.3 Justification for Dose

See Section 2.2.3 and refer to the Product package inserts

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Appendix Section 12.1. Proper referral and continuation of treatment after study discontinuation, with an option to continue the same medication for Vivitrol group and options to switch to oral preparation of buprenorphine or a biosimilar injectable extended release preparation that is available on the US market.. Participants will be offered referrals commensurate with their treatment preferences and the medication they received in the study. Individuals who drop out of study pharmacotherapy will be offered to continue their follow up visits. Individuals who drop out of study pharmacotherapy will be offered to continue their follow up visits. Participants completing the study will be referred to the clinical program of their choice using a "warm-handoff" procedure that will include (1) beginning to make arrangements for post-study referral before the effects of XRNTX or XRBUP wear off allowing one month for the project coordinator and the participant to establish clinical treatment (2) monitoring and assisting participants in making their follow up appointment and escorting them to their first appointment as needed (3) Providing psycho-education about opioid overdose risk and provide prescriptions for the nasal Naloxone spray used as a rescue in case of an overdose.

5 STUDY POPULATION

PARTICIPANTS:

Inclusion/Exclusion criteria:

Inclusion: Treatment-seeking men and women between 18 and 65 years of age, with OUD confirmed by history and physical including urine toxicology, medical records and self-report, and interested in injectable extended-release agonist or antagonist treatment. Eligible candidates may have concurrent non-opioid substance use disorders, but opioids must be their drug of choice. Mild to moderate Depressive and Anxiety disorders and Attention Deficit Hyperactivity Disorder that do not require prescription stimulants and DSM Cluster B and C personality disorders are also included. Participants must have a stable address, working command of the English language, and telephone access. ***Exclusion:*** (1) Major current DSM V psychiatric disorders except those listed in the inclusion criteria and lifetime history of psychotic disorders (American Psychiatric Association 2013); (2) Medical and surgical conditions such as a malignancy that may affect patients' ability to receive XRNTX or XRBUP treatment because it may interfere with opioid analgesia; (3) Women of child-bearing potential who are pregnant or contemplating pregnancy in the next 6 months, nursing or not using an effective contraception.

5.1 Inclusion Criteria

1. Males and Females
2. 18-65 Years old
3. OUD by DSM5 Criteria, confirmed by history and physical examination including urine toxicology, medical records and self-report
4. Opioids are the drug of choice
5. Interested in injectable extended release agonist or antagonist treatment
6. Have a stable address, working command of English language, and telephone access.
7. Women of childbearing age must use an effective contraceptive

5.2 Exclusion Criteria

1. Psychiatric Co-morbidities:
   a) Lifetime diagnoses of any psychotic disorder, e.g. schizophrenia, schizoaffective disorder, bipolar affective disorder type 1.
   b) Psychiatric co-morbidities: Psychiatric disorders requiring current medication treatment, e.g. moderate to severe depression. Mild to moderate Depressive and Anxiety disorders and Attention Deficit Hyperactivity Disorder that do not require prescription stimulants and DSM Cluster B and C personality disorders are also allowed.
   c) Polysubstance users whose drug of choice is not an opioid.
2. Contraindications for XRNTX or XRBUP e.g. active liver disease.
8. Medical and surgical conditions such as malignancy that may affect patients' ability to receive XRNTX or XRBUP treatment because it may interfere with opioid analgesia
9. Contraindications for MRI, e.g. claustrophobia, indwelling foreign magnetic agents.

5.3 Strategies for Recruitment and Retention

Recruitment: The project team has an established track record of recruiting for and conducting neuroimaging studies of OUD that include office-based detoxification and induction to XRNTX or XRBUP (Langleben et al 2014, Wang et al 2015, Shi et al 2018, Wang et al 2018). The team has established relationship with a network of addiction treatment facilities in the metro Philadelphia area, from which we have been recruiting participants with OUD for over a decade. This network includes two full-service academic opioid treatment programs as well as six community inpatient facilities and numerous office-based practices. The network guarantees access to a diverse and representative population spanning urban, suburban, and rural settings. Finally, our community and media outreach, (Bender 2013) as well as social media advertising, have been highly effective means of supplementing the clinical referrals of participants. From all these combined sources, we expect to recruit a total of 200 participants. Approximately 75% will achieve the opioid abstinence status to receive the 1st monthly XR MAT injection, to a total of 160 anticipated by the power analysis**.** We budget an additional 10% of scanner time to account for data loss due to motion artifacts and technical problems. Access is a challenge in health care and a research confound. Insufficient transportation could impose selection bias against individuals with lower SES, disabilities and history of impaired driving which are all overrepresented among individuals with OUD. We will address this issue by reimbursing for private or public transportation expenses and access to cost-effective prepaid car services and substituting some in-person visits by telephone and electronic communications.

6 STUDY INTERVENTIONS

Medications:

Investigational Agent **XRBUP (CAM 2038, Brixadi)** is a subcutaneous (SC) extended-release formulation of buprenorphine that has been developed by Camurus AB (Sweden) and licensed in the US by Braeburn Pharmaceuticals. Differences between Brixadi and the alternative FDA-approved injectable XRBUP Sublocade and will be used in a weekly doses comprised of 8mg, 16mg, and 24mg not exceeding 32mg and monthly doses or 64mg, 96mg, or 128mg, and unlike Sublocade, it does not require abdominal SC injection and is expected to be less expensive than Sublocade (Lofwall et al 2018). Brixadi was approved under brand name Buvidal for OUD by the European Medicines Agency and On May 23, 2023, The U.S. Food and Drug Administration granted approval of Brixadi to Braeburn Inc.,. Braeburn, the US licensee of Brixadi has agreed to provide the study medication at no cost (See Letter of support).

XRNTX (Vivitrol): is a monthly extended-release intramuscular injection of 380 mg of naltrexone manufactured by Alkermes Inc, that has been approved by the FDA for OUD since 2010 (Lee et al 2017) XRNTX maintains therapeutic levels of naltrexone and its active metabolites for approximately 4 weeks after each injection. We plan to purchase Vivitrol required for the proposal.

6.1 Study Procedures:

will be administered by a clinician with appropriate level of clinical training and certification (RN, CRNP, RT, MD):

Screening (Appendix Section 12.1): Candidates will be screened by phone or in person at a referral site. Contact information of perspective participants will be kept in a secured password-protected computer file accessible only by study personnel. After obtaining perspective participant contact information from voicemails left on the study recruitment hotline (phone number distributed via flyers) or in-person, study staff will enter their contact information for screening into a secured computer file. After screening, study staff will mark study eligibility status within the file so candidates are not repeatedly contacted. Those eligible and interested in participation will undergo informed consent procedure and intake.

Intake and Informed Consent

Participants who pass Screening will be invited to attend Intake session at UPenn Center for Studies of Addiction (3535 Market Street, Philadelphia, PA 19104). An IRB (UPENN) approved Informed Consent will be read verbatim by a trained research staff. At the end of the consent session, a quiz is given. Subjects scoring below 100% correct will receive additional instruction regarding the study and consent form. Incorrect questions from the quiz will be administered again until all questions are answered correctly. All participant questions will be answered as appropriate after which the Informed Consent will be completed (signed and dated).

After signing the consent, participants would also be asked to grant access to their medical records at University of Pennsylvania and other institutions to share their health information that may include diagnoses, medications, hospital admissions, laboratory and imaging studies and participation in treatment programs including substance use disorder. This will be done by signing a "**RESEARCH PARTICIPANT AUTHORIZATION TO OBTAIN AND REVIEW HIPAA-**

PROTECTED MEDICAL RECORDS AND COMMUNICATION WITH THEIR HEALTH CARE PROVIDERS"

Participants' eligibility for fMRI and XRNTX and XRBUP will be determined by history and physical examination and laboratory testing, e.g. Blood chemistry including Liver Functions and Complete Blood Count (CBC) (Cornish et al 1997). Additional tests relevant to the specific detoxification setting, such as 12 lead Electrocardiogram **(**ECG), Xray will be performed if clinically indicated.

Intake Procedures at Treatment Facilities:

Participants found to be eligible at screening who are unable to attend intake at our center because they are currently inpatient, will undergo intake procedures at their inpatient treatment facility. Private space for the intake sessions will be secured in coordination with inpatient clinical staff.

The following procedures will be done at the inpatient facilities to reduce the delay in enrolling eligible participants.

- Informed consent, informed consent quiz and HIPAA authorization form administered by the trained study member.

Non-invasive assessments and measures will be administered by the trained study members using portable tablets.

Opioid withdrawal management (detoxification) and induction to monthly MAT injections:

The clinical management of XRBUP is similar to XRNTX except that induction to XRBUP requires partial detoxification followed a weekly dose of injectable XRBUP, while induction on XRNTX requires complete abstinence (Lofwall et al 2018). The goal of the detoxification and induction phase of the experiment is to establish a uniform starting point for both monthly formulations. To achieve it, we will detoxify all participants to abstinence and randomize after abstinence from illicit opioids has been achieved. Outpatient detoxification to abstinence takes between 5 and 10 days. Following detoxification, the XRBUP participants will receive a combination of 8mg,16mg, and 24mg strengths of weekly XRBUP, not to exceed 32 mg/week, followed by the injection of 64mg, 96mg, or 128mg of monthly XRBUP. If clinically indicated, supplemental doses of sublingual buoprenorphine/naloxone (Suboxone) may be used. If clinically indicated, the induction procedure may be extended by up to one week, using the same approach. The total duration of induction to Brixadi will not exceed 14 days. The XRNTX participants will receive 50 mg of oral naltrexone for 7-10 days after detoxification followed by the 1st XRNTX (380 mg naltrexone IM) injection. The use of symptom-driven titration of weekly XRBUP during induction reflects current best practices in administration of the drug and increases participant safety and comfort. The XRBUP induction period is also intended to synchronize the timepoint at which both cohorts begin their monthly treatments. The non-opioid detoxification will follow the procedure described in our previous neuroimaging studies (Langleben et al 2014, Langleben 2015, Wang et al 2018). Participants who are opioid-positive upon screening will undergo office-based withdrawal management (detox) by the study physicians using FDA-approved generic medications to alleviate opioid withdrawal symptoms following a symptom-triggered approach that includes clonidine 0.1 mg tid, dicyclomine 20 mg qid, clonazepam 0.5 mg q12 hrs PRN, diphenhydramine 25 mg PRN, non-steroidal anti-inflammatory medicines PRN, Trazodone 50 mg qhs and oral hydration solutions (Molenberghs et al 2005). The induction to XRNTX or XRBUP will commence immediately after the baseline MRI session. The 1st monthly injection will be administered by an experienced nurse practitioner after induction is completed (approximately 7-14 days later).

Neuroimaging (MRI): The MRI session will take place after detoxification and immediately before MAT induction (Table 1, Figure 1). This baseline time-point has been used successfully in our prior studies (Langleben et al 2014, Wang et al 2015) Participants will be escorted to the MRI facility where the investigator will meet them, review the consent and MRI screening form, and answer any remaining questions. Participants will be placed in the scanner in a supine position. The stimuli are rear projected to the center of the visual field using a PowerLite 7300 Video projector system (Epson America, Inc.) and viewed through a mirror mounted on the head coil. Participants will be given a non-ferromagnetic scroll wheel (FORP™, Current Design Inc., Philadelphia, PA) to respond during the tasks. Neuroradiologists will review the scans for clinically significant abnormalities. fMRI data will be acquired during (a) MPRAGE T1 image acquisition (5 min), (b) resting-state fMRI (5 min), (c) Go-NoGo task (5.5 min), (d) visual opioid cue task (10.5 min). The Go-NoGo and the visual opioid cue task will be counterbalance between scan 1 and 2. The total time in the scanner, including time for positioning removal and structural imaging, will not exceed 60 minutes.

STUDY MEASURES: will be administered by the study coordinator or psychologist with appropriate level of clinical training and certification (MA, PsyD or PhD):

Demographic and Clinical (Appendix Section 12.1): We use PhenX protocols (phenxtoolkit.org).

Demographical Information: Standard demographical information will be collected during phone screening and baseline study appointments, such as height, weight, preliminary fMRI eligibility, contact information, years of education etc.

MINI International Neuropsychiatric Interview (MINI) (Sheehan DV, 1998; 59(suppl 20)). The MINI is a clinician administered neuropsychiatric interview for symptoms across 17 of the most common mental health disorders. The DSM-5 version of the MINI will be administered.

Addiction Severity Scale Lite (ASI-Lite) (McLellan, 1997) The Addiction Severity Scale Lite is a shortened version of the full clinical interview. The measure collects information on demographics, employment, legal status, alcohol/drugs, family/social relationships, and psychiatric status. This measure is administered by a clinician.

Shipley Institute of Living Scale (SILS) (Zachary, 1985) The Shipley institute of living scale is a 20-minute administered measure arriving at an estimate of IQ. The scale is divided into two sections, verbal and logic-based and is administered by study staff.

State Trait Anxiety Inventory (STAI-6) (Marteau, 1992) The STAI-6 is a 6 item self-report inventory design to evaluate anxiety.

Subjective Opiate Withdrawal Scale (SOWS) (Dijkstra, 2007) The SOWS is a self-report 16-tem scale measuring motoric, autonomic, gastrointestinal, and musculoskeletal opiate withdrawal symptoms as well as psychological symptoms like anxiety and craving due to opiate use.

Opiate Withdrawal Scale – Elman (OWSE) (Elman, 2001) The opiate withdrawal scale from Elman is an adapted 6-item self-report questionnaire looking to examine five aspects of opiate craving- currently intensity, projected intensity, resistance, responsiveness to drug-related stimuli, and imagined likelihood of use in a setting with access to the drug. The questionnaire was initially designed to assess cocaine craving. The measure shows good consistency being used to assess opiate craving.

Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1967). The HAM-A is a 15-minute, 14-item, clinician-administered instrument that measures current anxiety and changes in anxiety symptoms.

Hamilton Depression Rating Scale (HAM-D) (Hamilton 1959). The HAM-D is a 20-minute, 24-item interview that measures the severity of depression and changes in depressive symptoms.

Clinical Opiate Withdrawal Scale (COWS) (Wesson et al 2003). The COWS is a clinician-administered instrument that measures eleven common opioid withdrawal symptoms.

Short Form-McGill Pain Questionnaire-2 (SF-MPQ-2) (Dworkin et al 2015) (PhenX #190901) is a 22-item self-administered questionnaire that asks about the different qualities of pain and related symptoms. Respondents are asked to rate the intensity of each type of pain they felt during the past week on a scale from 0 to 10

Timeline Follow-Back Interview (TLFB) (Sobell et al 1992). The TLFB is a 15-30-minute, semi-structured interview designed to measure self-reported drug use. It will be used at baseline to capture all drug use in the past 30 days including prescribed concomitant medications (PhenX 27016266).

Weekly online self-reported TLFB is a modified TLFB interview that uses a calendar-based format to record participants' self-report of past week drug use.

Experimental Assessments:

Biochemical Assessments:

Urine Toxicology: Rapid semi-quantitative ELISA urine drug screen test for morphine, oxycontin, methadone, buprenorphine, fentanyl, cocaine, amphetamine, methamphetamine, benzodiazepines, PCP and THC. Urine sample collection procedure has been described in a recent paper (Wang et al 2015).

Neuroimaging and cognitive: Overview of BOLD fMRI paradigms design: BOLD fMRI is a relative (non-absolute) measure, and experimental results are typically reported as contrast between conditions. Two main strategies are event-related and block designs (Aguirre et al 1999, Laurienti et al 2003).

Resting-state fMRI (rs-fMRI): During the 5-min rs-fMRI, participants will be instructed to stay awake, still, and to keep their eyes open. A fixation crosshair will be shown on a black background throughout the scan. No task performance will be required.

Visual Opioid Cue Task: Forty-eight drug-related and 48 control stimuli are presented randomly for 500 msec, separated by variable inter-trial intervals (ITI, 0–18 s). The stimuli sets are tailored to a specific pattern of OUD: prescription opioids only, heroin (IV and IN) only, and mixed prescription opioids and heroin (Shi 2016). The control stimuli that depict household objects and

chores are graphically and contextually matched to the drug-related stimuli (Langleben et al 2008, Wang et al 2015). Opiate craving is assessed with a subjective craving score (SCS), before and after each MRI session on a 0–9 Likert scale. There is no response requirement in the task, avoiding the possible confounds of individual differences in motor coordination/reaction time.

fMRI Go-NoGo task (GNG): The Go-NoGo fMRI task is a validated task testing cognitive control aspect of executive functions adopted from previous research (Goldman et al 2015). The Go stimuli included 122 positively valanced pictures (e.g. sweets), and the No-go stimuli were 38 negatively valanced pictures (e.g. snakes). Each trial consisted of a stimulus displayed for 300 ms, followed by 1700-ms baseline period during which a crosshair was displayed. Pseudo-random order of the stimuli and baseline periods was generated. Total Task Time: ~8 min. Our preliminary task performance data indicate that Go-NoGo task performance predicted XRNTX treatment failure ($p<0.01$). Performance will be coded by the number of errors of commission.

Emotion regulation: We will use the Face Emotion Identification (IDEMO) task, a validated (Gur *et al*. 2002a,b, 2007; Loughead *et al*. 2008; Satterthwaite *et al*. 2010) probe using appraisal of emotional valence of facial expressions to evaluate emotional state and bias. Briefly, participants view 60 faces displaying neutral, happy, sad, angry or fearful expressions presented in a fast event-related fashion. Each face is displayed for 5.5 seconds followed by a variable inter-stimulus interval (0.5–18.5 seconds) during which a complex crosshair (matched to the faces' perceptual qualities) is displayed. While viewing the stimuli, participants are asked to select one of five labels (happy, sad, anger, fear, neutral) for each face presented, using a custom scroll wheel response device (Current Designs; Philadelphia, PA, USA). Accuracy and correct reaction time were assessed as secondary measures. Total task duration is 10.5 minutes.
MRI Image Acquisition: Neuroimaging will be performed on a 3-Tesla Siemens Prisma scanner equipped with a 64-channel head coil. Prior to scanning, participants review instructions and practice all fMRI tasks. An MR-compatible button-box is used to record task responses (Current Designs, Philadelphia, PA). A T1-weighted multi-echo magnetization-prepared, rapid acquisition gradient echo (MPRAGE) structural image is acquired using standard parameters at 1-mm resolution. Resting fMRI BOLD will be obtained after structural imaging, followed by task paradigms. fMRI T2*-weighted BOLD images will be acquired using a whole-brain, single-shot gradient-echo (GE) echo-planar imaging (EPI) sequence, using the following parameters: TR/TE=1500/32 ms, flip angle 90°, field of view (FOV)=192 mm, matrix= 96X96, isotropic voxel resolution 2.5 mm, slice thickness/gap=2.5/0mm, 38 slices axial-oblique parallel to AC-PC. We find that these parameters produce robust signal in ventral brain regions including ventral striatum, orbital/ventral prefrontal cortex and amygdala, with little distortion or signal loss.

6.1.1 Study Intervention Description

Medications:

***Investigational Agent* XRBUP (CAM 2038, Brixadi)** is a subcutaneous (SC) extended-release formulation of buprenorphine that has been developed by Camurus AB (Sweden) and licensed in the US by Braeburn Pharmaceuticals. Differences between Brixadi and the alternative FDA-approved injectable XRBUP Sublocade it that it is available in a range of weekly and monthly doses (8,16,24 and 32 mg weekly and 64mg and 96mg and 128mg monthly), unlike Sublocade, it does not require abdominal SC injection and is expected to be less expensive than Sublocade (Lofwall et al 2018). Weekly Brixadi doses for the study will use a combination of 8mg, 16mg, and 24mg doses not exceeding 32mg. Monthly Brixadi does will be either 64mg, 96mg, or 128mg.

Brixadi was approved under brand name Buvidal for OUD by the European Medicines Agency and On May 23, 2023, The U.S. Food and Drug Administration granted approval of Brixadi to Braeburn Inc. . Braeburn, the US licensee of Brixadi has agreed to provide the study medication at no cost (See Letter of support).

6.2 XRNTX (Vivitrol):
is a monthly extended-release intramuscular injection of 380 mg of naltrexone manufactured by Alkermes Inc, that has been approved by the FDA for OUD since 2010 (Lee et al 2017) XRNTX maintains therapeutic levels of naltrexone and its active metabolites for approximately 4 weeks after each injection. We plan to purchase Vivitrol required for the proposal.
Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability
Investigational agent (Brixadi, XRBUP) is manufactured and supplied by Braeburn. It will be stored and dispensed by the Research Pharmacy at the Hospital of the University of Pennsylvania consistent with regulations governing a DEA Schedule III medication.

Upon receipt of the of the study treatment supplies, an inventory will be performed, and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.

6.2.2 Formulation, Appearance, Packaging, and Labeling
Please refer to the Vivitrol and Brixadi product package insert

6.2.3 Product Storage and Stability
In compliance with Office of Clinical Research guidelines for outpatient clinical trials using industry drug, study medications will be received, packaged and stored at PENN's Investigational Drug Service (IDS). Upon receipt of the study medication, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. IDS staff will verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study medication in a given shipment will be documented in the study files. IDS will oversee assigning and labeling of all study medication.Study medications will be kept separate from all other samples, and drugs and clearly labelled as investigational product. XRNTX and XRBUP will be stored at the appropriate temperatures as determined by the manufacturer. Both cold and room temperature storage (if applicable) will be kept secured locked and accessible only to those working on the study. Accountability logs (subject level & study-wide) will be kept ensuring thorough documentation of shipping, handling, storage, preparation, and dispensing of study medication.

6.2.4 Preparation
Study medication will be prepared at PENN's Investigational Drug Service (IDS) and administered by clinical research staff (RNs) on-site at the Addiction Treatment Center (3535 Market St.) who have received documented and thorough training on the knowledge of the study medications, purpose, side effects, and precautions. Inventory, dispensing, and logging of study medications

will be conducted on a trial-level and individual subject basis. As per OCR guidelines, study medications are *not* re-packaged prior to administration. A separate study medication destruction log will be kept if unused medication is not returned to the manufacturer as per manufacturer's specifications for the trial. All procedures, instructions and documentation requirements as defined by the Office of Clinical Research for management of investigation sites using FDA regulated drugs using IDS will be followed.

6.3 Measures to Minimize Bias: Randomization and Blinding

Urn Randomization. We plan to use urn randomization to stratify subjects across the two treatment conditions. We will stratify subjects on sex on the day of randomization.

An off-site statistician will work with clinical research staff in setting up the urn randomization sequences and will ensure that the codes linking subject's ID numbers to treatments are secure. Randomization uses an electronic emergency-unmasking database in Microsoft Access accessible to the off-site statistician 24 hours a day.. Randomization tables are secured within Microsoft Access and are managed by an off-cite statistician and data management study personnel, who do not work directly with study participants. The system only provides access for one subject at a time and all transactions are recorded. If a subject is prematurely discontinued from the trial, all attempts will be made to not break the blind. If an emergency necessitates that the blind be broken, only the off-site statistician will have access to the blind to do so. They will be given the name of the staff members who have authority to request that the blind be broken. The off-site statistician can be reached 24 hours a day and can access a subject's code rapidly.

6.4 Study Intervention Compliance

Medication adherence. There will be observed medication injection on day 10 and 40.

6.5 Concomitant Therapy

Concomitant medications will be recorded for the time period of one month before the initial screening visit throughout the follow up phase.

Prohibited medications include: benzodiazepines, barbiturates, antipsychotics, antidepressants, psychomotor stimulants (such as methylphenidate and amphetamine), antianxiety medications, naltrexone, disulfiram, modafinil, anticonvulsants, GABAergic drugs. Gabapentin prescribed for pain and not for a seizure disorder is acceptable.

Acceptable forms of birth control are:

- Oral contraceptives ("the pill")
- Contraceptive sponge,
- Barrier (diaphragm or condom),
- Intrauterine contraceptive system (Mirena®, Paragard®)
- Levonorgestrel implant (Norplant®)
- Etonogestrel implant (Implanon®)

- Medroxyprogesterone acetate contraceptive injection (Depo-Provera®)
- Complete abstinence from sexual intercourse
- Hormonal vaginal contraceptive ring (NuvaRing®)
- Patch (Ortho Evra®)
  Surgically sterile
- Partner surgically sterile

Additional psychosocial therapies including self-help groups will be allowed during the randomized medication phase but will be measured using the Treatment Services Review (TSR).

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Stopping rules will be having SAEs or unexpected AEs attributable to study medication in 10% or more patients, or 3X as many SAEs or unexpected AEs in a single arm. Mild irritation at an injection site that resolves with treatment in 3-7 days will not be counted as an unexpected AE's; an infection that does not resolve in 7 days or progresses to an abscess that needs surgical intervention will be counted as an unexpected AE or SAE depending on the need for hospital treatment.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant missing a due injection for more than 14 days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the study Case Report Form (CRF) along with a note to file. Subjects who sign the informed consent form and are randomized but do not receive the injection may be replaced. Subjects

who sign the informed consent form and are randomized and receive the injection, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost To Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for more than 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENT AND PROCEDURES

STUDY MEASURES:

Demographic and Clinical (Appendix Section 12.1): We use PhenX protocols (phenxtoolkit.org).

Demographical Information: Standard demographical information will be collected during phone screening and baseline study appointments, such as height, weight, preliminary fMRI eligibility, contact information, years of education etc.

MINI International Neuropsychiatric Interview (MINI) (Sheehan DV, 1998; 59(suppl 20))**.** The MINI is a clinician administered neuropsychiatric interview for symptoms across 17 of the most common mental health disorders. The DSM-5 version of the MINI will be administered.

Addiction Severity Scale Lite (ASI-Lite) (McLellan, 1997) The Addiction Severity Scale Lite is a shortened version of the full clinical interview. The measure collects information on demographics, employment, legal status, alcohol/drugs, family/social relationships, and psychiatric status. This measure is administered by a clinician.

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State Trait Anxiety Inventory (STAI-6) (Marteau, 1992) The STAI-6 is a 6 item self-report inventory design to evaluate anxiety.

Subjective Opiate Withdrawal Scale (SOWS) (Dijkstra, 2007) The SOWS is a self-report 16-tem scale measuring motoric, autonomic, gastrointestinal, and musculoskeletal opiate withdrawal symptoms as well as psychological symptoms like anxiety and craving due to opiate use.

Opiate Withdrawal Scale – Elman (OWSE) (Elman, 2001) The opiate withdrawal scale from Elman is an adapted 6-item self-report questionnaire looking to examine five aspects of opiate craving- currently intensity, projected intensity, resistance, responsiveness to drug-related stimuli, and imagined likelihood of use in a setting with access to the drug. The questionnaire was initially designed to assess cocaine craving. The measure shows good consistency being used to assess opiate craving.

Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1967). The HAM-A is a 15-minute, 14-item, clinician-administered instrument that measures current anxiety and changes in anxiety symptoms.

Hamilton Depression Rating Scale (HAM-D) (Hamilton 1959). The HAM-D is a 20-minute, 24-item interview that measures the severity of depression and changes in depressive symptoms.

Clinical Opiate Withdrawal Scale (COWS) (Wesson et al 2003). The COWS is a clinician-administered instrument that measures eleven common opioid withdrawal symptoms.

Short Form-McGill Pain Questionnaire-2 (SF-MPQ-2) (Dworkin et al 2015) (PhenX #190901) is a 22-item self-administered questionnaire that asks about the different qualities of pain and related symptoms. Respondents are asked to rate the intensity of each type of pain they felt during the past week on a scale from 0 to 10

Timeline Follow-Back Interview (TLFB) (Sobell et al 1992). The TLFB is a 15-30-minute, semi-structured interview designed to measure self-reported drug use. It will be used at baseline to capture all drug use in the past 30 days including prescribed concomitant medications (PhenX 27016266).

Weekly online self-reported TLFB is a modified TLFB interview that uses a calendar-based format to record participants' self-report of past week drug use.

Experimental Assessments:

Urine Toxicology: Rapid semi-quantitative ELISA urine drug screen test for morphine, oxycontin, methadone, buprenorphine, fentanyl, cocaine, amphetamine, methamphetamine, benzodiazepines, PCP and THC. (Urine sample collection procedure has been described in a recent paper (Wang et al 2015).

Neuroimaging and cognitive: Overview of BOLD fMRI paradigms design: BOLD fMRI is a relative (non-absolute) measure, and experimental results are typically reported as contrast between conditions. Two main strategies are event-related and block designs (Aguirre et al 1999, Laurienti et al 2003).

Resting-state fMRI (rs-fMRI): During the 5-min rs-fMRI, participants will be instructed to stay awake, still, and to keep their eyes open. A fixation crosshair will be shown on a black background throughout the scan. No task performance will be required.

Visual Opioid Cue Task: Forty-eight drug-related and 48 control stimuli are presented randomly for 500 msec, separated by variable inter-trial intervals (ITI, 0–18 s). The stimuli sets are tailored to a specific pattern of OUD: prescription opioids only, heroin (IV and IN) only, and mixed prescription opioids and heroin (Shi 2016). The control stimuli that depict household objects and chores are graphically and contextually matched to the drug-related stimuli (Langleben et al 2008, Wang et al 2015). Opiate craving is assessed with a subjective craving score (SCS), before and after each MRI session on a 0–9 Likert scale. There is no response requirement in the task, avoiding the possible confounds of individual differences in motor coordination/reaction time.

fMRI Go-NoGo task (GNG): The Go-NoGo fMRI task is a validated task testing cognitive control aspect of executive functions adopted from previous research (Goldman et al 2015). The Go stimuli included 122 positively valanced pictures (e.g. sweets), and the No-go stimuli were 38 negatively valanced pictures (e.g. snakes). Each trial consisted of a stimulus displayed for 300 ms, followed by 1700-ms baseline period during which a crosshair was displayed. Pseudo-random order of the stimuli and baseline periods was generated. Total Task Time: ~8 min. Our preliminary task performance data indicate that Go-NoGo task performance predicted XRNTX treatment failure ($p<0.01$). Performance will be coded by the number of errors of commission.

MRI Image Acquisition: Neuroimaging will be performed on a 3-Tesla Siemens Prisma scanner equipped with a 64-channel head coil. Prior to scanning, participants review instructions and practice all fMRI tasks. An MR-compatible button-box is used to record task responses (Current Designs, Philadelphia, PA). A T1-weighted multi-echo magnetization-prepared, rapid acquisition gradient echo (MPRAGE) structural image is acquired using standard parameters at 1-mm

resolution. Resting fMRI BOLD will be obtained after structural imaging, followed by task paradigms. fMRI T2*-weighted BOLD images will be acquired using a whole-brain, single-shot gradient-echo (GE) echo-planar imaging (EPI) sequence, using the following parameters: TR/TE=1500/32 ms, flip angle 90°, field of view (FOV)=192 mm, matrix= 96X96, isotropic voxel resolution 2.5 mm, slice thickness/gap=2.5/0mm, 38 slices axial-oblique parallel to AC-PC. We find that these parameters produce robust signal in ventral brain regions including ventral striatum, orbital/ventral prefrontal cortex and amygdala, with little distortion or signal loss.

fMRI Image Processing will utilize standard image processing procedures (Langleben et al 2008, Langleben et al 2014, Wang et al 2015). Briefly, functional image analysis will utilize FSL platform (Functional MRI of the Brain Software Library) (Jenkinson et al 2012) and will include: B0 correction using FUGUE; slice time correction, motion correction (Jenkinson et al 2002), high-pass filter (120 sec), spatially smoothing (6 mm FWHM, isotropic) and mean-based intensity normalization. Resulting translational motion parameters will be examined to ensure that there is not excessive motion (i.e. >3 mm in any plane) and will be included in the General Linear Model (GLM). BET is used to remove non-brain areas (Smith 2002). Subject-level time-series statistical analysis will be executed with FSL's improved linear model (Woolrich et al 2001). Contrasts of interest are: drug vs. control stimuli (Cue Task); No-Go vs. Go (GNG); correct vs. incorrect No-Go (GNG). Preprocessed rs-fMRI data will undergo linear de-trending, band-pass filtering (.01–.08 Hz), and regression of confound variables (motion parameters, white matter/cerebrospinal fluid signals). The bilateral NAcc will serve as the seed region, and the connectivity with the NAcc will be indexed by the Fisher-transformed correlation coefficients between the time series of the NAcc and other brain regions as defined by the Power nodes (Power et al 2011). Subject level statistical maps will be co-registered to the T1 image using boundary-based registration (Greve et al 2009) and normalized to the MNI 2mm template using a highly accurate, deformable registration via attribute matching and mutual-saliency weighting (DRAMMS) (Ou et al 2011). Given our strong *apriori* hypotheses based on preliminary data and current literature, we will utilize a combination of hypothesis-driven regional analyses as well as follow-up whole-brain voxel-wise analyses.

Hypothesis-driven regional analyses*:* For each subject, regions of interest (see H1a) will be defined anatomically using the Harvard-Oxford Probabilistic Atlas (Hayasaka et al 2003) as well as by using in-house templates. For regional analyses, the signal to noise ratio will be maximized by averaging voxels within the region prior to extraction of mean percent signal change for entry to a hypothesis-specific statistical model as detailed in section C5.

Whole brain voxel-wise analyses*:* In order to identify significant effects beyond the a priori regions, an exploratory whole-brain voxel-wise analysis will also be conducted for each task. Voxel-wise analyses will be conducted using FSL's FLAME tool. For all voxel-wise analyses, type I error control will be achieved using cluster correction as implemented with Gaussian Random Field Theory (Desikan et al 2006) using a cluster height of $z>3.09$ and a corrected cluster probability of $p<0.01$. Functional clusters of activation will be anatomically labeled using the Harvard-Oxford Probabilistic Atlas (Hayasaka et al 2003).

8.1 Efficacy Assessments:

The following study measures will serve as primary and secondary efficacy endpoints:

Opioid withdrawal management (detoxification) and induction to monthly MAT injections will be performed by the study physicians. The 1st monthly injection will be administered by an experienced nurse practitioner after induction (7-14 days) is complete.

Neuroimaging (MRI): The MRI session will take place after detoxification and immediately before MAT induction (**Appendix Section 12.1**) by a trained and authorized technician.

Addiction Severity Scale Lite (ASI-Lite) (McLellan, 1997) The Addiction Severity Scale Lite is a shortened version of the full clinical interview. The measure collects information on demographics, employment, legal status, alcohol/drugs, family/social relationships, and psychiatric status. This measure is administered by a clinician

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Weekly online self-reported TLFB is a modified TLFB interview that uses a calendar-based format to record participants' self-report of past week drug use.

Urine Toxicology: is a standard procedure using commercial clinically approved kits that will be administered by trained staff member.

8.2 Safety and Other Assessments:

the following assessments will serve as safety measures when their results indicate change from baseline indicative of AE or baseline reading indicating that a participant meets an exclusion criterion.

Screening & Intake (Appendix Section 12.1): Candidates will be screened by phone or in person at a referral site by a trained staff member(research assistant, coordinator, RN, psychologist or physician). History and physical as well as basic chemistry and blood count will be done at Intake. [see section 6.1 above].

Opioid withdrawal management (detoxification) and induction to monthly MAT injections

will be performed by the study physicians. The 1st monthly injection will be administered by an experienced nurse practitioner after induction (7-14days) is complete.

Neuroimaging (MRI): The MRI session will take place after detoxification and immediately before MAT induction (**Appendix Section 12.1**) by a trained and authorized technician.

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Weekly online self-reported TLFB is a modified TLFB interview that uses a calendar-based format to record participants' self-report of past week drug use.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.3.2 Definition of Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to injection assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be considered.

- Related – The AE is known to occur with the injection there is a reasonable possibility that the injection caused the AE, or there is a temporal relationship between the injection and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the injection and the AE.
- Not Related – There is not a reasonable possibility that the administration of the injection caused the event, there is no temporal relationship between the injection and event onset, or an alternate etiology has been established.

8.3.3.3 Expectedness

The Medical Director will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the injection.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse events by medical history and physical examination and formal instruments [see section Safety Measures, above].

The severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.3.5 Adverse Event Reporting

Once per week, a medical sub-investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. However, research staff should notify a medical sub-investigator any time an adverse event is reported by a subject. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

8.3.6 All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.Serious Adverse Event Reporting

Adverse event reporting to the FDA will follow the study IRB protocol. Briefly, a serious adverse event will be reported to the study sponsor (Dr. Langleben) by 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 to the study sponsor within 72-hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to the study regulatory sponsor: Daniel D. Langleben, M.D. (o) 215-746-0107, (f) 215-746-7358, langlebe@pennmedicine.upenn.edu

At the time of the initial report, the following information would 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. 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.

Suspected adverse reactions to any of the medications used in the study will be reported appropriately to the IRB, FDA at 1-800-FDA-1088 or www.fda.gov/medwatch, Alkermes, plc at 1-800-VIVITROL (1-800-848-4876) or email: usmedinfo@alkermes.com or both or Braeburn Inc at 1-833-274-9234 .

8.3.7 Reporting of Pregnancy

Pregnancy and not using effective contraception are exclusion criteria for participation. Medications used in the study are Class C, i.e. their effects on pregnancy are not well known. In addition to pregnancy urine test conducted as part of screening, pregnancy will be monitored using betaHCG test prior to MRI scans and by self-report during follow up and treatment visits. When a pregnancy has been confirmed in a subject, and the fetus is exposed to study drug and/or process maternally, participant will be excluded from participation and referred to her treating physician for monitoring.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Overview of primary hypotheses: Our primary response will be a binary indicator of treatment failure on the XRNTX or XRBUP regimen, defined as ≥ 2 weekly UDS positive for opioids, or self-report of ≥ 2 periods of three of more days of opioid use, or refusing XRNTX or XRBUP, or dropping out of study entirely. In hypotheses H1a and H1b, we are examining the effects of small, pre-specified, sets of measures, so our analyses will focus on model fit and prediction, and not on model selection. In hypothesis H1c, we search for best sets of predictors among demographic and clinical-behavioral variables, and over sets of brain/neural measures, so our focus is on model selection and on avoiding overfitting to the available data.

R61 Phase:

Hypothesis H1 (fMRI): For each of the cue reactivity (H1a), response inhibition (H1b), and connectivity (H1c) brain measured, we have a small number of neural responses associated with one or two regions of interest. These variables are continuously distributed, so we will test Hypotheses 1a, 1b and 1c using a repeated measures analysis of variance (rm-anova). The models will include a within-subject factor for Session (PRE vs ON) and a between-subject factor Group (XRNTX vs XRBUP), and their interaction. To accommodate the anticipated non-normal distributions of the response, we will use a generalized estimating equation (GEE) approach, using robust standard errors, using a compound symmetry working correlation structure for the within-subject correlations between the PRE and ON fMRI scans (Diggle PJ et al 2002). We will perform the rm-anova separately for each ROI (mPFC and VS for H1a, IFC for H1b, and VS-rtIFG and VS-mPFC for H1c). The hypotheses will be addressed by the Session by Group interaction, and we will obtain estimates and standard errors of the PRE vs ON change within each of the two groups, along with the size, standard error and significance of the differences between these estimates.

Sample size considerations for sample: The sample size is adequate for application of the GEE methods to obtain robust standard error (Lipsitz et al 1994). For a test of the PRE vs ON effect, our sample yields 80% power for a one-sided test that the ON levels will be Cohen's d=0.4 lower than the PRE levels, consistent with a decrease of Cohen's d=0.5 observed in our preliminary data and a decrease of Cohen's d=0.3 in the Suboxone sample.

Milestone for transition from Phase 1 to Phase 2: Using the models described above, we will obtain (model-based) estimates of the Session (PRE vs ON) by Group (XRNTX vs XRBUP effects for the five hypotheses described above. If these estimates show at least small effects (Cohen's d ≥0.2) in at least two of the three domains, then we will continue to the R33 phase.

Primary Analyses for Phase 2: Session by Group interaction effects on neural response: First, we will formally test the interaction effects explored in the R61 phase. We will rerun the analyses described for H1a, H1b and H1c in the R61 phase, for the full sample of n=140 obtained through the R61 and R33 phases. The models will be exactly as described in the R61 phase.

Effects of neural response on relapse vulnerability: Our primary outcome combines adherence to treatment and frequency of illicit opioid use during treatment. The primary outcome is a binary indicator of treatment success: if a patient provides ≥ 2 weekly UDS positive for opioids, or self-report of ≥ two or more periods of ≥ 3 days of opioid use, or refuses XRNTX or XRBUP, or drops out of treatment entirely, then they will be classified as a treatment failure; otherwise they will be classified as a treatment success. We will calculate the PRE-ON change in %-signal-change for each of the regions and neural responses described in the R61 phase. We will use logistic regression models to predict the log-odds of treatment success (Aitkin et al 2009). The predictors in the model will be a binary factor for Group (XRNTX vs. XRBUP), and the neural change scores. We anticipate that there will be some greater PRE to ON changes in the XRNTX group than in the XRBUP group, so there will be some confounding between the effects of change score and the effects of Group on the rates of positive UDS. Thus, we will include Group first in our model, so evaluating the Group effect separate from the change-score effects, and then include the change scores in a model including Group, so evaluating the additional effect of change-scores in addition to the existing effects of Group. To assess whether the effects of the change scores differ between the XRNTX and XRBUP groups, we will also test for interaction effects between Group and each of the change-scores, by adding the interaction terms to the model that includes the group and neural change score main effects. We will check the assumptions underlying the logistic regression models (e.g. linearity of covariates effects on log-odds, outliers, influential observations) using standardized residuals, influence diagnostics, and graphical displays.

Sample size considerations for the sample: Analyses of Session by Group effects on neural response: For a one-sided test that the PRE vs ON effect is larger in the XRNTX group than in the XRBUP group, our sample of 70 per group yields 81% power for an effect of d=0.42 or greater. This effect is similar to the effects observed in the preliminary data. On the basis of the preliminary data we anticipate Group by Session effects of approximately d=0.38 in the VS and d=0.42 in the mOFC.

Analyses of effects of neural response on relapse vulnerability: We consider the effect for an individual neural change variable, in a model where Group is included, assuming a small effect for Group (odds ratio = 1.25). We have three domains, with two neural variables in two domains and one in the other, so we provide power for alpha=0.05 and for alpha=0.025. For alpha=0.05 we have 80% power for an odds ratio of 1.75 or higher per standard deviation increase in a neural variable; for alpha=0.025, we have 80% for an odds ratio of 1.86 or higher.

Analyses of polysubstance use outcomes: We will also examine the effects of Group and neural change variables on other substance use outcomes, including self-report and UDS measures of opioid, stimulant, and benzodiazepine use. Here, we will use the self-report and UDS measures to create binary weekly measures of use for each substance, and use GEE repeated measures logistic regression models, with Group and the neural change measures as predictors, to estimate and test effects. These secondary analyses will be subject to missing data. We anticipate 25% dropout rates. To assess possible effects of nonignorable missingness 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, and the resulting categorical factor is included in the analyses as a main effect and interaction with predictors of interest. Overall predictor effects may be found by averaging over the patterns (Molenberghs et al 2005). Selection models (Molenberghs et al 2005) take a different approach, by explicitly modeling the probability of drop out, and incorporating the predicted probabilities into the main longitudinal analysis, with the dropout and response processes included in a single bivariate model. 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.

Predictive modeling: The models for relapse/treatment-success addressed the effects of neural responses, in isolation from demographic and clinical measures. In further analyses, we will examine their effects in combination with demographic and non-imaging clinical predictors. As we can expect overlap between the effects of these sets of variables, we compare the effects of these domains on prediction of treatment success. Thus, we will compare models using various sets of predictors on the basis of AUC comparisons, rather than on goodness of fit (Sullivan Pepe 2003). In our model search, we will compare models containing interactions between Group and the various predictors, with the constraint that an interaction is included only in models where the corresponding main effects are also included. First, we will find the best fitting demographic model, searching over a set including age, race, gender, and educational status. Next, with the predictors from the best demographic model included, we will search over the clinical predictors (depression and anxiety scores, measures of withdrawal and craving, and the ASI composite scores) to find the set that most improves the predictive utility of the best demographic model. Third, with the predictors from the best demographic/clinical model included, we will search over the measures of neural change to find the set that most improves the fit of the best demographic/clinical model. We will then perform goodness of fit and ROC comparisons between the best demographic, demographic/clinical, and demographic/clinical/brain models. This process involves three searches over various sets of variables, and unconstrained searches are likely to yield complex models involving many predictors, resulting in a prediction rule that performs poorly in new samples. To avoid this, we will use a lasso approach to fitting the logistic regression models for this hypothesis. The usual algorithms for logistic regression estimate the model parameters by minimizing a measure of lack of fit of the model to the data, but do not penalize models for complexity. The lasso approach selects a best fitting model subject to the constraint that the sum of the magnitudes of the regression coefficients in the model is less than a small positive threshold value. The threshold is chosen adaptively from the data, by minimizing an estimate of the prediction error for the model, using ten-fold cross validation. Then, a best fitting model is chosen with the estimated threshold used in the penalty. The best fitting model is usually one in which a number of the coefficients are set to zero, i.e. a number of predictors are dropped from the model.

9.2 Sample Size Determination:

Analyses of Session by Group effects on neural response: For a one-sided test that the PRE vs ON effect is larger in the XRNTX group than in the XRBUP group, our sample of 80 per group yields 81% power for an effect of d=0.42 or greater. This effect is similar to the effects observed in the preliminary data. On the basis of the preliminary analysis, we anticipate Group by Session effects of approximately d=0.38 in the VS and d=0.42 in the mOFC.

9.3 Populations for Analyses

All-treated population: Any subject randomized into the study that received at least one dose of study drug.

9.4 Statistical Analyses

9.4.1 General Approach

Data Management. Data will be gathered using Penn's REDcap data collection system, a direct-entry data system where subjects can directly enter responses. REDcap is HIPAA compliant and data is secured on Penn Medicine's data management unit (DMU) network. Interview data and self-report data are entered directly into REDcap at the research sites, by research technicians and study subjects respectively. Field validation (eg, no out of range or otherwise invalid responses will be accepted) and form validation (e.g. logically impossible responses to different questions will not be accepted) are built into this entry process. Data are transmitted (128-bit encrypted form) over the internet to the DMU servers. After online reviews, the data are archived on the servers. Certain DMU staff members have permission to modify the archived data. Audit logs record any modification to the original entry. Password protection allows members of the research team appropriate levels of data access. At time of data collection clinical research staff will review data collected for completeness (field and form validation). Weekly routine data inspections will be performed by clinical research staff to ensure data integrity. Subject brain scan data are extracted via CAMRIS web-servers and are archived to lab-specific, encrypted servers for standard cleaning and analysis.

Data Analyses. Kevin Lynch, PhD, the CSA Statistician, and his staff will perform the data analyses. Prior to analyses, standard data screening/cleaning procedures will be applied [53]. 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. Due to sample size, it is unlikely that the randomization will result in significant imbalance of the distributions of demographic or other variables across treatment groups. Additional covariates will be considered for inclusion in the analyses, to improve the precision of estimation for the treatment effects. Covariates describing levels of cocaine use prior to the study may be included. Assumptions underlying the application of statistical methods will be examined, through use of standardized residuals, influence diagnostics, and graphical displays.

Primary Hypothesis: Estimate the differential brain fMRI response between XRNTX and XRBUP in OUD treatment groups. We hypothesize that **(H1)** XRBUP and XRNTX will modulate

the regional brain activity in the two-key cognitive-behavioral domains and measures of brain connectivity from pre-treatment (PRE) to on-treatment (ON) and this response will differ between the two medications. Milestone for transition to Phase 2: The MAT group (XRNTX, XRBUP) by Session (PRE, ON) **interaction** will have at least small (d' =/> 0.2) effect size in all brain measures.

H1a: Incentive salience (opioid cue-reactivity task): The decrease in the brain response to drug related stimuli (ON minus PRE) in the medial prefrontal cortex (mPFC) and the ventral striatum (VS) will be **greater** in the XRNTX than in the XRBUP group.

H1b: Executive function (Go-NoGo task): XRNTX will improve the efficiency of response inhibition more than XRBUP, leading to a greater **decrease** in the brain signal (ON vs PRE) during the NoGo trials in the inferior frontal cortex in the XRNTX group.

H1c: Resting state functional connectivity (rsFC): change (ON vs PRE) in the rsFC between the VS and the right inferior frontal gyrus (rtIFG) and the mPFC will be **greater** in the XRNTX (vs. XRBUP group).

Secondary Hypotheses: Confirm in the full sample (n=140), the significance of MAT (XRNTX, BUP-NTX) by Session (PRE, ON) interaction in all domains from Aim 1. Test the explanatory value of integrated brain-behavior models of relapse vulnerability, identify differences in variable loading between MAT group, and explore potential mechanism of individual variability in treatment outcome.

H2a: Using logistic regression, we will test the explanatory value of brain signal in modeling treatment failure and identify specific variables that differentiate MAT groups (interaction).

H2b (Exploratory): Test if the models that include brain response better explain treatment success or failure when compared to those fitted solely with demographic and clinical measures: demographic + clinical measures vs. demographic + clinical measures + brain response).

Missing Data and Nonadherence: For the longitudinal analyses described above, premature discontinuation from treatment and occasional missing daily use indicators will lead to incomplete data. The mixed effects models described above can make use of all available data provided by subjects, but the inferences drawn from them will be unaffected by the missing data only if the missing data can be regarded as ignorable, in the sense of Laird [55]. To assess the sensitivity of our analyses to this assumption, we will use shared parameter models, which allow for correlated random effects underlying the cocaine use measurements and the pattern of dropout [56]. We will also use selection models to examine the effects of missing data [57,58]. We will explicitly model the probability of premature discontinuation at a time point as a function of baseline characteristics and responses at previous time points, using a logistic regression model, and incorporate the predicted probabilities into a weighted analysis of the main hypotheses. We will do analyses in a range of assumptions and assess the sensitivity of results to them [58]. We will use urine drug screens, record of clinic visits and receipt of injectable medications as measures of compliance with assigned medication regime. We will use the methods of Nagelkerke et al [59] and Small et al [60], to obtain estimates of the intervention effect in a population compliant with treatment i.e. the Complier Average Causal Effect (CACE).

Safety: The adverse event responses will be analyzed as a measure of safety. Total number of adverse events, adverse events leading to discontinuation (in the judgment of the study physician), % of patients reporting at least one adverse event, clinical lab assessments, vital signs and

evidence of clinical worsening (by urine drug screen results and TLFB results) will be considered in assessment of safety. In a manner parallel to the analysis for therapeutic response, medication group, gender, age and other clinical variables will be entered into a generalized linear mixed effects model to predict adverse events.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process and HIPAA Authorization

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the injections, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention. The following consent materials are submitted with this protocol:

- XRBUP vs XRNTX Consent form.
- Informed consent quiz
- HIPAA Authorization form

10.1.1.2 Consent Procedures and Documentation

Informed Consent:

Study procedures will be described in detail to the subjects by a trained study staff member during the informed consent session.. The consent form and session will include detailed information about the study medication; that is, a description of the medication, rationale for why it is being studied, frequency of dosing and length of treatment, potential side effects, safeguards and emergency procedures. Information will also be provided about the psychosocial treatment, frequency of visits and length of treatment, safeguards and emergency procedures, etc. Collection of lab specimens (number of venipunctures and urine specimens required) will be reviewed. Eligibility will be reviewed. The number and frequency of the research interviews and self-assessments will be reviewed
In addition, subjects will be assured that their participation is voluntary and that withdrawal from the study does not jeopardize current or future treatment. Patients will also be told that if at any time during the study the research team and the clinical treatment team feel that the patient needs more intensive, standard treatment, the patient will be referred to one of the available inpatient treatment programs in Philadelphia. All subjects will be informed of potential risks and benefits involved in the study. Potential medication side effects will be described to all subjects. Patients will be informed that their participation in the treatment trial may be discontinued at any time because of serious medication side effects, their noncompliance with treatment, missing appointments or if continued participation is considered an endangerment to their welfare.

Informed Consent quiz:

At the end of the consent session, a quiz is given. Subjects scoring below 100% correct will receive additional instruction regarding the study and consent form. Incorrect questions from the quiz will be administered again until all questions are answered correctly. All participants are provided with a hard copy of the consent form that includes the name and telephone numbers of the investigative team, and the Chair of Penn's Institutional Review Board (IRB). A 24-hour Emergency contact is provided in case of an adverse consequence or any other emergency.
HIPAA Authorization Form:

After signing the consent, participants would also be asked to grant access to their medical records at University of Pennsylvania and other institutions to share their health information that may include diagnoses, medications, hospital admissions, laboratory and imaging studies and participation in treatment programs including substance use disorder. This will be done by signing a "**RESEARCH PARTICIPANT AUTHORIZATION TO OBTAIN AND REVIEW HIPAA-PROTECTED MEDICAL RECORDS AND COMMUNICATION WITH THEIR HEALTH CARE PROVIDERS"**).

Intake Procedures at Treatment Facilities:
Participants found to be eligible at screening who are unable to attend intake at our center because they are currently inpatient, will undergo intake procedures at their inpatient treatment facility. Private space for the intake sessions will be secured in coordination with inpatient clinical staff.

The following procedures will be done at the inpatient facilities to reduce the delay in enrolling eligible participants.

- Informed consent, informed consent quiz and HIPAA authorization form administered by the trained study member.
- Non-invasive assessments and measures will be administered by the trained study members using portable tablets.

10.1.2 Study Discontinuation and Closure

The study may be discontinued at any time by the IRB, the Sponsor, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

10.1.3 Confidentiality and Privacy

Information about study subjects will be kept confidential and managed according to the 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.

10.1.4 Safety Oversight

DATA AND SAFETY MONITORING:

10.1.5 During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal Investigator- James Loughead, PhD, Medical Director & Regulatory Sponsor- Daniel Langleben, MD, Study Physician- Kyle Kampman, MD, research staff, and the site IRB. The PI James Loughead PhD will have overall responsibility for data analysis and management, as well as overall responsibility for safety and data monitoring on a day-to-day basis. The PI will be responsible for reporting the adverse events and serious adverse events. This study will be monitored according to the monitoring plan as noted in DSMP. The study physician will be available to review medical issues related to participation for each participant on an ongoing basis as outlined in this protocol. The internal monitoring will be conducted on site at Center for Studies of Addiction by the study coordinator appointed by the PI. The study coordinator is qualified by education, experienced and have completed training on GCP. See their certifications and qualifications in the e-regulatory binder for the study. The study coordinator will be responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to GCP. Any inconsistencies/deviations will be documented. The study coordinator will perform regular chart reviews to verify data integrity. Quality Assurance and Quality Control

This study will be monitored according to the monitoring plan as noted above. The investigator will allocate adequate time for such monitoring activities. The Principal Investigator will 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.

10.1.6 Data Handling and Record Keeping

Subject Confidentiality

This study will utilize directly identifiable protected health information (PHI). PHI, as defined by HIPAA, means individually identifiable health information about an individual that is transmitted or maintained by electronic media or in any other form or medium. PHI includes demographic information that is created or received by a health care provider, health plan, employer, or health clearinghouse. PHI relates to the past, present, or future physical or mental health or condition of an individual; the provisions of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and identifies the individual or can reasonably be used as a basis to identify an individual. The following PHI will be collected for this study:

- Name
- Postal address information
- All elements of dates, such as birthdate and date of visit, (except year) for dates directly related to an individual and all ages over 89)
- Telephone and fax number
- Electronic mail addresses
- Social security numbers *(for study compensation)*
- Medical record numbers (*for ordering MRIs, medications,*
- *Access to medical records to determine eligibility and safety for participation*

In accordance to University of Pennsylvania's policy regarding how PHI is handled, managed, and disseminated, study personnel will utilize an institutionally secured and managed network drive.

Institutionally secured and managed network drive: The CSA/TRC utilizes a departmental shared drive to securely store PHI. The CSA/TRC shared drive is managed and secured by The Penn Medicine Academic Computing Services (PMACS). Access to the shared drive requires password access to a departmental device (CSA/TRC desktop or laptop) then additional password access to the departmental shared drive. After being granted access to the shared drive, one must have an encryption code to access the files storing PHI. Therefore, the only CSA/TRC employees that will have access to the PHI connected to this study will be the approved study personnel (Principal Investigator, Project Supervisor, Clinical Research Coordinators).

Any paperwork that includes PHI (such as SSN on subject compensation forms) will be kept in a locked draw within a locked office. To reduce the possibility of breaches in subject confidentiality, subjects will be given a unique identifier to place on their demographic information, questionnaires, behavioral ratings, and data from scan sessions. Only the study personnel will have access to the code. Five years after completion of the study, the subject code will be destroyed. Data will be destroyed 8 years after study completion.

Subject Privacy

The study personnel will maintain a high level of privacy for this research study. To respect those boundaries, several safeguards will be in place. Subjects will be screened and interviewed in a private office at the CSA/TRC offices located at 3535 Market Street or at participant's treatment facilities. When contacting subjects, information about mental and physical health will not be

disclosed; telephone messages or voicemails will be worded so as to not reveal the subjects study status, diagnoses, or any other confidential information.

10.1.7 Protocol Deviations

Exception

A one-time, intentional action or process that departs from the IRB-approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented approval from the Regulatory Sponsor, IRB, and other local regulatory review committees per institutional guidelines is required. Approval from the Regulatory Sponsor must be received prior to submission to the IRB and local regulatory review committees for approval.

Deviation

A one time, unintentional action or process that departs from the IRB-approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the Regulatory Sponsor within 10 business days of PI knowledge, and to local regulatory review committees per institutional guidelines. Acknowledgement from the Regulatory Sponsor must be received prior to submission to local regulatory review committees.

Other deviations should be appropriately documented (such as a subject missing a visit unless a critical/important treatment or procedure was missed and must have been done at that specific time) per site policies/procedures.

We will include the following information on the Sponsor-supplied exception/deviation form: protocol number, subject study number, comprehensive description of the exception/deviation from the protocol, rationale and corrective and preventative action plan (deviations only). All completed exception/deviation forms will be signed by the Principal Investigator (or physician sub-investigator) and submitted to the Sponsor Project Manager for review.

Once approval of the exception request or acknowledgement of the deviation has been granted by the Regulatory Sponsor, the exception or deviation will be submitted to all applicable committees for review and approval.

10.1.8 Publication and Data Sharing Policy

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.

10.1.9 Conflict of Interest Policy

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

10.2 LIMITATIONS

LIMITATIONS AND ALTERNATIVE RESULTS: We have carefully considered **potential limitations of our study and alternate designs**. Several domains that may be of interest are not included (e.g., Affect Regulation) because task selection is based on a conceptual model and to optimize subject burden. In our past experience, scanning participants for > 1-hour results in substantial movement artifact that can bias imaging results. Regarding affect regulation, we are including a well-validated self-report measure and other psychological measures as baseline predictors/covariates in the analysis. We have focused on a model-driven analysis. However, this sample may allow a data-driven, model-free approach. This limitation can be addressed by exploratory analyses using advanced methods (e.g. machine learning). Although our proposed sample size provides ample power to test our primary hypotheses and model building, validation will likely require an independent sample rather than resampling techniques for cross validation.
Strengths of Proposed Research: To our knowledge, this would be the first investigation of the use of = BOLD fMRI signal during cognitive tasks and connectivity to characterize treatment outcomes for two extended release MAT medications. The study is carefully designed and powered to evaluate the outcomes of interest. The use of larger sample sizes than previous research and novel medication will provide the strongest possible test of our hypotheses. We have demonstrated the feasibility of recruitment to studies with similar requirements, have identified brain regions of interest through our prior research, and have performed extensive pilot-testing of all paradigms. The significance of this project is its potential to advance theory and treatment by elucidating brain-behavior mechanisms.

11 RESEARCH STAFF

The following research staff will be directly involved with the implementation and execution of the study:

- James Loughead, Ph.D., Principal Investigator
- Daniel Langleben, MD., Co-Principal Investigator,
- Kyle Kampman, MD., Study Physician
- Kevin Lynch, Ph.D., CSA Statistician
- Susan Ware, Database Developer/Manager
- Joseph Smith, Data Management Specialist
- Urooj Iqbal, Research Staff
- Dominique Spence, Research Staff

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13 APPENDIX

13.1 Schedule of Activities (SoA)

	Screening detox and randomization (Day -14)	MRI Scan 1 Baseline (day 0)	Induction to XRBUP or XRNTX (day 0-10)	Injection 1 (day 10) + weekly follow up	Injection 2 (day 40)	MRI Scan 2 On Treatment (day 55)	Injection 3 (Day 70	Weekly Follow-up End of study and referral (Day 100)
Psychiatric and medical								
Demographics (age[1], sex[1], edu.[1])	X							
History, physical and labs (**C.4.a**)	X							
SILS	X							
MINI (EOS* – end of study)	X							X EOS*
Addiction Severity Index[1]	X							X EOS*
Clinical/Behavioral (C.3.a)								
HAM-D[2], HAM-A[2],COWS[2]	X	X	X		X	X		X
SOWS, Opioid Craving Scale[2] ,SF-MPQ-2[2], STAI-6	X	X	X		X	X		X
TLFB interview	X	X	X		X	X		X
Ten-drug urine drug screen (UDS)	X	X	X	X	X	X		X
Go-NoGo errors of commission[2]		X			X			
Neuroimaging (Section C.3.b)								
Go-NoGo fMRI[3]		X			X			
Opioid Cue task fMRI[3]		X			X			
Resting-state fMRI[3]		X			X			
MPRAGE (anatomical MRI scan)		X			X			

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	Daniel Langleben, MD
STUDY TITLE:	**Open label comparison of injectable extended release preparations of buprenorphine (Brixadi®) and naltrexone (Vivitrol®) for the treatment of opioid use disorder**
STUDY ID	843403
PROTOCOL VERSION	V5.0

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	James Loughead, Ph.D	Signature	
Affiliation:	University of Pennsylvania	Date	7/17/2023

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