NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

August 13, 2018

TO: Dr. Elizabeth Evans

FROM: Dr. Edward Nunes, Co-Chair, IRB
Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE: CONTINUATION**
Expedited per 45CFR46.110(b)(1)(f)(8)(c)

Your protocol # **6999** entitled **BUPRENORPHINE/NALOXONE STABILIZATION AND INDUCTION ONTO INJECTION NALTREXONE: AN OUTPATIENT DETOXIFICATION FOR OPIOID DEPENDENCE** (version date 08-13-18) and Consent Forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **September 8, 2018** to **September 7, 2019.**

Consent requirements:

X Not applicable: (RECRUITMENT COMPLETED. DATA BEING ANALYZED)

☐ 45CFR46.117 (c)(2) waiver of documentation of consent for the telephone interview.

☐ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special:

√ **Only copies of consent documents that are currently approved and stamped by the IRB may be used to obtain consent for participation in this study.**

√ **A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.**

√ **Changes to this research may be not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.**

√ **All serious and/or unanticipated problems involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.**

CC: RFMH Business Office (3 RO1 DA030484-04S1)

EN/AW/Scr

Signed copy on file at IRB

Protocol Title:
Buprenorphine/Naloxone Stabilization and Induction onto Injection Naltrexone: An Outpatient Detoxification for Opioid Dependence

Version Date:
08/13/2018

Protocol Number:
6999

Clinic:
Substance Treatment And Research Services (STARS)

First Approval:
09/23/2014

Expiration Date:
09/07/2019

Contact Principal Investigator:
Elizabeth Evans, MD
Email: evansel@nyspi.columbia.edu
Telephone: 646-774-6123

Principal Investigator:
Adam Bisaga, MD

Research Chief:
Herbert Kleber, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Substance Abuse
Within the division/department, what Center or group are you affiliated with, if any?
Substance Treatment and Research Service (STARS)

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

None

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
We are currently analyzing the data and preparing a manuscript.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
9/30/2016

Overall Progress

Approved sample size

67
Total number of participants enrolled to date
30
Number of participants who have completed the study to date
8
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Adults ages 18-60 who meet criteria for opioid use disorder of at least moderate severity
Total number of participants enrolled from this population to date
30
Gender, Racial and Ethnic Breakdown
Male
White:16
Hispanic:5
Black:3
Asian: 1
Other: 0

Female
White:3
Hispanic:1
Black:1
Asian: 0
Other: 0

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50
✓ Individuals with HIV/AIDS
✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
Improved Strategies for Outpatient Opioid Detoxification
Grant Number
3 R01 DA030484-04S1
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

We will randomize **46** opioid-dependent participants who have initially failed outpatient induction onto XR-NTX; participants will receive buprenorphine/naloxone on a weekly basis for 30 days. Buprenorphine/naloxone will be dispensed weekly during the 30-day stabilization and twice weekly during taper phase, and all patients who successfully complete the detoxification will be offered induction onto XR-NTX. All participants will receive weekly therapy with a study psychiatrist. All participants will receive open-label medication. The primary outcome of this study will be percentage of patients successfully inducted onto XR-NTX. Secondary outcomes will be time to relapse, defined as opioid use or dropout.

Background, Significance and Rationale

Background, Significance and Rationale
Rates of prescription opioids and heroin use and related morbidity and mortality continue to grow at an alarming rate (CDC, 2012; SAMHSA, 2013), and there are currently more than 2.5 million individuals affected in the U.S. While heroin use remains prevalent, prescription opioid abuse has risen dramatically in the past decade (SAMHSA, 2012). There has also been a dramatic increase in unintentional overdose deaths (CDC, 2012). Unfortunately, most people with opioid dependence are not receiving treatment (SAMHSA, 2013). Reasons for this gap between treatment need and delivery include lack of access to opioid dependence treatment programs, lack of training for providers such that the healthcare workforce is not, for the most part, knowledgeable about effective treatment options. Expanding available treatment options and attracting more opioid-dependent individuals into effective treatment represent important public health priorities (CASA Columbia, 2012).

Treatment with agonist medication (methadone, buprenorphine) is one effective treatment approach (Ball 1991; Johnson 2000; Stotts 2009). Since its approval by the US Food and Drug Administration (FDA) in 2002 as a pharmacotherapy for opioid dependence, buprenorphine is increasingly utilized both by opioid treatment centers as well as office-based physicians. While agonist maintenance is currently an effective strategy for long-term retention, it may not be a viable option for many individuals for a variety of reasons, including preference or access (Rounsaville 2000; Cunningham 2007). Further, the acceptability of opioid maintenance treatment is limited by perceived stigma attributed to opioid dependence and its treatment on the part of both affected individuals and clinicians (Cicero et al., 2007; Knudsen et al., 2007). Long acting

naltrexone (XR-NTX, brand name: Vivitrol), a mu opioid receptor antagonist, completely blocks the effects of opioids, and was approved by the FDA in 2010 for relapse to opioid dependence following detoxification (O'malley 2007; Krupitsky 2010). Clinical trials have shown retention rates similar to those observed with buprenorphine, with little or no opioid use (Brooks et al., 2010; Comer et al., 2006; Hulse et al., 2009; Krupitsky et al., 2011, 2012). XR-NTX is an important option for those desiring abstinence from opioids. Initiation of naltrexone in patients dependent on opioids is a barrier, as patients must undergo detoxification. Inpatient detoxification is not a realistic option for many opioid-dependent patients because of (1) occupational or domestic responsibilities which do not permit such an absence, and (2) lack of adequate insurance, as carriers have become increasingly unwilling to cover the costs associated with inpatient stays for detoxification (Mark et al. 2001). Thus, for XR-NTX to be an effective alternative, and one that is readily incorporated into clinical practice, detoxification must occur in a wider range of settings, including outpatient. Further, in addition to the growing population on buprenorphine maintenance, buprenorphine is also increasingly used to assist with outpatient detoxification (Raistrick 2005; Caldiero 2006). Thus, an effective outpatient strategy detoxing from (or with) buprenorphine for purposes of naltrexone induction will increase viability of maintenance treatment with XR-NTX.

To date, there is no standard buprenorphine detoxification design, and data of duration of buprenorphine detoxification, and its impact on treatment outcomes, has been mixed. A review of the literature by Dunn et al. in 2011 suggests buprenorphine taper duration is associated with opioid abstinence, but not retention (Dunn et al. 2011). However, there are relatively few randomized, clinical trials of taper duration. Some trials suggest longer tapers are associated with less withdrawal, less opioid use and better retention (Amass et al. 1994; Woody et al. 2008; Sigmon et al. 2013). However, Ling et al. found a larger percentage of opioid negative urines in their shorter taper group (Ling et al. 2009). In a recent randomized, double-blind trial, Sigmon et al. compared the relative efficacy of 1-,2-, and 4-week buprenorphine tapering regimens and subsequent naltrexone induction (Sigmon et al 2013). They found a significant effect of taper duration on abstinence, retention, and naltrexone ingestion at the end of their 12-week study (Sigmon et al 2013).

In one of our ongoing studies, Long-acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification with Naltrexone vs. Buprenorphine (PI: Adam Bisaga M.D., (#6374) opioid-dependent participants are randomized to one of two outpatient detoxification strategies: (1) a standard 7-day buprenorphine induction and gradual taper from 8 mg to 0 mg vs. (2) 7-day oral naltrexone induction. Both groups receive a single administration of a long-acting injectable naltrexone (XR-NTX): at Day 8 for the naltrexone induction group and Day 15 for the buprenorphine group. Thus far, we have demonstrated successful outpatient induction onto long-acting injectable naltrexone (XR-NTX) at a rate of about 50%; the naltrexone treatment arm has achieved better rates of successful induction onto XR-NTX compared to the buprenorphine-assisted detoxification arm, but the difference has not yet reached statistical significance (53% vs. 42%).
In another one of our ongoing studies, A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Prior to First Dose of Vivitrol (PI: Adam Bisaga M.D., (#7190) opioid-dependent participants are randomized to one of three outpatient 8-day detoxificiation schedules: (1) oral naltrexone + buprenorphine (2) oral naltrexone+ placebo buprenorphine (3) placebo oral naltrexone + placebo buprenorphine. All three groups receive a single administration of a long-acting injectable naltrexone (XR-NTX) on Day 8.
Therefore, in the current pilot study, we would like to implement a procedure for retaining in treatment patients who fail the initial attempt at outpatient detoxification and XR-NTX induction. This procedure will

be similar to the approach of Sigmon et al. 2013, with a 4-week period of buprenorphine stabilization and taper off. Participants will then repeat the detox using a 2-day washout followed by a 4-day ascending taper of oral naltrexone (1, 3, 12, and 25 mg), with the purpose of XR-NTX induction. Including a buprenorphine maintenance arm allows for a period of stabilization and relief from withdrawal symptoms, followed by a taper, with the thought that this may be more tolerable to these individuals that have previously had a difficult time modulating and tolerating the distress of the more rapid detoxification.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
SPECIFIC AIM #1: To test the efficacy of a second-line treatment for the 50% of opioid-dependent individuals who fail their first attempt at outpatient XR-NTX induction. The primary outcome is successful induction onto XR-NTX.
EXPORATORY AIMS: We will also examine secondary outcomes retention (time to drop-out); severity of opioid withdrawal; and 2-week abstinence at 3rd and 4th weeks after XR-NTX injection.

Description of Subject Population

Sample #1

Specify subject population
Adults 18-60 years old, who meet current DSM-5 criteria for OUD of at least moderate severity
Number of completers required to accomplish study aims
14
Projected number of subjects who will be enrolled to obtain required number of completers
46
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown
Both genders and all ethnic groups are eligible. It is estimated that the sample will be 75% male, 25% female, 50% Caucasian, 30% Hispanic-American, and 15% African-American, and 5% other minorities based on data from previous trials.
Description of subject population
Participants will be **46** men and non-pregnant women and meet criteria for opiate dependence. Participants will be recruited from the pool of participants that fail XR-NTX induction as part of either protocol #6374: Long-acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification with Naltrexone vs. Buprenorphine or protocol #7190: A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Prior

to First Dose of Vivitrol.

Recruitment Procedures

Describe settings where recruitment will occur
Participants will be recruited from the pool of participants that fail XR-NTX induction as part of one of the two trials: Long-acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification with Naltrexone vs. Buprenorphine (IRB #6374: PI: Adam Bisaga M.D.) or A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Prior to First Dose of Vivitrol (PI: Adam Bisaga M.D.). Participants are recruited for that study via IRB-approved advertisements placed in local newspapers and radio stations. Additionally, prospective participants are recruited by word of mouth and through liaison to other local clinical services. All potential participants will be evaluated at the Substance Treatment and Research Service (STARS) at the New York State Psychiatric Institute. All patients are seen by one of our psychiatrists or psychologists for a screening evaluation and mental status examination as part of routine admission procedures at STARS (Evaluation of Potential Substance Abuse Research Participants, IRB # 6582R: PI: Mariani).
How and by whom will subjects be approached and/or recruited?
Prospective participants will have already been evaluated and recruited at the Substance Treatment and Research Service (STARS), and enrolled in protocol #6374 or protocol #7190. Participants who fail XR-NTX induction will meet with a study psychiatrist, who will offer the participant the option of enrolling in the study.
How will the study be advertised/publicized?
Advertising, recruitment, and screening is covered under the STARS Umbrella Screening protocol 6582R. We will use IRB-approved advertisements to reach our target population.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02294253

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

DA030484-04: " Long-acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification with Naltrexone vs. Buprenorphine." (IRB# 6374). In the ongoing study funded by DA030484-04, we compare a rapid, 7-day induction method (one day of buprenorphine followed by a gradual titration of oral naltrexone and injectable naltrexone administration) to a standard 14-day procedure (involving a week-long buprenorphine taper followed by a week-long washout and injectable naltrexone

administration). To date we have enrolled 110 participants in 3 years of enrollment; recruitment has been twice as fast as predicted (based on previous inpatient studies) because of a high level of interest in the outpatient procedure.

ALK6428A-301. "A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Prior to First Dose of Vivitrol" (IRB #7190). In the ongoing study funded by Alkermes Inc., in a randomized double-blind trial, we compare three different treatment arms (1) oral naltrexone + buprenorphine, (2) oral naltrexone + placebo buprenophine, (3) placebo oral naltrexone + placebo buprenorphine over 8 days, followed by administration of XR-NTX. To date we have enrolled 12 participants, randomized 4 , and 1 participant has been successfully inducted onto XR-NTX.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Adults 18-60 years old
Create or insert table to describe the inclusion criteria and methods to ascertain them

1) Age 18-60.
Method of Ascertainment: Clinical interview
2) Meets DSM-IV criteria for current opiate dependence disorder of at least six months duration, supported by urine toxicology OR COWS score > or =6 OR Naloxone Challenge.
Method of Ascertainment: Clinical and MINI interview, urine toxicology or COWS score > or = 6, or naloxone challenge.
3) Voluntarily seeking treatment for opioid dependence.
Method of Ascertainment: Clinical interview.
4) In otherwise good health based on complete medical history and physical examination.
Method of Ascertainment: Clinical interview and physical examination; vital signs, ECG, laboratory tests (hematology,blood chemistry, urinalysis) within normal ranges, including AST or ALT < 3 times normal limits.
5) Able to give written informed consent.
Method of Ascertainment: Clinical interview and mental status exam.
6) Failed outpatient induction onto XR-NTX in Protocol #6374 or Protocol #7190.
Method of Ascertainment: Chart review and clinical interview.

Create or insert table to describe the exclusion criteria and methods to ascertain them
1) Methadone maintenance treatment or regular use of illicit methadone (> 30 mg per week).
Method of Ascertainment: Clinical interview; urine toxicology
2) Maintenance on, or regular use of, buprenorphine or other long-acting opioid agonists.
Method of Ascertainment: Clinical interview; urine toxicology
3.) Pregnancy, lactation, or failure in a sexually active woman to use adequate contraceptive methods.

Method of Ascertainment: Clinical Interview, physical examination, urine pregnancy test during screening, serum pregnancy test at admission and day 6, at least one day prior to administration of injectable naltrexone.
4) Active medical illness which might make participation hazardous, such as untreated hypertension, acute hepatitis with AST or ALT > 3 times normal, AIDS, unstable diabetes.
Method of Ascertainment: Clinical Interview, physical examination,laboratory (Chem-20, CBC, urinalysis), ECG.
5) Active psychiatric disorder which might interfere with participation or make participation hazardous, including DSM-5 Schizophrenia or any psychotic disorder, severe Major Depressive Disorder, or suicide risk or 1 or more suicide attempts within the past year.
Method of Ascertainment: Clinical and MINI interview, clinical mental status examination, discussions with previous psychiatrist or treatment provider if formerly in treatment.
6) Physiologically dependent on alcohol or sedative-hypnotics with impending withdrawal. Other substance use diagnoses are not exclusionary.
Method of Ascertainment: Clinical and MINI interview; urine toxicology.
7) History of allergic or adverse reaction to buprenorphine, naltrexone, naloxone, clonidine, or clonazepam.
Method of Ascertainment: Clinical interview.
8) Chronic organic mental disorder (e.g. AIDS dementia).
Method of Ascertainment: Clinical Interview, mental status, physical and laboratory examination.
9) History of accidental drug overdose in the last 3 years as defined as an episode of opioid-induced unconsciousness or incapacitation, whether or not medical treatment was sought or received.
Method of Ascertainment: Clinical interview.
10) Painful medical condition that requires ongoing opioid analgesia or anticipated surgery necessitating opioid medications.
Method of Ascertainment: Clinical interview, physical examination.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes

Indicate NYSPI IRB #
6582R
Describe Study Consent Procedures
Screening procedures will be standardized and a standard set of instruments will be utilized.
Participants will be recruited from current participants in Protocol #6374 or Protocol #7190 who have failed the initial attempt at outpatient injection naloxone induction. Patients will sign consent for the review of recently completed assessments including: The MINI International Neuropsychiatric Interview to assess current and lifetime DSM-5 diagnoses; a psychiatric evaluation, medical history, and physical and laboratory examination. The research psychiatrist will offer eligible patients participation in the study and will obtain informed consent.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Bisaga, Adam, MD
Brezing, Christina, MD
Evans, Elizabeth, MD
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Nunes, Edward, MD
Shulman, Matisyahu, MD
Vaezazizi, Leila
Vaughan, Barney, MD
Williams, Arthur
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Buprenorphine induction/stabilization/taper: Buprenorphine induction will be conducted at our STARS clinic and according to current clinical guidelines. Participants who have initially failed outpatient induction onto XR-NTX will receive buprenorphine/naloxone (BUP) on a weekly basis **t**hat they will take daily, according to the following schedule: 8/2 mg (Days 1-10), 6/1.5 mg (Days 11-15), 4/1 mg (Days 16-20), 3.0/0.75 mg (Days 21-25), 2.0/0.5 mg (Days 26-30). Participants will attend the clinic twice weekly and will be assessed for opioid and other substance use (urine toxicology and self-report), vital signs, opioid withdrawal symptoms, opioid cravings, and dose adjustments of buprenorphine will be made as needed by study physicians. If a dose reduction is needed, the stabilization and taper schedule will be adjusted to occur over 30 days. Participants will be stabilized on, and tapered off, buprenorphine over a 4-week period.

Reductions will occur in a graded fashion, with the stabilization dose reduced to 2 mg. This approach to buprenorphine taper is intended to resemble standard clinical practice, in which patients seeking transition off buprenorphine undergo a slow taper. A gradual taper over approximately 4 weeks has established precedent (Sigmon et al. 2013, Ling et al. 2009, Nielsen et al. 2013) as a well-tolerated taper strategy for transitioning off buprenorphine. The purpose is in part to provide a slow transition with minimal withdrawal symptoms. Participants will have at least two study visits a week during the buprenorphine taper, but may be seen more regularly at STARS if deemed clinically necessary.

Naltrexone induction procedure: Participants who successfully complete the taper must then complete a two-day washout (abstinence for opioids, buprenorphine). During this 48-hr period, participants will report to the STARS clinic daily for vital sign monitoring and to receive ancillary medications (clonidine, clonazepam, zolpidem, prochlorperazine) to alleviate withdrawal and discomfort as needed. After abstinence of >/=48 hours from the last buprenorphine dose, to allow for mu receptor availability, participants will begin the naltrexone induction,using a 4-day ascending taper of oral naltrexone (1, 3, 12, and 25 mg), followed by injection naltrexone . The administration of naltrexone will occur within a detoxification suite provided at STARS, consisting of a private room outfitted with two comfortable reclining lounge chairs for resting, adjustable lighting, and an entertainment system. Participants will be monitored by clinical staff at least every 1-2 hours with frequent vital signs checks and withdrawal assessments. A research psychiatrist or study physician will be present at all times to conduct frequent clinical assessments and provide adjuvant medications and naltrexone. Patients will be monitored on a daily basis (Monday to Friday) for up to 8 hours per day. Transportation home by car service will be provided at the end of the day for any patient deemed to have this clinical need.

As per the dosing schedule in the protocol #6374, on Day 1 of the naltrexone induction, participants are pre-treated with prochlorperazine 10 mg for nausea, followed be the first dose of naltrexone 1mg. Ascending doses of naltrexone will then be titrated upward slowly (3mg, 12mg, 25mg). Adjuvant medications will be available to patients and will include clonidine for myalgias, prochlorperazine for nausea, clonazepam to reduce anxiety and dysphoria, and trazodone or zolpidem for insomnia. Participants will be provided take-home doses of adjuvant medications in small doses and on a tapering schedule for one week post-administration of XR-NTX. Participants will be required to visit the clinic daily and remain there for at least 1 hour to permit close monitoring, with an option to stay as long as necessary to achieve relief of symptoms and medical stability prior to being discharged home.

Once 25 mg of naltrexone has been tolerated, the participant may receive 380 mg IM XR-NTX. Additionally, for female participants, a urine pregnancy test will be obtained on the day of XR-NTX administration. Prior to administration of XR-NTX, participants who have been non-compliant with the oral naltrexone schedule, accompanied by lapses to opioid use, or in any case for which the challenge appears clinically indicated in the judgment of the study physician or research team, will receive a naloxone challenge prior to XR-NTX administration. Referrals to local treatment providers will be arranged for participants who successfully complete the study and request to continue XR-NTX maintenance.

XR-NTX injections: XR-NTX will be administered once naltrexone 25 mg has been tolerated, as an intramuscular injection (380 mg) in one buttock by one of the research psychiatrists or research nurses of STARS, who are currently trained and administer XR-NTX in other protocols. Participants will be observed for at least 2 hours after the first injection. Participants will be offered a second injection at Week 5 (four

weeks post-administration of the first injection), and a third injection at Week 9. Prior to receiving second and third injections at STARS, patients will either provide an opioid-negative urine or pass a naloxone challenge test.

Clinic visits: At each STARS visit the patient meets with the research assistant to complete research ratings, including self-report of withdrawal, mood, and drug use. Blood samples are drawn according to the protocol for naltrexone serum levels and liver enzymes. The patient provides a urine sample under observation by a staff member at each visit. STARS is staffed by both male and female research assistants so that all urines can be appropriately monitored. The sample is tested immediately for opioids with the iScreen system (Instant Technologies, Inc.) Vital signs are also taken. All data are brought to the research psychiatrist conducting the therapy, and the therapy session is held. Liver function tests will be drawn one week prior to each subsequent injection and at the end of the study(Weeks 4, 8, and 12). Serum pregnancy tests will be performed during screening and a urine pregnancy test prior to administration of XR-NTX for female participants. Any participant who is experiencing protracted opioid withdrawal will be offered clinical contact on a frequent, even daily, basis if needed. For clinical matters arising in the evenings or on weekends, participants will have access to the 24-hour emergency telephone service at STARS, staffed by physicians familiar with this protocol who can address patients' concerns.

Behavioral Therapy: All participants will receive a weekly medication adherence-focused psychosocial intervention informed by relapse prevention strategies we previously developed in Behavioral Naltrexone Therapy and delivered by the study physician (Rothenberg, Sullivan et al. 2002). We have developed a relapse prevention approach which includes an emphasis on compliance with NTX. Participants will receive this therapy during weekly visits in outpatient Weeks 1-12 following induction onto XR-NTX. We will implement our standard procedures for training, supervision, and ongoing fidelity assessments of therapy sessions. At study end, participants who have successfully completed the trial and wish to continue injection naltrexone maintenance will be referred to local XR-NTX providers or treatment programs. Participants will be encouraged to attend 12-step and other self-help groups, as well as other treatment providers, according to the selected follow-up plan they have developed with their research therapist and Study MD by Week 12.

Evaluation of dysphoria and antidepressant treatment: During the first week after XR-NTX induction, the research psychiatrist assists the patient with tapering off anti-withdrawal medications, and he/she may be continued on zolpidem or trazodone for assistance with sleep. At one visit weekly, the psychiatrist reviews the history and completes the Hamilton Depression Scale (HAM-D). Patients who continue to meet criteria for major depression or dysthymia, with HAM-D > 12, are offered antidepressant treatment based on their past experience with antidepressants, if any, and an algorithm based on our clinical experience treating opioid-dependent patients (Sullivan et al. 2006). Also, any patient with CGI severity >3 for two consecutive weeks, or CGI >5 in any week, will trigger evaluation by the study psychiatrist and initiation of antidepressant medication as clinically indicated.

Handling of Missed Doses, Lapses and Relapses

Oral Naltrexone: If the patient misses more than 1 day of oral naltrexone during the detoxification

week, and fails to provide an opioid-negative urine, relapse will be suspected, and, if appropriate, the psychiatrist will perform a naloxone challenge using 0.8 mg naloxone, administered intramuscularly. The patient is followed clinically and withdrawal symptoms are assessed over the next hour. If the challenge is negative, the oral administration of naltrexone will be resumed. If positive, then oral naltrexone cannot be resumed without risk of precipitating withdrawal, and the patient will have relapsed. Based on our experience in previous trials, the results of the naloxone challenge may be equivocal in some cases. For instance, a patient may tolerate the challenge with only minimal or mild signs of opiate withdrawal. Any patient who has experienced a recent lapse but remains compliant with attendance at his/her therapy sessions will be permitted to undergo a second naloxone challenge within 72 hours of the first failed challenge. Patients who fail two consecutive naloxone challenges are considered to have relapsed and are referred for inpatient detoxification or agonist maintenance, as deemed clinically appropriate and in accordance with the patient's wishes.

XR-NTX: Use of opiates presents different concerns in the management of patients receiving XR-NTX maintenance. Failure mode with XR-NTX is similar that a patient misses a scheduled injection, resumes using opioids, and becomes re-addicted. However, because of the long duration of action of depot naltrexone (full blockade lasts up to 5 weeks after the last injection), a grace period of at least 7 days can be expected during which the injection can be rescheduled without risk of relapse. If the patient misses a scheduled XR-NTX injection and takes an opioid during at least two of the seven days following the date of the scheduled injection, relapse will be suspected. In this case the psychiatrist will perform a naloxone challenge, if appropriate, using 0.8 mg naloxone administered intramuscularly. The patient is followed clinically and withdrawal symptoms are assessed over the next hour. If the challenge is negative, the depot administration of naltrexone will be resumed. If fully positive, then depot naltrexone risks of precipitating withdrawal, and the patient will have relapsed. However, because there are blood levels and partial blockade beyond Week 5, vulnerability to relapse may be more gradual, and the instance of mild or equivocal reactions to naloxone challenge more common. In this instance, a second challenge within 72 hours, or escalating doses of oral naltrexone over 3 days will be attempted, and if tolerated, the next injections can be given.

Procedures for Missed Doses of XR-NTX: Missing a scheduled XR-NTX injection is the most important threat to the success of long-acting naltrexone maintenance. In the event of a patient missing a scheduled injection, the clinic staff will immediately attempt to contact the patient to re-establish commitment to the naltrexone treatment and reschedule the injection within a 48-hour period. If the patient cannot attend the treatment clinic within that two-day time-frame, or cannot be located, the treatment team will use previously obtained locator information in an effort to locate the patient through emergency contacts and get him/her in for a clinic visit. If opioid use occurs in combination with a missed XR-NTX injection, a naloxone challenge will be administered to confirm that the next XR-NTX injection will be safely tolerated.

Currently the study is run under the NYS Controlled Substance license # 0400081 held by the NYS OMH and the DEA Researcher Registration # PN0093461 held by the NYSPI Pharmacy Department. As soon as the joint PI, Dr. Adam Bisaga, obtains his own NYS Controlled Substance license and DEA Researcher Registration # the projects will be run under both his researcher specific NYS license, his DEA Researcher Registration and the NYS/OMH license and NYSPI DEA Researcher Registration. The drug stock of controlled substances for each project will be ordered, maintained and prepared under the Institutional registration at the NYSPI Pharmacy (OMH/NYS Controlled Substance license # 0400081). Packaged drugs (kits) will be transferred to the Principal Investigator (Dr. Adam Bisaga) using a DEA 222 form

with the address where the study will take place (e.g. 3 Columbus Circle, Suite 1408, NY, NY 10019). Drugs or kits for individual patients will be transferred from the Institutional registration (#0400081) to the investigator registration using DEA 222 forms and transported by Marcia Loughran, FNP (supervisor of controlled substance activity) to the 3 Columbus Circle Suite 1408, NY, NY 10019 research site. Drug will then be kept in the wall mounted, double-door, double locked storage cabinets at 3 Columbus Circle until it is given to the participant.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Criteria for Study Dropout During the Buprenorphine Stabilization/Taper:
1. Participant is unable to tolerate sublingual buprenorphine/naloxone as demonstrated by continued opioid use.
2. Participant in unable to tolerate a buprenorphine taper, as indicated by moderate or severe withdrawal (COWS score 13-36).
3. Participant refuses continued buprenorphine/naloxone maintenance.
4. Participant requests withdrawal from study to receive agonist maintenance or to pursue other treatment options.
5. Participant experiences medical or psychiatric worsening of a condition deemed to make further study participation hazardous.
6. Participant is absent from study visits for 10 days.

Criteria for Study Dropout During the Detoxification are as follows:
1. Participant is unable to tolerate oral naltrexone as demonstrated by continued opioid use or a failed naloxone challenge.
2. Participant demonstrates moderate or severe opioid withdrawal in response to 25 mg oral naltrexone (COWS score 13-36).
3.Participant in unable to tolerate a buprenorphine taper, as indicated by moderate or severe withdrawal (COWS score 13-36).
4. Participant refuses XR-NTX injection.
5. Participant requests withdrawal from study to receive agonist maintenance or to pursue other treatment options.
6. Participant experiences medical or psychiatric worsening of a condition deemed to make further study participation hazardous.
7. Participant is absent from study visits for 7 days.

Criteria for Study Dropout following Detoxification:
1. Relapse to opioid dependence; patient resumes opioid use for more than 3 days and is unable to provide an opioid-negative urine or to pass a naloxone challenge.
2. Binges of opioid use resulting in overdose or severe somnolence, or in attempts to override the blockade.
3. Clinical deterioration rendering further study participation hazardous (e.g. significant worsening

of medical or psychiatric condition, elevation of liver enzymes to >3 times normal, dangerous escalation of non-opioid drug or alcohol use).
4. Participant's continued opiate use places him or her at risk for harm for self-destructive behavior or other harm as indicated by and Opiate CGI improvement score of 6 or greater for two consecutive weeks.
5. Non-compliance with study procedure (missing at least 6 consecutive visits or 2 weeks).

The Principal Investigator may also decide to administratively withdraw participants who show other clinically significant worsening of medical or psychiatric symptoms, evidence of significant discomfort related to the withholding of rescue medication, any behavior which suggests significant risk from attempts to over-ride blockade or subject request.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Serum pregnancy testing will be performed during screening. For patients whose screening bloodwork (CBC, basic metabolic panel, liver function tests) for #6374 **or #7190** were completed more than 90 days ago, these labs will be redrawn. Liver function tests will be performed during screening and at 4 weeks following administration of each XR-NTX injection. Urine toxicology screens, conducted at each visit, will serve as an objective marker of current opioid use.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Ongoing Psychiatric and Medical Assessments: The research psychiatrist will conduct weekly assessments of the psychiatric and medical status of the study participants. Participants who meet criteria for clinical worsening or the development of unacceptable medical or psychiatric risks will be removed from the trial and referred for appropriate treatment.
Study Assessments

Adverse Effects measures: The Systematic Assessment for the Treatment and Emergent Events (SAFTEE) (Johnson et al. 2005) adapted for buprenorphine and XR-NTX injections will be performed weekly to identify adverse symptoms.

Clinical Status measures: The Clinical Global Impression Scale-Observer (CGI) (Guy 1976) will be used to measure the overall clinical status of the participant as well change from baseline in the symptom severity. The Clinical Global Impression-Self (CGI-S) is a two-item scale that asks the subject to rate his or her current level of symptoms and estimate changes from baseline (Guy 1976).

Medical Evaluation and Monitoring: A medical history and physical exam will be performed during screening. Serum pregnancy testing will be performed during screening and urine pregnancy testing will be performed monthly during the study. Complete blood count, electrolyte, urinalysis, and liver function tests

will be performed during screening and monthly during the study. Height and weight will be measured and baseline body mass index (BMI) calculated during screening. Temperature, pulse, blood pressure, and weight will be measured at every study visit.

Mood and Anxiety measures: A structured interview version of the Hamilton Depression Scale (HAM-D) (Williams 1988) will be used to assess mood and anxiety symptoms at baseline and changes associated with treatment.

Psychiatric Evaluation and Diagnosis: The MINI International Neuropsychiatric Interview will be performed during screening and as part of a complete psychiatric diagnostic assessment.

Opiate Craving Scales- Self: A visual analog scales is used for patients to rate the intensity of craving experienced over the previous week for opiates (Bisaga, Sullivan et al. 2011).

Spielberger State-Trait Anxiety Test (SSTAT)- Self: The SSTAT is a well-validated measure of anxiety consisting of two self-rated subscales, one rating Trait anxiety and the other State anxiety (Spielberger, Gorsuch et al. 1970).

Beck Depression Inventory (BDI): The BDI is a 21-item self-report questionnaire. It has been used in many studies and validly and reliably assesses depression in many patient groups including substance abusers (Beck, Steer et al. 1996).

Subjective Opiate Withdrawal Scale (SOWS)- Self: The SOWS is a 19-item self-report scale reliably eliciting severity of common physical and mental symptoms of opiate withdrawal, and also yielding a total withdrawal severity score (Handelsman, Cochrane et al. 1987). It will be used to examine occurrence of symptoms resembling opiate withdrawal during naltrexone maintenance.

Risk Assessment Battery (RAB) The RAB provides a self-report measure of drug use, injection-related risk behavior, and sexual risk during the preceding six months (Navaline, Snider et al. 1994).

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
At the conclusion of the protocol, the participants will be offered supportive therapy for at

least one additional month or until an appropriate referral for on-going treatment is made. If the patient is interested to continue on XR-NTX, we will try to work with the patient's insurance to provide coverage to continue XR-NTX. If the patient wishes to be on oral naltrexone, we will provide him/her with a 30-day supply of oral medication, and will help patients to obtain referrals to treatment providers in the community.
Participants who had no response to naltrexone treatment, such as those who continued using opioids while on naltrexone as well as those who stopped taking naltrexone (missed scheduled injections) and/or resumed opioids after missing naltrexone, are considered to be at very high risk of a full relapse and overdose. These individuals will be immediately directed toward either inpatient detoxification followed by a residential treatment, or toward agonist maintenance with either buprenorphine/naloxone or methadone. Methadone maintenance treatment is widely available in the community; however, access to buprenorphine treatment is more restricted.

In order to minimize the risk of relapse due to the lack of access to the medication and the gap between treatment providers we would like to offer 2-week supply buprenorphine/naloxone 8mg to participants who are in the process of being referred out to either inpatient treatment or an agonist maintenance program. We will continue to provide additional support including frequent, daily if needed visits at our clinic for a maximum of 2 weeks.

Clinical Treatment Alternatives

Clinical treatment alternatives
Naltrexone maintenance and Relapse Prevention Therapy are effective and accepted treatments for opioid dependence. The major alternatives for outpatients with opioid dependence would be either methadone or buprenorphine/naloxone maintenance, which has a high success rate for patients willing to take it; injection naltrexone maintenance without research procedures; outpatient methadone detoxification; or inpatient detoxification followed by "drug-free" outpatient or residential counseling. Both inpatient and detoxification methods are associated with high relapse rates in the absence of antagonist maintenance.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Risks of the Buprenorphine-Clonidine-Naltrexone Procedure: In this procedure, opiate-dependent patients are stabilized for 30 days on the partial opiate agonist buprenorphine. During subsequent administration of naltrexone and throughout the detoxification, withdrawal symptoms are treated with clonidine, an alpha-2-adrenergic receptor agonist which reduces sympathetic nervous system output produced by opiate withdrawal, clonazepam, a benzodiazepine which reduces the anxiety and dysphoria and permits sleep, and other prn medications such as trazodone or zolpidem for insomnia. Opiate withdrawal causes agitation, elevated pulse and blood pressure and other signs of sympathetic arousal, and sometimes confusion. Clonidine may produce somnolence or

hypotension. Clonazepam commonly may produce somnolence. **An extremely rare potential side effect of trazodone is priapism .**The procedure is conducted in a setting equivalent to a day hospital, with a STARS study physician present at all times, to permit close monitoring of vital signs and mental status.

Buprenorphine taper: The risks associated with buprenorphine dose reduction are minimal. During the buprenorphine taper, opioid withdrawal symptoms (e.g., anxiety, muscle aches, rhinorrhea) may emerge. If the participant does not tolerate well this discomfort, he or she will meet with the study physician, and discuss options (i.e. receiving more adjuvant medications, modifying a given daily dose of buprenorphine). The participant will also be offered the option of discontinuing the taper and transitioning to buprenorphine maintenance at a dose of buprenorphine/naloxone that is comfortable, which would mean discontinuation from the study and would be considered a treatment failure in terms of achieving opioid-free status. Medications will be dispensed by medical staff trained in the use of opioids, and in the management of adverse effects of opioids. The doses proposed for use in the current application are within the recommended dose range for treating opioid addiction.

Buprenorphine diversion and abuse: The use of buprenorphine in opioid-abusing, opioid-dependent volunteers is also associated with the risk of using the medication for the purposes of getting high. If sublingual buprenorphine is crushed and used parenterally, there is a risk of precipitated opioid withdrawal, due to the release of the sequestered naloxone. Attempts to administer buprenorphine by injection have also been associated with granulomatous reactions and infections. Participants will be warned of the risks of diversion and abuse and advised not to use the medication in this manner. They will also be warned of the risks of accidental ingestion. If it is determined that patients have been abusing their buprenorphine in such a manner, they will be removed from the study and referred to methadone maintenance.

Side Effects of Naltrexone: The possible side effects of naltrexone may include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint muscle pain, and headaches. It is important to note that these symptoms may represent protracted opioid withdrawal symptoms. The most common adverse events associated with XR-NTX in clinical trials for alcohol dependence were nausea, vomiting, headache, dizziness, asthenic conditions and injection site reactions. Cases of urticaria, angioedema, and anaphylaxis have been observed with use of XR-NTX.
Naltrexone has been associated with reversible hepatocellular injury indicated by elevated liver enzymes when administered at doses substantially greater than the 50 mg per day dose recommended for maintenance treatment of opiate dependence and proposed for the present studies. When used in the recommended dose range in opiate-dependent patients, this risk is remote (Brahen et al 1988). Naltrexone is therefore contraindicated in patients with acute hepatitis or liver failure, and such patients are excluded from the study. Patients with hepatic enzyme levels greater than two times the upper limit of normal are therefore excluded. Liver enzymes will be repeated frequently. Depot naltrexone achieves higher bloodlevels than oral naltrexone initially, but these should remain lower than levels associated with hepatitis. If naltrexone-induced hepatitis were to occur in the setting of a long-acting preparation,where the naltrexone would be only very slowly eliminated, this would prolong exposure to the offending agent. However, our experience with long-acting naltrexone also suggests it is safe. In our studies with long-acting naltrexone several patients experienced elevation in liver enzymes, which were determined to be related to hepatitis C. One patient developed diabetes mellitus,

which was deemed unlikely to be study related. In the proposed study we will use a long-acting, injectable preparation of naltrexone (Vivitrol 380 mg). This preparation has been used in a large clinical trials as a treatment for alcohol dependence and is considered to have a good safety profile (Garbutt et al 2005). XR-NTX is currently approved by the FDA for the treatment of alcohol dependence.

If a patient misses a scheduled injection of XR-NTX and resumes regular opiate use, then taking a dose of naltrexone will precipitate opiate withdrawal, which may be quite severe in proportion to the time since the last naltrexone dose and the level of opiate dependence. Patients will be warned not to take the naltrexone if they have missed their dose for more than a week and resumed opiate use for more than two days. They will be

instructed instead to contact their therapist and/or research psychiatrist, who will see the patient and perform a naloxone challenge test to determine whether or not naltrexone can be safely resumed. Patients who fail two consecutive naloxone challenges (withdrawal is precipitated), are considered to have relapsed and are referred for inpatient detoxification .

Self-administration of large doses of opiates may over-ride the blockade produced by naltrexone resulting in an opiate overdose with its attendant risks, including respiratory depression and death. Patients will be warned of the severe danger of using opiates, including trying to over-ride the blockade. Also patients who have stopped naltrexone and resume opiates will not be tolerant initially, so that the quantities of opiates self-administered prior to treatment, when they were tolerant, may be quite dangerous in the non-tolerant state. Patients will be warned of this. Patients who self-administer opiates to the point of somnolence or stupor will be removed from the trial and referred to inpatient detoxification or agonist maintenance treatment. Until such patients are accepted for treatment elsewhere, they will remain in treatment at our clinic, where they will be offered therapy and treated in the open label manner for the duration of trial.

In the event of a medical emergency requiring opiate analgesia, a patient on naltrexone will require higher doses of opiates than normally administered. Patients will be informed of this and will be given a naltrexone medication card to carry in their wallet.

Naloxone Challenge Test: This test will be performed under the supervision of a study physician and will take approximately 45 min to complete. The risks of a dose of 0.2-0.8 mg naloxone administered IM are the signs and symptoms associated with opioid withdrawal (“gooseflesh,” “vomiting,” “tremor,” “uncontrollable yawning,” etc.). These will be assessed every 10 min. for up to 45 min. During the procedure, we will measure blood pressure and heart rate before and up to 30 min. after the naloxone dose.

Pregnancy: Both the buprenorphine-clonidine-naltrexone procedure and naltrexone maintenance are considered contraindicated in pregnancy. Several small case series (Hulse et al., 2001; 2004)are reassuring in suggesting favorable pregnancy outcomes in women detoxified and maintained on naltrexone while pregnant. However, standard practice suggests methadone maintenance is the treatment of choice for opioid dependent pregnant women, and we do not consider the small size of these case series sufficient to amend that recommendation. Absence of pregnancy will be confirmed at baseline and monthly during the study with urinary HCG. During the inpatient detoxification period, a serum (quantitative) pregnancy test will be obtained on admission and repeated on the day prior to administration of depot naltrexone. For women, regular use of an adequate contraception method (diaphragm with spermicide, condom with spermicide, birth control pills) is required for inclusion in the study. Patients who become pregnant during the trial

will be removed from the trial and treated as clinically indicated.

Blood Tests: Blood drawing may cause slight discomfort at site of needle entry, resulting in a small bruise. Other risks include patients' discomfort with being asked uncomfortable questions or the psychological distress that may occur if a patient agrees to be tested for HIV.

Risks associated with receiving vouchers or cash equivalents: An incentive system is being used to compensate patients for their time and travel and to encourage compliance with study procedures. For that purpose we have adopted procedures used widely in the context of Contingency Management Therapy. We believe that using low-value incentives is essential to maximize participation in study-related procedures, including nursing and physician visits for safety monitoring, study outcomes collection, and therapy participation. Risks that participants will attempt to use study payments to purchase drugs, though still present, are rather small with current procedures.
Describe procedures for minimizing risks
The exclusion criteria of this study are designed to minimize the risks to participants.
Patients are excluded if they have severe psychiatric illness (mood disorder with functional impairment or suicide risk, schizophrenia) which might interfere with their ability to participate in the outpatient therapy. A history of drug overdoses will be exclusionary. Pregnancy, lactation, or failure to practice a reliable birth control method is exclusionary, and patients are instructed to inform their psychiatrist immediately if they suspect they may be pregnant. Urine HCG is tested during screening and monthly throughout the trial. Serum (quantitative) pregnancy test will be obtained during screening. The baseline medical evaluation includes physical examination, blood chemistry profile (including liver function tests), complete blood count, urinalysis (including HCG), and electrocardiogram, urine toxicology, and naloxone challenge if opiate dependence diagnosis is unclear. The evaluating psychiatrist reviews all these and takes a medical history. Any disorders which might make buprenorphine-clonidine-naltrexone or naltrexone maintenance hazardous, such as uncontrolled hypertension, diabetes, heart disease, hepatitis with transaminase levels greater than three times the upper limit of normal, renal disease, or advanced AIDS are exclusionary. Patients with acute hepatitis infection and increasing liver function tests during screening will be excluded from study participation. The patient will be assisted in obtaining appropriate medical evaluation and treatment, and may be eligible for the research study once the problem is controlled. History of an allergic reaction to any of the medications used is an exclusion criterion.

Patient Education: All patients will be informed through the informed consent form and discussions with the research psychiatrist of the possible side effects and risks enumerated above. In addition, at weekly visits the psychiatrist will query side effects in general, and events of specific concern including missing naltrexone doses in conjunction with resumed opiate use or heavy opiate use in an effort to over-ride the blockade, and the risk of overdose and death in these situations. Patients will give informed consent before entering the study. Patients are instructed to call us if any untoward effects occur and are given the phone number of our 24-hour answering service.

Patient Monitoring and Removal from Study: The psychiatrist and/or therapist will assess appropriateness for continuation in the research study on a continuous basis, and will remove

from the trial patients with significant clinical deterioration or noncompliance of a type which could be dangerous.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
A Certificate of Confidentiality has been acquired for this study from the National Institute on Drug Abuse to offer protection for the privacy of subjects by protecting identifiable research information from forced disclosure (e.g., through a subpoena or court order). The Certificate of Confidentiality allows investigators and others with access to research records to refuse to disclose information that could identify subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. The Certificate of Confidentiality is granted for studies that collect information that, if disclosed, could damage subjects' financial, employability, insurability, or reputation, or have other adverse consequences.

We use coded records (i.e. initials and numbers), store signed consent forms in a locked safe, and try, to the best of our ability to maintain confidentiality. Only coded records will be entered into the computer and the security of electronic data is ensured at the level of the server, the user, and the database. We do, however, point out to prospective patients, that we cannot assure that their drug histories and other personal records might not become know.
Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects

Participants may benefit from many of the components of the treatment that they receive, including buprenorphine stabilization, induction onto injection naltrexone, naltrexone maintenance, and components of behavioral therapy.

Further, because participants are recruited from the pool of participants that fail XR-NTX induction as part of one of two trials, an additional potential benefit is a decrease in time to treatment following study discontinuation from the parent protocols (IRB #6734 or IRB #7190). Immediately following discontinuation from the initial protocol, participants are eligible for the current protocol and if enrolled can be stabilized on buprenorphine, thereby potentially reducing overdose risk, in a more timely fashion than if referred to treatment in the community.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will receive $10 for completion of study assessments at each visit and will receive compensation for travel ($5 per visit). They will also be offered $25 for completing a follow-up visit at week 12 and will receive $5 for travel. Thus participants could earn up to $480 for completion of study assessments and reimbursement for travel.

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