A STRATEGY TO IMPROVE SUCCESS OF TREATMENT DISCONTINUATION IN BUPRENORPHINE RESPONDERS

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New York State Psychiatric Institute - Columbia University
Department of Psychiatry
Institutional Review Board

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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 proposing an amendment only to an existing protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
SUBSTANCE USE
Within the division/department, what Center or group are you affiliated with, if any?
SUBSTANCE TREATMENT AND RESEARCH SERVICES

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

Amendment

Describe the change(s) being made

1.We are also requesting to collect blood, urine and saliva at Baseline, after randomization (3 weeks after 1st injection of XR-NTX, or 1 week after completing bup taper), during post randomization month 2 (1 week after 2nd XR-NTX injection, or 4 weeks after completion of bup taper), and at end of study to be examined for biomarkers.

Provide the rationale for the change(s)
Additional study aim.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
None
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
yes

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

✓ Medically and Psychiatrically Healthy Subjects
✓ 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 application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
National Institute on Health
Grant Name
A Strategy to Improve Success of Treatment
Grant Number
1R21DA042243
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

Study Location

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

Lay Summary of Proposed Research

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The current guidelines for buprenorphine (BUP) treatment advocate an open ended, long-term maintenance approach. However, many individuals initiating treatment with BUP, particularly youth and those with brief history of prescription opioids abuse, expect a short treatment episode and are disappointed that treatment extends and may even be indefinite. As such, many patients that responded favorably to treatment intend to discontinue medication, whether by deciding unilaterally to stop it, or by a route of physician-directed BUP taper. However, it is not known what is a best strategy to assure a successful BUP discontinuation without

the risk of relapse.

We propose an open--label randomized outpatient trial to evaluate feasibility and efficacy of rapid buprenorphine (BUP) discontinuation followed by brief course of treatment with long--acting naltrexone (XR--NTX) and to compare it to the standard method of gradual BUP taper. Individuals with opioid use disorder (OUD) (N=60) who have successfully completed at least 6 months of buprenorphine treatment and do not wish to remain in a long--term buprenorphine maintenance program will be recruited. The first phase includes a 4--week period of stabilization on buprenorphine **2**--8 mg at the research clinic to assure that patients are stable, compliant, and free from illicit opioids. Participants that meet the above criteria will be randomized 1:1 to: 1) buprenorphine discontinuation and outpatient transition to XR--NTX with 3 monthly injections, or 2) buprenorphine discontinuation using a gradual 5-week long taper. In both groups participants will receive weekly relapse prevention therapy and will be monitored for the duration of the trial, which is 25 weeks post randomization.
The primary outcome will be the percent of patients successfully transitioned off buprenorphine and abstinent from any opioids at the 25--week trial endpoint. Secondary outcomes will include measures of opioid withdrawal, mood, anxiety and sleep problems, abstinence from other substances, time to relapse or dropout, and adverse effects. We hypothesize that more patients will successfully discontinue buprenorphine in the group that received XR--NTX.
This proposed exploratory trial will be able to inform the design of future research and clinical work.

Background, Significance and Rationale

Background, Significance and Rationale
The number of individuals with Opioid Use Disorder (OUD) continues to rise with more than 2.5 million affected, along with substantial morbidity and mortality. Maintenance treatment with the opioid partial agonist buprenorphine or buprenorphine/naloxone (BUP) is becoming a treatment of choice in the primary care setting. As many patients who had good treatment response desire to discontinue the medication there is a need for evidence on the best strategy to accomplish that. We propose to evaluate whether an addition of a short course of a long--acting, injectable naltrexone (XR--NTX) improves the chances of successful BUP discontinuation and transition to sustained abstinence off all opioids.
The current guidelines for BUP treatment advocate an open ended, long--term maintenance approach. However, many individuals initiating treatment with BUP expect a time--limited and short treatment, a “detoxification--like” experience rather than “methadone--like maintenance treatment,” and are disappointed that treatment is protracted and may even be indefinite. This is especially relevant for youth and those with brief history of addiction to prescription opioids. More than 60% of patients maintained on BUP or methadone expressed interest in discontinuing medication in the near future and more than 70% have previously tried that (Winstock et al., 2011). It is not known how many patients with a positive treatment response are interested in stopping BUP but more than half of such patient may eventually drop out of treatment (Fiellin et al., 2008). It is not well understood to what extent withdrawal--like symptoms play a role in relapse and how the addition of a brief course of naltrexone may influence the severity of

withdrawal and the success of BUP discontinuation. To our knowledge none of these questions have been evaluated experimentally and we believe that it may have a
significant impact on the field considering that up to 1 million patients are treated with BUP every year.

Benefits of and challenges associated with buprenorphine discontinuation
Determining when and how individuals can be safely tapered from BUP using a "planned approach" has several potential benefits. First, patients may feel encouraged that they may be able to discontinue treatment in the near future and therefore will be less likely to discontinue it unilaterally. Second, patients who do not need to be maintained on BUP indefinitely and are taken off it, will have lower risk of medication--related adverse effects and have lower treatment cost. Third, in areas of the country where BUP providers have reached the limits of prescribing for 100 patients, and patients on waiting lists for treatment remain at serious risk for overdose and other adverse consequences of use, safely transitioning patients off BUP would enable more patients to access treatment. Finally, a number of fee--for--service Medicaid plans have implemented lifetime limits on prescriptions for BUP, ranging from 12 to 36 months (Rinaldo and Rinaldo, 2013), and a strategy that can shorten BUP treatment without compromising outcome may help patients in those states.

The main challenge to BUP discontinuation is that many patients experience significant and protracted discomfort, withdrawal--like symptoms with increase in craving as well as mood anxiety and sleep disruptions (Dunn et al., 2015). These symptoms emerge even as the dose is being gradually reduced. As a result, many will abandon the attempt at discontinuation and resume BUP maintenance. If the patient stops medication on their own, and cannot easily resume treatment, they may relapse to illicit opioids. Therefore, the question of how to discontinue treatment in patients who favorably responded to BUP is of high significance to the field as it may address several important questions with clinical relevance.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
The primary outcome will be the percent of patients successfully transitioned off buprenorphine and abstinent from any opioids at the 25--week trial endpoint.

Secondary outcomes will include measures of opioid withdrawal, mood, anxiety and sleep problems, abstinence from other substances, time to relapse or dropout, and adverse effects.

Additionally we will examine in biofluid derived extracellular vesicle content for the existence of biomarkers related to naltrexone treatment.

We hypothesize that more patients will successfully discontinue buprenorphine in the group that received XR--NTX.

Description of Subject Population

Sample #1

Specify subject population
Adults ages 18-60 currently treated with buprenorphine for opioid use disorder
Number of completers required to accomplish study aims
50
Projected number of subjects who will be enrolled to obtain required number of completers
60
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown
Both males and females will be recruited. All eligible subjects are accepted; however, past experience with recruitment for other studies in this population suggests that that the sample will be 75% male, 60% Caucasian, 30% Hispanic or Latino, and 10% Black or African-American.
Description of subject population
Adults ages 18-60 currently treated with buprenorphine for opioid use disorder

Recruitment Procedures

Describe settings where recruitment will occur
All potential participants will be evaluated at the BSU clinic at the New York State Psychiatric Institute.
How and by whom will subjects be approached and/or recruited?
All patients will be seen by one of our psychiatrists or Master's level therapist for a screening evaluation and mental status examination as part of routine admission procedures or BSU clinic . Patients who appear to meet criteria are told about the study and offered further evaluation. Final informed consent for the study will be obtained after full psychiatric and medical workup is complete. The physicians listed above work regular weekly shifts, know the protocol well, and are able to explain study consent to the participant. Procedures for training staff physicians in each protocol and consent form include initial presentations by the Principal Investigator at weekly staff meetings, and weekly discussion of inclusion/exclusion criteria and study eligibility for each screening participant.
How will the study be advertised/publicized?
Once approved by the IRB, advertisements for study will be placed **on the subway and in** local newspapers and radio stations. Additionally, prospective participants are recruited by word of mouth and through liaison to other local clinical services.
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
NCT03232346

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
No

Inclusion/Exclusion Criteria

Name the subject group/sub sample
All participants
Create or insert table to describe the inclusion criteria and methods to ascertain them
Inclusion Criteria:
• A documented history of treatment with buprenorphine or buprenorphine/naloxone for at least 6 months with sustained abstinence from illicit opioids for at least 3 months. Participants must be maintained on daily dose of buprenorphine in the **2**--8 mg range.(MINI interview by therapist, Clinical interview by psychiatrist, consultation with previous prescriber or the verification patients's self-report with the prescribing records (PMP) with patient's permission)
• Aged 18 to 60 years (Clinical interview)
• In otherwise good health based on complete medical history, physical examination, vital signs measurement, ECG, and laboratory tests (hematology, blood chemistry, urinalysis) within normal ranges (Medical history and physical examination by psychiatrist or NP, laboratory tests (serum Chem-20 and CBC, urinalysis), ECG)
• Seeking buprenorphine discontinuation and willing to accept randomization to either taper from buprenorphine or injection naltrexone (clinical interview)
• Able to give written informed consent to participate in the study
Create or insert table to describe the exclusion criteria and methods to ascertain them
1. Lifetime history of DSM-5 diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder (MINI interview by therapist, Clinical interview by psychiatrist)
2. Current DSM-5 criteria for any other psychiatric disorder that in the investigator's judgment is unstable, would be disrupted by the study medication, or is likely to require pharmacotherapy or psychotherapy during the study period. Concurrent treatment with other psychotropic medication is **not** exclusionary, **as long as participants have been stable on their current dose for at least 3 months**.
(MINI interview by therapist, Clinical interview and mental status exam by psychiatrist, contact with collateral information as needed and available)
3. Individuals who meet DSM-5 criteria for any substance use disorders - severe, other than opioid and nicotine use disorder. Physiological dependence on alcohol or sedative-hypnotics is exclusionary.
(MINI interview by therapist, Clinical interview by psychiatrist)
4. A recent history of binge-use of alcohol or sedative-hypnotics (using large amounts in a short time to severe intoxication or blackouts).
(Clinical interview by psychiatrist)
5. Pregnancy, lactation, or failure to use adequate contraceptive method in female patients who are currently engaging in sexual activity with men.
(Clinical interview by psychiatrist, physical examination and medical history by psychiatrist or NP, urine pregnancy test, serum HCG)

6. Unstable medical conditions, such as AIDS, cancer, uncontrolled hypertension (blood pressure > 140/90), uncontrolled diabetes, pulmonary hypertension or heart disease.
(Medical history and physical examination by psychiatrist or NP, laboratory tests (serum Chem-20 and CBC, urinalysis), ECG)
7. Legally mandated to participate in a substance use disorder treatment program.
(Participant self-report, Clinical interview by psychiatrist)
8. Current or recent history of significant violent or suicidal behavior, risk for suicide or homicide (MINI interview by therapist, Clinical interview by psychiatrist)
9. History of accidental opioid overdose in the last three years or any other significant history of overdose following detoxification within past 10 years defined as an episode of opioid-induced unconsciousness, whether or not medical treatment was sought or received.
(MINI interview by therapist, Clinical interview by psychiatrist)
10. Elevated liver function tests (AST and ALT > 3 times the upper limit of normal)
(Laboratory tests -serum Chem-20)
11. Known history of allergy, intolerance, or hypersensitivity to naltrexone or any other study medications
(Participant self-report, Clinical interview by psychiatrist)

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?
No
Describe procedures used to obtain consent during the screening process
Potential participants will sign a consent form prior to initiating the screening process. Following review of screening informed consent, an evaluation team consisting of a Masters- or Doctoral-level research psychologist and psychiatrist meets with potential participants. The baseline evaluation includes a full battery of self-report measures, a structured psychiatric evaluation (MINI interview), Hamilton depression scale, a physical examination, and laboratory assessments. Medical screening and laboratory work, include vital signs, a physical examination, ECG, serum chemistry, liver function tests, complete blood count, and

urinalysis obtained by study personnel. Pregnancy tests will be conducted for women.
Describe Study Consent Procedures
After the screening evaluation, the study physician will review the study inclusion/exclusion criteria to determine if the participant is eligible for the study based on the screening materials. If the participant is eligible for the study, they will be given the consent form to read, and review with the consenting physician. The study consent will only be signed after all of the participant's questions are asked, and after all the risks and benefits are explained to and understood by the participant. Study related procedures will only be initiated after the consent form is signed by both the participant and consenting physician.
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
Blevins, Derek
Brezing, Christina, MD
Kidd, Jeremy
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Shulman, Matisyahu, MD
Vaezazizi, Leila
Wai, Jonathan, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

This is an open-label randomized outpatient trial to compare the safety and efficacy of two methods of transitioning patients off BUP. Opioid-dependent individuals who have successfully completed at least 6 months of BUP treatment and do not wish to remain in a long-term BUP maintenance will be screened for enrollment.

In the first stage (led-in phase) participants will be maintained on their usual dose of BUP (**2**-8 mg) at the research clinic for 1 month to assure that they are stable, compliant, and free from illicit opioids. Following that, participants will be randomly assigned to begin treatment with one of two regimens: 1) rapid BUP discontinuation and transition to XR-NTX, or 2) 5-week long BUP taper. Participants randomized to XR-NTX will receive a total of 3 injections. In both groups, participants will receive weekly individual therapy and monitoring for **3 months** post-randomization. During months 4-6 participants will be seen twice

monthly for therapy and monitoring. The primary outcome will be a binary indicator of discontinuation success, the percent of patients successfully transitioned off BUP and abstinent from opioids at the end of the trial, 25 weeks after randomization. We hypothesize that success rate will be greater in patients that received treatment with XR-NTX.

Setting and Screening: This study will be conducted at the BSU clinic at NYSPI where we have previously carried out recruitment and treatment of opioid-dependent subjects using similar methodology. A combination of radio, print, and Internet advertising will be directed at prospective participants in the New York metropolitan area. Screening procedures are standardized for clinical trials including a telephone interview, the MINI International Neuropsychiatric Interview, psychiatric evaluation, medical history, physical and laboratory examination. The research psychiatrist will offer eligible individuals participation in the study and will obtain informed consent.

Randomization. We predict that 50 participants (out of 60 enrolled) will complete lead-in phase successfully and will be available for randomization. The 1:1 randomization will be stratified by the BUP maintenance dose (4 mg/d vs. greater than 4 mg/d) and the type of the primary drug (prescription opioids vs. heroin) distributing these potential prognostic factors equally between groups to ensure comparable representation. The randomization sequence will be carried out by a research pharmacist, balanced in random blocks to protect allocation concealment.

Regimen 1 will include a rapid Monday to Friday oral naltrexone-induction procedure: last dose of BUP on Sat, Sun-Mon 0 mg, Tue 1 mg, Wed 3 mg, Thu 6 mg dose of oral NTX respectively. On Friday, a final 25 mg dose of oral NTX will be given followed by an injection of XR-NTX (Vivitrol; 380 mg IM). All doses of oral NTX will be given in a single or split doses depending on patients' tolerability of the protocol. Throughout the induction adjuvant medications will be administered on standing basis: clonidine 0.1 mg qid, clonazepam 0.5 mg qid, and zolpidem 10 mg HS. Additional injections of XR-NTX will be administered 4 and 8 weeks after the first injections to participants who provide an opioid-negative urine or pass a naloxone challenge test.

Procedures for Missed Doses of Long-acting Naltrexone:Missing a scheduled Vivitrol 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, or as soon as possible thereafter, based on clinical judgement(i.e., after a clinical assessment and naloxone challenge if indicated). If the patient cannot attend the treatment clinic within that 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 Vivitrol injection, a naloxone challenge will be administered to confirm that the next long-acting naltrexone injection will be safely tolerated.

Regimen 2 will include a 5-week BUP taper from the maintenance dose of 8, 6, 4, or 2mg (wk 1: 6, 5, 3 **2**mg/d, wk 2: 4, 4 or 2 mg/d, wk 3: 3, 3 or 2 mgd/, wk 4: 2 mg/d, wk 5: 1 mg/d). A buprenorphine/naloxone generic product will be used. Participants will be offered adjuvant medications, which will be administered on standing basis: clonidine 0.1 mg qid, clonazepam 0.5 mg qid, and zolpidem 10 mg HS**.** Additional

injections of XR-NTX will be administered 4 and 8 weeks after the first injections to participants who provide an opioid-negative urine or pass a naloxone challenge test.

Participants in both regimens will be seen in the clinic for 25 weeks for follow-up after randomization, which will include both the week induction onto Vivitrol in Regimen 1 and the 5 week buprenorphine taper in Regimen 2.

We will collect 4ml of saliva, 50ml of urine, and 4, 6-7ml blood from subjects at baseline, after randomization (3 weeks after 1st injection of XR-NTX, or 1 week after completing bup taper), during post randomization month 2 (1 week after 2nd XR-NTX injection, or 4 weeks after completion of bup taper), and at end of study to be examined for biomarkers. From these we will isolate extracellular vesicle-containing pellets and evaluate their contents using advanced -OMICs analyses, in order to identify molecular signatures that differ across subjects before and after ending treatment with buprenorphine.

Study blinding. All participants will receive open-label medication as this is an effectiveness trial of two different regimens for managing patients discontinuing BUP treatment, tested as they would be used in community-based clinical treatment.

Psychotherapy platform. Following study enrollment, all participants will be offered weekly therapy, delivered by a therapist, that will follow the Community Reinforcement Approach: CRA (Budney and Higgins, 2000). CRA is a skills oriented treatment that emphasizes building a lifestyle which increases the opportunities for alternative reinforcers to drug use. CRA has been a central component of the behavioral treatment program developed by our group to improve the efficacy of naltrexone based treatments for OUD (Nunes et al., 2006; Rothenberg et al., 2002; Sullivan et al., 2015) and we have extensive experience implementing this flexible treatment protocol and assuring treatment fidelity. We will offer the following modules: Building and enhancing social support network; Social skills and relationship enhancement training; Management of mood and emotions; Increasing pleasant activities; Job-seeking skills; and Termination (Rothenberg et al., 2002). We will also incorporate a contingency reinforcement schedule to reinforce clinic visits to increase frequency of outcomes collection. As patients progress in treatment, we will support patient-directed recovery plan focusing on individual's strengths to build meaningful and satisfying life and we will proactively link patients to recovery support resources. We have been implementing evidence-based therapy in our clinic for close to 20 years and we have established procedures for therapist training, supervision, and treatment fidelity assurance (e.g. recording of therapy sessions).

Outpatient Study Visits and Assessments will occur weekly during the period of BUP maintenance and taper to ensure adherence and to monitor for abstinence. Study visits will take place daily during XR-NTX induction and weekly following injection naltrexone or BUP taper in both regimens for the remainder of the study period. Once per week participants will meet with a therapist and complete study assessments. They will have scheduled meetings with a study psychiatrist weekly to inquire about medication effects and any changes in their medical/psychological condition following medication discontinuation.

Evaluation of Depression and Anxiety symptoms: Participants who meet criteria for a Mood Disorder (MDD) of mild to moderate severity or an Anxiety Disorder will be followed closely during detoxification and subsequently. Mood and anxiety will be assessed both in therapy sessions and during MD visits. If a

patient demonstrates significant symptoms which persist following detoxification, we will offer the participant the option of beginning an antidepressant or an anti-anxiety treatment if deemed clinically warranted.

Managing controlled substances: 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. Dr. Bisaga has obtained his own NYS Controlled Substance license and a federal DEA research license. . 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).

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Drop out criteria during the study period include:

1) Development of serious psychiatric symptoms as indicated by the Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks or psychiatric or medical deterioration that cannot be managed safely in the context outpatient treatment offered at the study (in cases where the investigator determines that the participant needs immediate study discontinuation).

2) If the participant's continued opioid or other drug use places him/her at risk for self-destructive behavior or other harm as indicated by a CGI improvement score of 6 or more (much worse than baseline) for 2 consecutive weeks. In cases where the investigator determines that the participant needs immediate study discontinuation for continued opioid or other drug use, participants will be provided with referrals.

3) Development of serious medical condition(s) that may or may not be related to study participation as assessed by weekly visits with the psychiatrist, vital sign measurements, and weekly weight-ins.

4) If the participant becomes pregnant as assessed by monthly urine pregnancy testing

5) Ongoing non--adherence with recommended clinical visits, absence from study visits for 21 days.

Patients who are exited from the trial for any reason will be offered continued treatment in the community unless a higher level of care is indicated (inpatient or residential treatment), or the patient requests treatment elsewhere, in which care help with arranging referrals will be offered. A clinic staff member, with physician backup, is available 24 hours per day by phone in case of emergency.

Participants may be removed from the trial if they repeatedly miss scheduled appointments or clinical

worsening necessitates more intensive treatment (drop out criteria are defined above). Subjects who develop serious psychiatric symptomatology (e.g., psychosis, suicidal ideation, severe depressive symptoms) during the study period will be dropped from the study and appropriate clinical referrals will be made. A patient who's continued opioid use places them at risk for self-destructive behavior or otherwise places them at significant risk will be discontinued from the study. This would include, but not be limited to, patients who become unconscious after using, engage in destructive or violent behavior while intoxicated, report driving while intoxicated, or develop medical complications from their opioid use. In all cases where subjects are discontinued from the study, the clinical research staff will assume clinical responsibility for the subjects until clinical referrals are operational.

In case that the patient is removed from the research trial for medical reasons, or is requesting withdrawal from the study, he/she will be retained in open treatment for the remaining study period. Upon removal of a patient from the trial due to clinical deterioration, the patient will be referred for appropriate follow-up treatment, in most instances either intensive outpatient or residential treatment. The PI or a study psychiatrist is available 24 hours/day by phone and/or beeper in case of emergency.

If a patient is discontinued from the study, or decides to withdraw, or relapses during study the participation, the patient will get treated with buprenorphine until they are linked with a referral for continuing buprenorphine treatment. Participants will receive a one-week supply of buprenorphine at a time during the transition process.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

Urine samples will be collected at every visit, and we will use onsite testing to provide immediate feedback on opiate use to the participant and the treatment team. Blood chemistry will be obtained at baseline and end of study (week 25). Urine Pregnancy tests will be obtained at baseline, at once monthly (or prior to administration of XR-NTX).

We will collect 4ml of saliva, 50ml of urine, and 4, 6-7ml blood from subjects at Baseline, after randomization (3 weeks after 1st injection of XR-NTX, or 1 week after completing bup taper), during post randomization month 2 (1 week after 2nd XR-NTX injection, or 4 weeks after completion of bup taper), and at end of study to be examined for biomarkers. From these we will isolate extracellular vesicle-containing pellets and evaluate their contents using advanced -OMICs analyses, in order to identify molecular signatures that differ across subjects before and after ending treatment with buprenorphine.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Physiological Measures
Medical History and Physical Exam: A comprehensive medical history and physical examination will be performed during the screening process. All potential participants will be offered the opportunity to be referred to receive free HIV risk reduction education, as well as HIV testing and counseling.

Pregnancy Testing: Serum pregnancy testing will be performed on all females during screening and urine pregnancy tests will be performed at baseline and monthly afterwards.

Serum laboratory examination: Complete blood count, electrolyte, and liver function tests will be performed during the screening process and at the end of study.

Urinalysis: Laboratory urinalysis (glucose, protein, ketones, pH, specific gravity, and microscopic analysis) will be performed during the screening process and at the end of study.

Urine Toxicology: Urine samples will be collected under directly--observed conditions during screening and at each study visit. To provide immediate feedback to the participant, the Abuscreen On--Trak system (Roche Diagnostics) will be used to identify opiates (morphine, oxycodone, buprenorphine, methadone). In addition, the sample will be analyzed for substances of abuse, including THC, alcohol, opioids, cocaine, benzodiazepines, amphetamines, and barbiturates.

Vital Signs: Temperature, pulse, and blood pressure will be measured at every study visit for data collection and safety monitoring purposes. Height and weight will be measured and baseline body mass index (BMI) calculated during screening. Weight will be recorded and monitored at each visit throughout the study period.

Interviews

Clinical Global Impression Scale--Observer (CGI): The CGI Severity and CGI Improvement scales (Guy, 1976) will be used to measure the overall clinical status of the participant as well as change from baseline in symptom severity, functional impairment, and psychiatric symptoms. The CGI Improvement scale will be used to determine whether a participant needs to be discontinued from the study and provided with an appropriate clinical referral.

Hamilton Depression Scale (HAM--D): This is the standard clinician--rated instrument used to assess depressive symptoms in clinical trials to assess baseline severity and changes associated with treatment. We use a 25--item, structured interview version (SIGH--D--DES) that incorporates the reverse vegetative symptoms of the atypical subtype of major depressive disorder (Williams, 1988), but permits calculation of the standard 17-- and 21--item scores imbedded in the scale. In addition to mood symptoms, the HAM--D has items that measure anxiety, irritability, and insomnia, which are symptoms of interest for this study. The HAM--D will be performed at baseline and twice per month thereafter throughout the trial.

Hamilton Anxiety Scale (HAM--A): The HAM--A is a standard clinician--rated instrument used to assess

the severity of anxiety symptoms (Maier et al., 1988). The scale consists of 14 items, measuring both psychic anxiety and somatic anxiety. The HAM--A will be preformed at baseline and and twice per month thereafter throughout the trial.

The MINI International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) will be performed during screening as part of a complete psychiatric diagnostic assessment.

Structured Medication Count Interview is a Timeline Follow--Back assessment of study medication compliance accounting for each dose of prescribed study medication during the study period. Structured pill count interviews will be conducted weekly.

Systematic Assessment for Treatment and Emergent Events (SAFTEE): The SAFTEE as modified for Project COMBINE (Johnson et al., 2005) will be performed weekly, **and twice-monthly during study months 4-6** to identify any adverse symptoms. If participants report experiencing adverse symptoms since the previous visit, the research nurse will record the symptom as well as the date of onset, severity, and resolution (if applicable) and research psychiatrist will review it at least weekly and more frequently if symptoms are present.

Timeline Follow--Back (TLFB): The Timeline Followback method (Litten and Allen, 1992) will gather self-- reported opioid use data for each day during the month prior to study enrollment and each day during the study period. The TLFB confirmed by urine toxicology will be the primary outcome measure of psychoactive substance use and will be performed at **every study visit.**

Therapist Contact Log (TCL): The number and duration of treatment sessions will be documented by the therapist on a contact log.

End of Study Form (ESF): At study completion or the point of termination for patients who relapse or drop out, the research psychiatrist fills out an End of Study Form, which indicates whether or not a patient completed 25 weeks of treatment, the date of termination, the number of weeks of treatment completed from randomization to termination, and reasons for early termination, including documented relapse to opiates, resumption of buprenorphine maintenance, psychiatric worsening, medical worsening, or lost to follow--up.

Self--Report

Clinical Global Impression--Self (CGI--S): The CGI--Self 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). The CGI--S will serve as the primary self--reported measure of overall functioning.

Medical Outcomes Study—Sleep Scale (MOS--SS): The MOS--SM is a 12--item measure for characterizing the quality of sleep (Hays et al., 2005). Opioid withdrawal, both acute and protracted is characterized by insomnia and other sleep disturbances. The MOS--SM will be the primary outcome of sleep quality and length and will be collected at each visit.

Craving Scales-- Self: A visual analog scales is used for patients to rate the intensity of craving for opiates experienced since the previous visit (Bisaga 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 et al., 1970).

Beck Depression Inventory (BDI)-- Self: 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 et al., 1996) and it will be collected weekly, **and twice-monthly during study months 4-6.**

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 et al., 1987). It will be used to examine occurrence of symptoms resembling opiate withdrawal during naltrexone maintenance and will be collected at each visit.

Locator Form-- Self: In order to facilitate the location of drop--outs for follow--up evaluation, a standard location form will be administered at baseline and updated monthly. This indicates names, addresses and phone numbers of family members and close friends likely to know patients' whereabouts along with permission to contact them in the future.

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?
Yes
Maximum duration of delay to any treatment
A delay of up to 2 weeks is possible prior to enrollment.
Maximum duration of delay to standard care or treatment of known efficacy
Up to two weeks.
Treatment to be provided at the end of the study

Discharge and aftercare planning and implementation will be incorporated into the study. A Discharge Plan will be completed by a clinician and approved by a study physician prior to the End of Study visit. After the End of Study, participants will continue in a follow-up phase with once weekly clinic visits with their therapist for up to one month in order to facilitate transition and permit overlap with another treatment program for aftercare. Discussion of treatment recommendations as well as risks and benefits of accepting and refusing referrals will take place and will be documented.

Clinical Treatment Alternatives

Clinical treatment alternatives
The major alternatives for long-term treatment of opiate dependence are "drug-free" treatment on either an outpatient or residential basis, or agonist maintenance with methadone or buprenorphine, all available by referral. Other options available in the community include either hospital-based detoxification (often agonist-assisted) to a "drug-free" state, which is available to the patients by referral, or outpatient methadone detoxification, which is available at some methadone clinics. Regardless of treatment, the risk of relapse to illicit opiate use is very high once the detoxification is completed without medication-based relapse prevention treatment. XR-naltrexone is FDA-approved for relapse prevention treatment of opiate dependence.
During the initial informed consent process, patients will be informed about alternative treatments and their availability, and that they are free to choose among the options, at baseline or at any time during the study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Side Effects, Risks, and Interactions of Buprenorphine
Buprenorphine has been associated with adverse effects typical of opioid agonist drugs (e.g. sedation, constipation, insomnia, headache, nausea), although as a partial agonist such effects are typically less pronounced than they would be with a full agonist. The most common adverse event associated with the sublingual administration is oral hypoesthesia. Other adverse events were constipation, headache, intoxication, disturbance in attention, palpitations, insomnia, sweating, and blurred vision. Buprenorphine by itself has little tendency to suppress respiration and is associated with a low risk of overdose, a safety advantage. However, there is a risk of overdose if buprenorphine is combined with sedative drugs such as benzodiazepines or alcohol, analogous to the risk of combining such sedating medications with a full agonist like methadone. As a partial agonist, buprenorphine can precipitate an acute opioid withdrawal reaction if taken within 12--18 hours of another short--acting full opioid agonist, or within 48--72 hours of a longer--acting full opioid such as methadone.
Discontinuation of buprenorphine is associated with opioid withdrawal symptoms ranging from mild--moderate to more severe reactions. Study physicians have extensive experience, in both research and

clinical settings, in administering buprenorphine and in the management of opioid withdrawal symptoms. The use of buprenorphine is also associated with the risk of using the medication for the purposes of intoxication. In the present study we will use buprenorphine/naloxone combination product, which has lower abuse liability. If sublingual buprenorphine is used parenterally, there is a risk of precipitated opioid withdrawal. Such an event, if it were to occur, would be short--lived and not life threatening. Participants will be warned of this risk and advised not to use the medication in this manner. If it is determined that patients have been abusing their buprenorphine in such a manner, they will be declared to have failed BUP discontinuation, and a new treatment plan will be developed by the patient's clinical team, with possibilities including transfer to naltrexone or methadone maintenance. To minimize the risk of diversion, medication will be dispensed for short time intervals (1--2 weeks of medication at a time).
Buprenorphine is metabolized principally by CYP3A4. Co--administration of other CYP3A4 inhibitors (e.g. anti-- retrovirals efavirenz, delavirdine, atazanavir or atazanavir/ritonavir;; the anti--fungal agent ketoconazole;; antibiotics erythromycin or clarithromycin) may cause an increase in systemic levels of buprenorphine, although this does not usually have clinically significant effects. When a patient being prescribed buprenorphine is also receiving other medications, the prescribing physician will check for potential interactions ahead of time and monitor during treatment.

Side Effects of Extended--Release (XR), Injectable Naltrexone
The most common side effect associated with injectable naltrexone is injection site reaction. XR-naltrexone is administered as a gluteal intramuscular injection and injection site reactions, mostly pain, and occur in approximately 5% of patients in opioid treatment studies. These reactions are generally mild and include pain, tenderness, indurations, bruising, pruritus and swelling. Generally these reactions last 1--3 days. Rare skin reactions at the site of the injection have been reported, including sterile abscesses, which may relate to inadvertent injection into fatty tissue, rather than muscle. Patients will be informed of this risk, and baseline physical evaluation will include examination of the buttock for excessive adiposity. If a patient is examined by a physician and found to have an abscess, necrosis, cellulitis or extensive swelling, an appropriate surgical referral will be made.
Naltrexone has been associated with reversible hepatocellular injury indicated by elevated liver enzymes when administered at doses substantially greater than the 380 mg im per month, dose recommended for relapse prevention treatment of opiate dependence and proposed for the present study. When used in therecommended dose range in opiate--dependent patients, this risk is remote (Brahen et al., 1988;; Brewer and Wong, 2004). 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 three times the upper imit of normal are excluded. Injectable naltrexone achieves higher blood levels 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 long--acting preparation, where the naltrexone would be only very slowly eliminated, this would prolong exposure to the offending agent. However, the experience with injectable naltrexone also suggests it is safe. In our studies with extended--release naltrexone several patients experienced elevation in liver enzymes, which were determined to be related to hepatitis C. In the proposed study we will use a long--acting, injectable preparation of naltrexone (Vivitrol 380 mg).
Several recent reports have documented that naltrexone pose significantly lower risk of hepatotoxicity than previously suspected, even among alcohol-- and opioid--dependent persons including those with HCV and/or HIV infection (Lucey et al., 2008;; Mitchell et al., 2012;; Tetrault et al., 2012;; Vagenas et al., 2014). These reports were used to support decision taken by FDA in July of 2013 to remove the Boxed Warning on

the hepatotoxicity. Other adverse events seen most frequently in association with XR--naltrexone treatment for opioid dependence include nasopharingitis, insomnia and toothache (Vivitrol;; Package Insert).
During the outpatient phase of the study, if a patient misses scheduled injection of Vivitrol and resumes regular opiate use, then receiving injectable naltrexone will precipitate opiate withdrawal, which may be quite severe in proportion to the time since the last injection and the level of opiate dependence. The physician will evaluate the patient and perform a naloxone challenge test to determine whether or not naltrexone can be safely resumed. If the naloxone challenge is positive (withdrawal is precipitated), then the patient will be removed from the study and offered another treatment option such as agonist maintenance (buprenorphine or methadone) according to clinical judgment and the patient's preferences.
Self--administration of large doses of opiates may over--ride the blockade produced by naltrexone resulting in opiate overdosage 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 topped 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. 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.

Risks of the Rapid Naltrexone Induction Procedure:
In this procedure withdrawal is then precipitated through administration of oral naltrexone and 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 adjunctive medications. In the proposed protocol the risk of severe withdrawal has been minimized by starting naltrexone at the very low dose. 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. The procedure is contraindicated in patients with unstable medical problems or histories of hypersensitivity to any of the medications used, and these are exclusions in the proposed study. The procedure is conducted in the outpatient setting that permits monitoring of patients for up to 8 hours daily to permit close monitoring of vital signs and mental status.

Pregnancy
Buprenorphine and naltrexone are Pregnancy category C agents, although the safety of buprenorphine in pregnancy has been supported in clinical trials (Jones et al., 2010). Female participants will be required to use adequate methods of birth control (condom with spermicide, diaphragm with spermicide, birth control pills) to be included in the study and will be strongly encouraged to use more effective methods like a subdermal implant, IUD, or a depot contraceptive injection. Serum pregnancy tests will be evaluated at baseline and urine for pregnancy will be tested as clinically indicated during treatment according to standard clinical procedures. If a female patient does become pregnant she will be withdrawn from study medication and offered continuing treatment with methadone or buprenorphine, which remains the current treatment of choice for pregnant opioid dependent patients.

Randomization to injection naltrexone or buprenorphine taper
The implications of random assignment to treatment conditions will be discussed with patients. One of the treatments could be more or less effective for a given patient. The alternative choices of continuing buprenorphine maintenance outside of the study or injection naltrexone, detoxification and counseling without medication (so called "drug--free" treatment), will be discussed with patients, as well as options of pursuing such treatments at other treatment programs available to the patients in the New York area. These will be discussed with patients at the time of consent, and revisited if Relapse occurs. Patients will also be informed, and reminded that the study is voluntary and that they can opt for any of these options at any point during the study.

Assessments
The structured interviews, rating scales, and questionnaires should add no physical risk. However, because many of the interviews and assessments are time--consuming to complete and involve topics of a sensitive nature, some people have found them to be physically or emotionally tiring. Patients are informed prior to study entry that they can refuse to answer any questions and that they can request to stop at any time. If a participant becomes agitated during any of the interviews or assessments, he or she will be provided with therapeutic assistance.

Blood Tests
Blood drawing may cause slight discomfort at site of needle entry, resulting in a small bruise.

Describe procedures for minimizing risks
Monitoring
Any study of medication efficacy carries risk. However, the investigators have conducted a series of studies administering medications to patients with opioid use disorder. Further, Dr. Bisaga has specifically conducted a study at the clinic in which the outpatient method of rapid naltrexone induction was developed. Other clinic physicians have extensive experience in administering oral and injectable naltrexone to opioid--dependent patients as well as experience providing treatment with buprenorphine. Patients are seen weekly by a physician **until month 4, and twice-monthly during months 4-6** for evaluation of medication and side effects, medication compliance therapy, or dose adjustments or adverse effects, and for evaluation of safety and emergence of any safety related issues (e.g. pregnancy, clinical worsening including serious medical or psychiatric conditions, or worsening of substance use). Adverse Events and Serious Adverse Events will be carefully monitored during the study.

Relapse during outpatient naltrexone induction
During the detoxification phase of the study, particularly during washout day and during first few days when naltrexone is introduced if a patient resumes regular opiate use, then taking naltrexone, particularly naltrexone injection, may precipitate opiate withdrawal, which may be severe. Patients will be warned not to take the naltrexone if they resumed any level of opiate use, and opiate abstinence will be confirmed by urine toxicology prior to administering the next daily dose of naltrexone.

Psychiatric Monitoring and Removal from Study

Participants' mental and physical status is monitored weekly **until study month 4, and twice monthly during study months 4-6** by the physician. The psychiatrist 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 that could be dangerous. Although unlikely, it is possible that patients may become psychotic or depressed, requiring discontinuation of study medication, and possibly psychiatric intervention. The weekly monitoring of patients, along with ongoing evaluations with structured assessments, such as the Hamilton Depression Scale, should allow us to detect these psychiatric disturbances early and intervene appropriately.

Although a patient might potentially attempt to overdose with buprenorphine, individuals who are at significant risk for suicidality will be excluded. Further, buprenorphine is a partial agonist and has a ceiling effect on respiratory depression; overdoses involving sublingual buprenorphine are rare and typically involve taking of toxic amounts of alcohol or benzodiazepines in combination with buprenorphine. Patients will be provided with a 1--2 weeks supply of buprenorphine/naloxone throughout the study.

Criteria for removal from the study will include: include:
1) Development of serious psychiatric symptoms as indicated by the Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks or psychiatric or medical deterioration that cannot be managed safely in the context outpatient treatment offered at the study (in cases where the investigator determines that the participant needs immediate study discontinuation).

2) If the participant's continued opioid or other drug use places him/her at risk for self-destructive behavior or other harm as indicated by a CGI improvement score of 6 or more (much worse than baseline) for 2 consecutive weeks. In cases where the investigator determines that the participant needs immediate study discontinuation for continued opioid or other drug use, participants will be provided with referrals.

3) Development of serious medical condition(s) that may or may not be related to study participation as assessed by weekly visits with the psychiatrist, vital sign measurements, and weekly weight-ins.

4) If the participant becomes pregnant as assessed by monthly urine pregnancy testing.

5) Ongoing non--adherence with recommended clinical visits, absence from study visits for 21 days.

Patients who are exited from the trial for any reason will be offered continued treatment in the community unless a higher level of care is indicated (inpatient or residential treatment), or the patient requests treatment elsewhere, in which care help with arranging referrals will be offered. A clinic staff member, with physician backup, is available 24 hours per day by phone in case of emergency.

Patient Education
All patients will be informed through the consent process and consent form and discussions with the research psychiatrist of the possible side effects and risks enumerated above. In addition, at weekly visits the research nurse or psychiatrist will query about side effects and treatment emergent symptoms. Patients will be warned that risks, as yet unknown, may occur when combining study medication with opioids or with other street drugs or alcohol. 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. One of the study-- affiliated physicians is on call 24 hours per day to answer questions and handle clinical emergencies.

Significant Other Contact
Upon entry to the study, the participant is informed that, if s/he agrees, the staff would prefer to have the contact information of someone who knows them well, to periodically assess how they are doing or to aid in case of emergency. Providing this information is not contingent on participating in the study. The participant, if he or she agrees, will then inform the individual that they may be contacted by the study staff. Only after the participant has informed the individual about the possible contact by the staff will the contact information be provided and the consent form addendum be signed.

Adverse Events and Serious Adverse Events are carefully monitored during medication studies. The physician queries the patient and log side effects and other treatment emergent events during the past week, recording their severity, what action was taken, and whether they are continuing or resolved. NIDA/VA Serious Adverse Event Form and NIDA Serious Adverse Event Tracking and Reporting System (SAETRS, on line) is used whenever a serious adverse event occurs. The research physician evaluates the patient, completes this form detailing the event, and reports the event immediately to both Investigators' IRBs and to NIDA. SAETRS is a web--based application that helps collect, track, store, analyze and report serious adverse events (SAETRS).

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Confidentiality
Patients will be asked to divulge information, such as their drug use or legal, psychiatric or medical problems, which are sensitive and could have adverse social consequences if released. This would include information released to insurance companies, family members, or made public in any way. Patient records are kept in locked files and released only with the patient's consent. We will obtain a Federal Certificate of Confidentiality to further safeguard the confidentiality of the participants enrolled in the trial. The Certificate of Confidentiality will allow 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. Contact with family members or significant others will only be with the patient's express consent. All computer data are stored without names or other uncoded identification.

Will the study be conducted under a certificate of confidentiality?
Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
The potential benefits to patients are cessation of BUP use and achievement of abstinent, opioid--free status

following successful stabilization off BUP, as well as improvements in daily functioning. Further, the knowledge gained from this study will contribute to the effort of finding medication strategies to treat OUD. The risks listed above are reasonable in this context. Individual patients may benefit from the treatment they receive in the context of the trial. Given the limited efficacy and implementation to date of XR--NTX for patients with OUD, the development of additional pharmacotherapy options would be of great public health benefit. We believe that measures described above to minimize risks for participants make the balance between risk to participants and the potential benefit to participants and others reasonable.

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.
Contingency Management and Subject Compensation: Subjects will be encouraged to come for the clinical evaluations and for CBT sessions as described in this protocol. To minimize missed sessions, they will be reimbursed for transportation expenses, for providing data, and for time spent in completing study assessments in accordance with local site's IRB policies. Contingency management procedures which have been shown to successfully improve many behaviors ranging from medication compliance to adherence to protocol activities will be applied to this study. Subjects will earn chances at each visit to draw vouchers from a prize-bowl. A subject must complete all visit requirements to be able to draw vouchers at the end of a visit. If study medication is discontinued due to adverse events, subject will continue to draw vouchers based on the schedule below as long as they continue all other visit requirements are completed. Participants will earn one draw for each consecutive visit made, with a bonus 3 draws for every 3 consecutive weeks . If a participant misses a visit, their draws are reset. Each draw has a probabilistic chance of yielding one of four outcomes; an encouraging statement (e.g. ‘good job’), a small prize valued at $2.50, a large prize valued at $20, or a jumbo prize valued at $100. The probability of each particular outcome is fixed for every draw and is based on the relative number of slips for each prize category in the prize bowl. Using Petry et al.s (2005) framework each prize bowl will have 500 prize slips. 250 slips will be an encouraging statement (50% of the total slips), 209 will be for small prizes (41.8%), 40 slips will be for large prizes (8%), and 10 slips will be the jumbo prize (0.2%). Patients will earn 1 additional draw for every consecutive week of abstinence (all urine samples for a treatment week test negative). The increasing number of earned draws during the protocol follows the escalating incentive structure employed in other CM based treatments (Higgins et al., 1993). During the treatment (contingency management) subjects can earn up to **340** draws from the prize bowl if demonstrating 100% attendance during the 25 weeks of the protocol. Total earnings will vary depending on attendance. With an expected earning of $2.85 per draw the maximum potential earnings for the CM for 25 weeks is **$969.** However, actual observed earnings will be significantly less than the potential maximum due to attrition and missed visits.

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NEW YORK STATE PSYCHIATRIC INSTITUTE COLUMBIA UNIVERSITY DEPARTMENT OF PSYCHIATRY

Informed Consent for Participation in Research

A Strategy to Improve Success of Treatment Discontinuation in Buprenorphine Responders

I. Purpose and Overview

You are invited to participate in a research study because you are diagnosed with opioid use disorder, have been successfully treated with buprenorphine and would like to stop taking buprenorphine. The main purpose of this research study is to evaluate two methods of buprenorphine discontinuation: a standard method of a graduated taper compared to a rapid discontinuation and transition onto Vivitrol. **This study is funded by a grant from the National Institute on Drug Abuse (NIDA).**

Vivitrol is a long-acting injection that contains enough naltrexone to last up to one month; it is approved by the FDA for preventing relapse in those with opioid use disorder. It works by blocking the effects of opioids and reducing cravings, but is not a controlled substance and has no opioid-like effect itself. You are being asked to participate in this study because you are currently prescribed buprenorphine and meet other study entry criteria. If you are not eligible, you will be assisted in finding free or low-cost treatment services near your home. If you are eligible for the study, you will receive your current dose of buprenorphine for one month, and will be randomized to either a five-week gradual taper off buprenorphine, or a week long rapid taper followed by an injection of Vivitrol. You will receive individual therapy for 25 weeks, and if you have been randomized to receive Vivitrol, you will receive two additional injections.

This study will also look at biomarkers, which are biological molecules found in blood, which can be used to see how well the body responds to treatment for opioid use disorder.

II. Voluntary

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Medical Center. You will be notified of significant new findings that may relate to your willingness to continue to participate.

III. Alternative Treatments/Alternatives to Participation

You do not need to participate in this research study to receive treatment for your opioid use disorder or to receive treatment with Vivitrol or buprenorphine. Other treatments are available, including methadone maintenance, buprenorphine maintenance, inpatient or other outpatient detoxification programs, and "drug-free" treatments including outpatient counseling or residential or therapeutic community treatment.

IV. Procedures

Screening

The study begins with a screening visit. The medical examinations and laboratory tests for screening may be done on one day or over multiple days. You and the study doctor will arrange those times. If you agree to be in this study, you will sign this form before any study procedures are done.

In order to participate in the study you must first have a psychiatric and medical screening, which will include questions about your drug use, health, and other problems you may be having. Depending on the results of that, you may also have a cardiogram (a test to measure the electrical activity of your heart), blood tests, a physical exam, and a urine toxicology screen. After the initial screening visit(s), you will be told whether you may be eligible for this research treatment study. The screening process may take between a few days to a few weeks depending on the frequency of your visits. If you are not eligible, or if you are not interested in taking part in the research treatment, then the clinician will assist you in finding treatment for your problems elsewhere.

If you are eligible for the study, you will come to the clinic once a week to receive your current dose of buprenorphine and for monitoring. At the end of this month you will be randomly assigned to one of two regimens of stopping buprenorphine: (Regimen 1) rapid discontinuation of buprenorphine followed by treatment with Vivitrol or (Regimen 2) a gradual taper off of buprenorphine.

Regimen 1: Rapid Discontinuation + Vivitrol
You will begin your outpatient visits to the clinic at the beginning of the week, and you will be asked to come to the clinic daily (5 visits, at least one hour each day) during this first week, in order to receive medications, naltrexone and other medications to reduce the discomfort of withdrawal from opioids. At each outpatient visit, you will need to provide an observed urine sample, which will be tested for opiates as well as other drugs. You will have your blood pressure, heart rate, and rate of breathing checked by our staff. The anti-withdrawal medication you will receive include: clonidine (a medicine used to treat high blood pressure), clonazepam (for anxiety), prochlorperazine (anti-nausea drug), and zolpidem or trazodone (for insomnia). If you experience significant withdrawal while at the clinic, you will be strongly encouraged to remain at the clinic for observation, and you may receive additional doses of medications.

If you are assigned to Regimen 1, you will be asked to stop taking buprenorphine and you will start taking medications to prevent withdrawal. Two days after the last dose of buprenorphine you will start taking naltrexone by mouth, first taking very low doses. If you do use buprenorphine or another opioid drug during this period, you may receive a naloxone challenge to determine whether it is safe to continue with the rest of the dosing schedule. At the end of the first week, you will receive an intramuscular injection of Vivitrol, a long-acting form of naltrexone that lasts in your system for 3-4 weeks. You will be asked to stay at the clinic for at least one hour after receiving this injection, for clinical observation.
While at the clinic, you will have the opportunity to rest in a private room fitted with lounge chairs, adjustable lighting, and an entertainment system. Light snacks and sports drinks such as Gatorade will be available to keep you comfortable. It is important to drink plenty of fluids. Clinical staff will determine any changes to your medication necessary for your well-being. The clinic staff will advise you on ways to minimize withdrawal symptoms, and you will also meet daily with a therapist who will provide you with counseling.

You will be free to leave the clinic each day once you have received all necessary medication doses and have been evaluated for medical stability by the clinic nurse and/or psychiatrist. If you experience fatigue or medication side effects, car transportation home will be provided to you. After you have received Vivitrol, you will continue to come to the clinic once a week to meet with a therapist and psychiatrist for 3 months, and twice-monthly during treatment months 4-6. You will also receive two additional injections of Vivitrol 4

and 8 week after the first injection.

Regimen 2: Gradual Taper
If you are assigned to Regimen 2, you will continue receiving buprenorphine on a weekly basis for five weeks, with the dose of buprenorphine gradually decreasing to minimize any possible withdrawal. At the end of the taper buprenorphine will be stopped. During this time we ask that you come to the clinic once a week so that staff can assess for withdrawal symptoms and so you can meet with a therapist and psychiatrist. After you have been tapered off buprenorphine you will continue to come to the clinic once a week to meet with a therapist and psychiatrist for 3 months, and twice-monthly during treatment months 4-6.

Outpatient Treatment
After stopping buprenorphine, you will continue to be monitored and receive counseling, regardless of the regimen you were assigned to. Your visits to the clinic should take between 30 and 60 minutes to meet with a counselor and research psychiatrist. These sessions will help you to work on your treatment goals and remain abstinent. During each visit, you will fill out several questionnaires and answer questions about your alcohol use and other drug use. You will also have your vital signs monitored at every visit. If during the course of treatment you resume taking opioids (buprenorphine, heroin or other opioids) and are unable to give an opioid-free urine, you will be provided with referrals to alternative treatment programs. If you use opioids during the study but are able to receive your next Vivitrol injection you will continue in the program.

Approximately one tablespoon of blood will be drawn at the beginning and end of the study to check your liver enzymes. Additionally approximately six tablespoons blood, saliva and urine will be collected at the beginning **and 3 times throughout the study to check for biochemical markers.** You will be asked to give supervised urine at every visit to the program throughout the study. The urine samples are tested for drugs, and the purpose of this is to help monitor your progress. Results of the urine are discussed at counseling sessions. At the beginning, if your liver enzymes are elevated, we may test your blood to determine whether you have been infected with viral hepatitis (Hepatitis B, and Hepatitis C). We are required by law to report positive hepatitis test results to the Department of Health.
If you are a woman, approximately one tablespoon of blood will be drawn to check for pregnancy before starting treatment. Also, since pregnant women may not participate in this research, women must practice an effective method of birth control until the end of the study. You will have a pregnancy urine test monthly.

If you suffer from depression or anxiety, you will have the opportunity to receive therapy to address those symptoms. You will also be seeing a psychiatrist who can evaluate your symptoms and may be offered the option of taking an antidepressant or anti-anxiety medication.

End of Study
At the end of Week 25 you will be asked to meet for an hour with the psychiatrist to answer questions, have another physical examination and blood test, complete questionnaires, and receive referrals for further treatment as part of an aftercare plan outside the clinic. This follow-up care could entail treatment at local drug-treatment clinics, other hospital-based treatment programs, or with private medical practitioners or therapists. After the study is completed, you will have the option to meet with your therapist weekly for up to a month until you have transitioned into the follow-up treatment.

If you remain abstinent throughout the study, we strongly encourage you to continue treatment after study completion, and will work with you to help find another treatment provider. If you find difficult to remain

abstinent (e.g., have strong cravings) we will offer you an additional month of medication (Vivitrol injection or 30-day supply of buprenorphine) and we will provide you with referrals for Vivitrol, buprenorphine, methadone, and behavioral treatment options. You should know that when you are provided with referrals, both injection and oral forms of naltrexone are available in the community, as well as forms of therapy similar to, as well as more intensive than, the behavioral therapy offered in this study. In the event that you decide to discontinue from the study, or are withdrawn from the study, you will be treated with buprenorphine until you have been transitioned to another buprenorphine treatment program or provider.

The doctors conducting this research study are also responsible for your clinical care. If during the course of the study, you have a medical emergency or require urgent medical care, the research medical staff will consult with your treating physician(s) regarding any information relevant to your medical care. In the event of an emergency or if you have questions while in the study, you can reach the clinic at (646)774-6174 during regular business hours.

V. Risks and Inconveniences

You are entering this study because you have been doing well on buprenorphine, but would like to stop taking it. A significant risk of stopping medication like buprenorphine is that you may relapse to use of opioids. Relapse is dangerous in several ways including risk of overdose. If you change your mind at any point and want to resume buprenorphine, you should let the study staff know and buprenorphine can be resumed. As you are reducing the medication, or once you have stopped the medication, if you begin to experience cravings or to use opioids, it is important to seek help right away -i.e. let the study staff know right away, since medication like buprenorphine can be restarted and can protect you.

Another serious risk of study participation is that after stopping buprenorphine you will lose tolerance to opioids and therefore the effects of heroin or another opioid on the body becomes much more potent at a lower dosage. This means that resuming use of opioids after detoxifying could cause you to overdose, stop breathing and die. If you complete the detoxification and receive injectable naltrexone monthly, it will help protect you against death due to opioid overdose by blocking the effects of the drug. However, if you stop taking naltrexone, restarting opioids could result in accidental overdose and/or death.

Opioid detoxification carries a moderately high risk of relapse and overdose if you use a significant amount of opioids after losing tolerance. We seek to minimize these risks by monitoring you closely with urine drug tests and asking about any opioid use. If you do relapse, you will be given referrals for methadone or buprenorphine maintenance, or inpatient detoxification and follow-up treatment. There may be a delay of up to 2 weeks after your first screening clinic visit and before treatment begins.

Naltrexone
You will be given naltrexone while your body is still dependent on opioids, which can induce withdrawal symptoms. We will use very low doses of naltrexone at the beginning of treatment to minimize the severity of withdrawal and prepare your body for naltrexone injection. The withdrawal symptoms are treated with clonidine, clonazepam, trazodone, prochlorperazine and zolpidem, but despite their use you may experience significant discomfort. The side effects of these medications may include insomnia or possible sleepiness, lowered blood pressure which may produce dizziness or a tendency to feel faint, nausea, vomiting, diarrhea, muscle and abdominal cramping, irritability, anxiety, and an allergic reaction involving a narrowing of the airways in the lungs, similar to what people with asthma sometimes develop.

Once you have been stabilized on naltrexone it generally has few side effects. However, it can cause irritation to the liver or may occasionally cause or contribute to depressive symptoms. Additional side effects may include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint muscle pain, or headaches. It is important to note that these symptoms may represent persisting withdrawal symptoms, and the psychiatrist who is monitoring you can prescribe medications to reduce the discomfort.

If you take small amounts of heroin or other opioids while on naltrexone, you should feel no opioid-like effects. **However, it is possible to overpower naltrexone if you take large amounts of heroin or other opioids. Also, if you miss your Vivitrol injection, it is possible that you may be much more sensitive to opioids. This means that amounts of heroin or other opioids that you used to take routinely could cause you to overdose, stop breathing and die.**
Naltrexone does not block the effects of other drugs such as cocaine, tranquilizers, or alcohol, and it does not reduce the risks when using these substances, such as getting drunk or high.
You should be aware that you may be more sensitive to the effects of heroin and other opioids upon completion of this study, and therefore would be at a greater risk for overdose. This increased sensitivity to opiates means that doses of heroin or other opiates that you used to take before entering treatment could be enough to cause you to stop breathing and die. Fentanyl and carfentanil are powerful synthetic opioids that can be added to heroin without your knowledge and this addition would further increase your risk of overdose.

Naloxone Challenge Test
If you use opioids prior to receiving the Vivitrol injection, you may be given a naloxone challenge test to determine whether or not you are dependent on opioids. We may administer up to 0.8 mg naloxone intramuscularly (by injection), which – if you have recently used opioids -can produce a number of withdrawal symptoms. You may experience symptoms such as: sweating, restlessness, stomach pain, diarrhea, headache, anxiety, nausea, vomiting dizziness, runny nose, yawning, muscle aches, or tremors. We will monitor your reactions to naloxone for up to 45 min.

Vivitrol
Risks of Vivitrol are possible irritation (e.g., redness, swelling, possible scarring) or infection at the injection site. Injection site reactions have ranged from a small, painless area of hardness to pain, itching, redness, and swelling. These reactions have typically resolved spontaneously over a period of 1-3 weeks. Of the 1,000 naltrexone injections we have administered, three to date caused site swelling and an open sore to develop, which became infected and required a minor surgical procedure, antibiotic treatment and wound care. The wound healed completely over a period of approximately 3 months, but resulted in a scar.
Another study risk is that naltrexone may impair the functioning of your liver. Short-term increase of liver enzymes can occur, but this is usually reversible. This effect on your liver will resolve after naltrexone leaves your body. In addition, administration of naltrexone may increase blood sugar levels, which may produce symptoms such as dizziness, increased breathing, dehydration, and seizures. If you experience any of these symptoms, it is important that you tell the investigator immediately.

In rare cases, patients who received injectable naltrexone reported developing a form of allergic pneumonia, experiencing shortness of breath. If you have trouble breathing, it is important that you let us know right

away. In patients treated with the naltrexone injection, we have also observed hives, an allergic reaction of the skin with redness and itching. If you develop any of these symptoms it is important to let us know.

If you miss your visit to receive Vivitrol, and/or take opioids, you should come to the clinic immediately. There, you will be evaluated to determine if it is safe to restart the naltrexone. You may be asked to take an intramuscular injection of naloxone. If your body has become dependent on opioids, this dose will produce withdrawal symptoms lasting less than one hour. You may refuse the naloxone challenge but must be able to provide an opioid-negative urine or reconsider the challenge within 72 hours in order to determine whether you can safely restart naltrexone. If at this point, you are found to be dependent on opioids and unable to restart naltrexone, you will be provided with referrals to alternative treatment programs.
It is very important that you tell your study physician about any other medications you are taking (either prescription or non-prescription) before beginning naltrexone. It is also very important that, during the course of the study, you tell your research psychiatrist about any other medications you are prescribed or plan to take to avoid possible adverse reactions.

Buprenorphine
When lowering daily doses of buprenorphine, you may experience withdrawal symptoms such as difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint muscle pain, headaches, or runny nose. You may also experience a rapid and sudden onset of withdrawal symptoms if you crush your take-home buprenorphine pills and inject or snort them. These symptoms would be very uncomfortable but short-lived and not life threatening. If this occurs, your psychiatrist would evaluate you and provide you with referrals to alternative treatment.

Opioid medications, like buprenorphine, can interact with medicines, such as antidepressants and migraine medicines, meant to increase the effects of serotonin, a chemical in the brain. This interaction causes a serious response in the brain called serotonin syndrome. If you are taking an opioid along with a medicine that increases serotonin and develop symptoms such as agitation, hallucinations, rapid heart rate, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, and/or nausea, vomiting, or diarrhea, you should seek medical attention immediately. These symptoms generally start within several hours to a few days of taking an opioid with a medicine that increases the effects of serotonin in the brain, but symptoms may occur later, especially after either medication is increased in dose.

Taking opioids may lead to a rare, but serious condition where not enough of the hormone called cortisol is produced, particularly during stressful conditions when cortisol is usually produced. Consult your study doctor or seek medical attention (ensure that you communicate that you are participating in a clinical trial) if you experience symptoms such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. Long-term use of opioid pain medications may lead to decreased sex hormones. Inform your study doctor if you experience signs or symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.

Comfort Medications
You will be given comfort medications to help manage your withdrawal during the detoxification. When you are taking the comfort medications (clonidine, clonazepam, prochlorperazine, and zolpidem), you should use caution when driving a vehicle or operating appliances or machinery. Only the most common risks of each comfort medication are highlighted below, so if you would like to learn more about the medications or their side effects, please ask your study doctor who can provide you with the Patient Information Sheets. These medications may cause some side effects such as sleepiness, lowered blood pressure (which may produce

dizziness or a tendency to feel faint), or upset stomach.

Other Risks
(For females) Both the detoxification procedure and outpatient naltrexone treatment may pose risk to a fetus. You will have a pregnancy test before beginning treatment and monthly thereafter to determine that you are not pregnant. You will be asked to use adequate birth control throughout your treatment such as: (a) any form of hormonal contraception such as Depo-Provera, daily oral contraceptive, transdermal patch or Nuva ring, (b) intra-uterine devices, (c) sterilization, or (d) double barrier contraception, which is a combination of any two of the following methods: condoms, spermicide, diaphragm.

The only risk to the blood-drawing procedures used in this study is the possibility that slight discomfort and/or a small bruise or, rarely, a local infection may develop at the site of the needle puncture. This seldom occurs. If taking any medication orally, it is being dispensed to you in packages that are not childproof. Extra precautions need to be taken to keep the oral medication away from children.

You will be carefully monitored throughout your participation to minimize the chance of any serious adverse side effects. We will provide you with any significant new findings that may develop during the course of the study, which may relate to your willingness to continue study participation. If you suspect that you might be pregnant, you must inform the study team immediately.

VI. Benefits

You may benefit directly from the treatment you receive with reduction in drug use and improvement in problems related to your drug use. The findings of the study may help doctors know more about how to treat opioid dependence and help others with this problem.

VII. Confidentiality

We will do everything we can to keep others from learning about your participation in the research. **Your private information or biospecimens will only be used for the purposes of this research study, and will not be distributed to another investigator for future research studies. Any biospecimens that are collected as part of this research will not be used for commercial profit.** To further help us protect your privacy, the investigators will obtain a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, the investigators cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for the purpose of audit or evaluation. A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note however, that if an insurer, employer or other outside party, learns of your participation, and obtains your consent to receive research information, then the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy. Finally, the Certificate does not prevent the researchers from reporting suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others. Such information will be reported to the appropriate authorities.

Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Your name and other personal identifying information will be

stored in an electronically secure database at New York Psychiatric Institute. Signed consent forms and other forms containing identifying information will be kept in a locked file, and all interviews, assessments, etc. will be coded with initials and numbers. Electronic data are also coded and are stored on computers that are password protected. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

VIII. Study Compensation

During the study, you will receive $10 in cash to help pay for your transportation costs. You will have the chance to earn prizes for attending consecutive study visits. Each study visit will result in a draw from the prize bowl. Each draw has a chance of getting one of four outcomes: an encouraging statement (e.g. 'good job'), a small prize valued at $2.50, a large prize valued at $20, or a jumbo prize valued at $100. The chance of winning a jumbo prize us (0.2 %), the large prize (8%), the small prize (42%), and 50% of the time you will get an encouraging statement. You will accumulate an additional draw for each consecutive visit made. If you miss a visit your draws will be reset. The maximum amount over 25 weeks you may potentially earn for attending all study visits is approximately $969 in cash prizes, and $190 in cash for transportation costs.

We are required by law to report your earnings to the IRS. Therefore, your Social Security Number and amount earned will be reported, and you will receive the appropriate IRS form at the end of the year in which you were paid. Please note that payment for this study may affect your eligibility for Medicaid and other city and state support services. No information about which study you participated in will be provided to the IRS.

IX. In Case of Injury

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. Please be aware that:
1. The New York State Psychiatric Institute, Columbia University, Research Foundation for Mental Hygiene, and New York Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital.
2. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.
3. No monetary compensation for wages lost as a result of injury will be paid to you by the New York State Psychiatric Institute, Columbia University, Research Foundation for Mental Hygiene, or by New York Presbyterian Hospital.
4. By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

X. Questions

The investigators will answer to the best of their abilities any questions you may have now or in the future about the study procedures or about your response to the procedures. You should contact the Principal Investigator, Dr. Adam Bisaga, at (646)744-6155 if you have any questions. If a medical emergency occurs at night or over the weekend, you should go to the nearest hospital emergency room and have them call (914)419-8921.If you have any questions about your rights as a research participant, want feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). An IRB is a committee that protects the rights of human subjects in research studies). You may call the IRB Main Office at (646) 774-7155 during regular office hours.

XI. Documentation of Consent for Screening

I voluntarily agree to participate in the screening for the research study described above.

Print name : _____
(Participant)

Signed: _____Date: _____
I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name: _____
(Person Designated to Obtain Consent)

Signed: _____ Date: _____

Consent for Future Contact
You permit the Opioid Treatment Research Program staff to contact you in the future.

Print name : _____
(Participant)

Signed: _____Date: _____

XII. Documentation of Study Consent

I voluntarily agree to participate in the research study described above.

Print name: _____
(Participant)

Signed: _____Date: _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name: _____
(Person Designated to Obtain Consent)

Signed: _____ Date: _____

ADDENDUM 1
CONSENT FOR SIGNIFICANT OTHER CONTACT

It may be important for the staff at the clinic to discuss your problems with a close family member or friend to assess how you are doing, to help contact you if you miss a visit, or in case of an emergency. By signing this page, you consent to allow the staff to contact the following person(s) to discuss your case throughout the course of your treatment. You may refuse to grant this permission, and it will not affect your eligibility for treatment in this study.

Name:_____Relationship:_____

Address:_____

Phone Numbers:_____

Name:_____Relationship:_____

Address:_____

Phone Numbers:_____

Name:_____

Significant other contact information refused:____

Participant Signature:_____ Date_____

Investigator Signature:_____ Date_____

NEW YORK STATE PSYCHIATRIC INSTITUTE COLUMBIA UNIVERSITY DEPARTMENT OF PSYCHIATRY

Informed Consent for Participation in Research

A Strategy to Improve Success of Treatment Discontinuation in Buprenorphine Responders

I. Purpose and Overview

You are invited to participate in a research study because you are diagnosed with opioid use disorder, have been successfully treated with buprenorphine and would like to stop taking buprenorphine. The main purpose of this research study is to evaluate two methods of buprenorphine discontinuation: a standard method of a graduated taper compared to a rapid discontinuation and transition onto Vivitrol. This study is funded by a grant from the National Institute on Drug Abuse (NIDA).

Vivitrol is a long-acting injection that contains enough naltrexone to last up to one month; it is approved by the FDA for preventing relapse in those with opioid use disorder. It works by blocking the effects of opioids and reducing cravings, but is not a controlled substance and has no opioid-like effect itself. You are being asked to participate in this study because you are currently prescribed buprenorphine and meet other study entry criteria. If you are not eligible, you will be assisted in finding free or low-cost treatment services near your home. If you are eligible for the study, you will receive your current dose of buprenorphine for one month, and will be randomized to either a five-week gradual taper off buprenorphine, or a week long rapid taper followed by an injection of Vivitrol. You will receive individual therapy for 25 weeks, and if you have been randomized to receive Vivitrol, you will receive two additional injections.

This study will also look at biomarkers, which are biological molecules found in blood, which can be used to see how well the body responds to treatment for opioid use disorder.

II. Voluntary

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Medical Center. You will be notified of significant new findings that may relate to your willingness to continue to participate.

III. Alternative Treatments/Alternatives to Participation

You do not need to participate in this research study to receive treatment for your opioid use disorder or to receive treatment with Vivitrol or buprenorphine. Other treatments are available, including methadone maintenance, buprenorphine maintenance, inpatient or other outpatient detoxification programs, and "drug-free" treatments including outpatient counseling or residential or therapeutic community treatment.

IV. Procedures

Screening

The study begins with a screening visit. The medical examinations and laboratory tests for screening may be done on one day or over multiple days. You and the study doctor will arrange those times. If you agree to be in this study, you will sign this form before any study procedures are done.

In order to participate in the study you must first have a psychiatric and medical screening, which will include questions about your drug use, health, and other problems you may be having. Depending on the results of that, you may also have a cardiogram (a test to measure the electrical activity of your heart), blood tests, a physical exam, and a urine toxicology screen. After the initial screening visit(s), you will be told whether you may be eligible for this research treatment study. The screening process may take between a few days to a few weeks depending on the frequency of your visits. If you are not eligible, or if you are not interested in taking part in the research treatment, then the clinician will assist you in finding treatment for your problems elsewhere.

If you are eligible for the study, you will come to the clinic once a week to receive your current dose of buprenorphine and for monitoring. At the end of this month you will be randomly assigned to one of two regimens of stopping buprenorphine: (Regimen 1) rapid discontinuation of buprenorphine followed by treatment with Vivitrol or (Regimen 2) a gradual taper off of buprenorphine.

Regimen 1: Rapid Discontinuation + Vivitrol

You will begin your outpatient visits to the clinic at the beginning of the week, and you will be asked to come to the clinic daily (5 visits, at least one hour each day) during this first week, in order to receive medications, naltrexone and other medications to reduce the discomfort of withdrawal from opioids. At each outpatient visit, you will need to provide an observed urine sample, which will be tested for opiates as well as other drugs. You will have your blood pressure, heart rate, and rate of breathing checked by our staff. The anti-withdrawal medication you will receive include: clonidine (a medicine used to treat high blood pressure), clonazepam (for anxiety), prochlorperazine (anti-nausea drug), and zolpidem or trazodone (for insomnia). If you experience significant withdrawal while at the clinic, you will be strongly encouraged to remain at the clinic for observation, and you may receive additional doses of medications.

If you are assigned to Regimen 1, you will be asked to stop taking buprenorphine and you will start taking medications to prevent withdrawal. Two days after the last dose of buprenorphine you will start taking naltrexone by mouth, first taking very low doses. If you do use buprenorphine or another opioid drug during this period, you may receive a naloxone challenge to determine whether it is safe to continue with the rest of the dosing schedule. At the end of the first week, you will receive an intramuscular injection of Vivitrol, a long-acting form of naltrexone that lasts in your system for 3-4 weeks. You will be asked to stay at the clinic for at least one hour after receiving this injection, for clinical observation.
While at the clinic, you will have the opportunity to rest in a private room fitted with lounge chairs, adjustable lighting, and an entertainment system. Light snacks and sports drinks such as Gatorade will be available to keep you comfortable. It is important to drink plenty of fluids. Clinical staff will determine any changes to your medication necessary for your well-being. The clinic staff will advise you on ways to minimize withdrawal symptoms, and you will also meet daily with a therapist who will provide you with counseling.

You will be free to leave the clinic each day once you have received all necessary medication doses and have been evaluated for medical stability by the clinic nurse and/or psychiatrist. If you experience fatigue or

medication side effects, car transportation home will be provided to you. After you have received Vivitrol, you will continue to come to the clinic once a week to meet with a therapist and psychiatrist for 3 months, and twice-monthly during treatment months 4-6. You will also receive two additional injections of Vivitrol 4 and 8 week after the first injection.

Regimen 2: Gradual Taper
If you are assigned to Regimen 2, you will continue receiving buprenorphine on a weekly basis for five weeks, with the dose of buprenorphine gradually decreasing to minimize any possible withdrawal. At the end of the taper buprenorphine will be stopped. During this time we ask that you come to the clinic once a week so that staff can assess for withdrawal symptoms and so you can meet with a therapist and psychiatrist. After you have been tapered off buprenorphine you will continue to come to the clinic once a week to meet with a therapist and psychiatrist for 3 months, and twice-monthly during treatment months 4-6.

Outpatient Treatment
After stopping buprenorphine, you will continue to be monitored and receive counseling, regardless of the regimen you were assigned to. Your visits to the clinic should take between 30 and 60 minutes to meet with a counselor and research psychiatrist. These sessions will help you to work on your treatment goals and remain abstinent. During each visit, you will fill out several questionnaires and answer questions about your alcohol use and other drug use. You will also have your vital signs monitored at every visit. If during the course of treatment you resume taking opioids (buprenorphine, heroin or other opioids) and are unable to give an opioid-free urine, you will be provided with referrals to alternative treatment programs. If you use opioids during the study but are able to receive your next Vivitrol injection you will continue in the program.

Approximately one tablespoon of blood will be drawn at the beginning and end of the study to check your liver enzymes. Additionally approximately six tablespoons blood, saliva and urine will be collected at the beginning and 3 times throughout the study to check for biochemical markers. You will be asked to give supervised urine at every visit to the program throughout the study. The urine samples are tested for drugs, and the purpose of this is to help monitor your progress. Results of the urine are discussed at counseling sessions. At the beginning, if your liver enzymes are elevated, we may test your blood to determine whether you have been infected with viral hepatitis (Hepatitis B, and Hepatitis C). We are required by law to report positive hepatitis test results to the Department of Health.
If you are a woman, approximately one tablespoon of blood will be drawn to check for pregnancy before starting treatment. Also, since pregnant women may not participate in this research, women must practice an effective method of birth control until the end of the study. You will have a pregnancy urine test monthly.

If you suffer from depression or anxiety, you will have the opportunity to receive therapy to address those symptoms. You will also be seeing a psychiatrist who can evaluate your symptoms and may be offered the option of taking an antidepressant or anti-anxiety medication.

End of Study
At the end of Week 25 you will be asked to meet for an hour with the psychiatrist to answer questions, have another physical examination and blood test, complete questionnaires, and receive referrals for further treatment as part of an aftercare plan outside the clinic. This follow-up care could entail treatment at local drug-treatment clinics, other hospital-based treatment programs, or with private medical practitioners or therapists. After the study is completed, you will have the option to meet with your therapist weekly for up to a month until you have transitioned into the follow-up treatment.

If you remain abstinent throughout the study, we strongly encourage you to continue treatment after study completion, and will work with you to help find another treatment provider. If you find difficult to remain abstinent (e.g., have strong cravings) we will offer you an additional month of medication (Vivitrol injection or 30-day supply of buprenorphine) and we will provide you with referrals for Vivitrol, buprenorphine, methadone, and behavioral treatment options. You should know that when you are provided with referrals, both injection and oral forms of naltrexone are available in the community, as well as forms of therapy similar to, as well as more intensive than, the behavioral therapy offered in this study. In the event that you decide to discontinue from the study, or are withdrawn from the study, you will be treated with buprenorphine until you have been transitioned to another buprenorphine treatment program or provider.

The doctors conducting this research study are also responsible for your clinical care. If during the course of the study, you have a medical emergency or require urgent medical care, the research medical staff will consult with your treating physician(s) regarding any information relevant to your medical care. In the event of an emergency or if you have questions while in the study, you can reach the clinic at (646)774-6174 during regular business hours.

V. Risks and Inconveniences

You are entering this study because you have been doing well on buprenorphine, but would like to stop taking it. A significant risk of stopping medication like buprenorphine is that you may relapse to use of opioids. Relapse is dangerous in several ways including risk of overdose. If you change your mind at any point and want to resume buprenorphine, you should let the study staff know and buprenorphine can be resumed. As you are reducing the medication, or once you have stopped the medication, if you begin to experience cravings or to use opioids, it is important to seek help right away -i.e. let the study staff know right away, since medication like buprenorphine can be restarted and can protect you.

Another serious risk of study participation is that after stopping buprenorphine you will lose tolerance to opioids and therefore the effects of heroin or another opioid on the body becomes much more potent at a lower dosage. This means that resuming use of opioids after detoxifying could cause you to overdose, stop breathing and die. If you complete the detoxification and receive injectable naltrexone monthly, it will help protect you against death due to opioid overdose by blocking the effects of the drug. However, if you stop taking naltrexone, restarting opioids could result in accidental overdose and/or death.

Opioid detoxification carries a moderately high risk of relapse and overdose if you use a significant amount of opioids after losing tolerance. We seek to minimize these risks by monitoring you closely with urine drug tests and asking about any opioid use. If you do relapse, you will be given referrals for methadone or buprenorphine maintenance, or inpatient detoxification and follow-up treatment. There may be a delay of up to 2 weeks after your first screening clinic visit and before treatment begins.

Naltrexone
You will be given naltrexone while your body is still dependent on opioids, which can induce withdrawal symptoms. We will use very low doses of naltrexone at the beginning of treatment to minimize the severity of withdrawal and prepare your body for naltrexone injection. The withdrawal symptoms are treated with clonidine, clonazepam, trazodone, prochlorperazine and zolpidem, but despite their use you may experience significant discomfort. The side effects of these medications may include insomnia or possible sleepiness, lowered blood pressure which may produce dizziness or a tendency to feel faint, nausea, vomiting, diarrhea,

muscle and abdominal cramping, irritability, anxiety, and an allergic reaction involving a narrowing of the airways in the lungs, similar to what people with asthma sometimes develop.

Once you have been stabilized on naltrexone it generally has few side effects. However, it can cause irritation to the liver or may occasionally cause or contribute to depressive symptoms. Additional side effects may include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint muscle pain, or headaches. It is important to note that these symptoms may represent persisting withdrawal symptoms, and the psychiatrist who is monitoring you can prescribe medications to reduce the discomfort.

If you take small amounts of heroin or other opioids while on naltrexone, you should feel no opioid-like effects. **However, it is possible to overpower naltrexone if you take large amounts of heroin or other opioids. Also, if you miss your Vivitrol injection, it is possible that you may be much more sensitive to opioids. This means that amounts of heroin or other opioids that you used to take routinely could cause you to overdose, stop breathing and die.**
Naltrexone does not block the effects of other drugs such as cocaine, tranquilizers, or alcohol, and it does not reduce the risks when using these substances, such as getting drunk or high.
You should be aware that you may be more sensitive to the effects of heroin and other opioids upon completion of this study, and therefore would be at a greater risk for overdose. This increased sensitivity to opiates means that doses of heroin or other opiates that you used to take before entering treatment could be enough to cause you to stop breathing and die. Fentanyl and carfentanil are powerful synthetic opioids that can be added to heroin without your knowledge and this addition would further increase your risk of overdose.

Naloxone Challenge Test
If you use opioids prior to receiving the Vivitrol injection, you may be given a naloxone challenge test to determine whether or not you are dependent on opioids. We may administer up to 0.8 mg naloxone intramuscularly (by injection), which – if you have recently used opioids -can produce a number of withdrawal symptoms. You may experience symptoms such as: sweating, restlessness, stomach pain, diarrhea, headache, anxiety, nausea, vomiting dizziness, runny nose, yawning, muscle aches, or tremors. We will monitor your reactions to naloxone for up to 45 min.

Vivitrol
Risks of Vivitrol are possible irritation (e.g., redness, swelling, possible scarring) or infection at the injection site. Injection site reactions have ranged from a small, painless area of hardness to pain, itching, redness, and swelling. These reactions have typically resolved spontaneously over a period of 1-3 weeks. Of the 1,000 naltrexone injections we have administered, three to date caused site swelling and an open sore to develop, which became infected and required a minor surgical procedure, antibiotic treatment and wound care. The wound healed completely over a period of approximately 3 months, but resulted in a scar.
Another study risk is that naltrexone may impair the functioning of your liver. Short-term increase of liver enzymes can occur, but this is usually reversible. This effect on your liver will resolve after naltrexone leaves your body. In addition, administration of naltrexone may increase blood sugar levels, which may produce symptoms such as dizziness, increased breathing, dehydration, and seizures. If you experience any of these symptoms, it is important that you tell the investigator immediately.

In rare cases, patients who received injectable naltrexone reported developing a form of allergic pneumonia, experiencing shortness of breath. If you have trouble breathing, it is important that you let us know right away. In patients treated with the naltrexone injection, we have also observed hives, an allergic reaction of the skin with redness and itching. If you develop any of these symptoms it is important to let us know.

If you miss your visit to receive Vivitrol, and/or take opioids, you should come to the clinic immediately. There, you will be evaluated to determine if it is safe to restart the naltrexone. You may be asked to take an intramuscular injection of naloxone. If your body has become dependent on opioids, this dose will produce withdrawal symptoms lasting less than one hour. You may refuse the naloxone challenge but must be able to provide an opioid-negative urine or reconsider the challenge within 72 hours in order to determine whether you can safely restart naltrexone. If at this point, you are found to be dependent on opioids and unable to restart naltrexone, you will be provided with referrals to alternative treatment programs.
It is very important that you tell your study physician about any other medications you are taking (either prescription or non-prescription) before beginning naltrexone. It is also very important that, during the course of the study, you tell your research psychiatrist about any other medications you are prescribed or plan to take to avoid possible adverse reactions.

Buprenorphine
When lowering daily doses of buprenorphine, you may experience withdrawal symptoms such as difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint muscle pain, headaches, or runny nose. You may also experience a rapid and sudden onset of withdrawal symptoms if you crush your take-home buprenorphine pills and inject or snort them. These symptoms would be very uncomfortable but short-lived and not life threatening. If this occurs, your psychiatrist would evaluate you and provide you with referrals to alternative treatment.

Opioid medications, like buprenorphine, can interact with medicines, such as antidepressants and migraine medicines, meant to increase the effects of serotonin, a chemical in the brain. This interaction causes a serious response in the brain called serotonin syndrome. If you are taking an opioid along with a medicine that increases serotonin and develop symptoms such as agitation, hallucinations, rapid heart rate, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, and/or nausea, vomiting, or diarrhea, you should seek medical attention immediately. These symptoms generally start within several hours to a few days of taking an opioid with a medicine that increases the effects of serotonin in the brain, but symptoms may occur later, especially after either medication is increased in dose.

Taking opioids may lead to a rare, but serious condition where not enough of the hormone called cortisol is produced, particularly during stressful conditions when cortisol is usually produced. Consult your study doctor or seek medical attention (ensure that you communicate that you are participating in a clinical trial) if you experience symptoms such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. Long-term use of opioid pain medications may lead to decreased sex hormones. Inform your study doctor if you experience signs or symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.

Comfort Medications
You will be given comfort medications to help manage your withdrawal during the detoxification. When you are taking the comfort medications (clonidine, clonazepam, prochlorperazine, and zolpidem), you should use caution when driving a vehicle or operating appliances or machinery. Only the most common risks of each comfort medication are highlighted below, so if you would like to learn more about the medications or their

side effects, please ask your study doctor who can provide you with the Patient Information Sheets. These medications may cause some side effects such as sleepiness, lowered blood pressure (which may produce dizziness or a tendency to feel faint), or upset stomach.

Other Risks

(For females) Both the detoxification procedure and outpatient naltrexone treatment may pose risk to a fetus. You will have a pregnancy test before beginning treatment and monthly thereafter to determine that you are not pregnant. You will be asked to use adequate birth control throughout your treatment such as: (a) any form of hormonal contraception such as Depo-Provera, daily oral contraceptive, transdermal patch or Nuva ring, (b) intra-uterine devices, (c) sterilization, or (d) double barrier contraception, which is a combination of any two of the following methods: condoms, spermicide, diaphragm.

The only risk to the blood-drawing procedures used in this study is the possibility that slight discomfort and/or a small bruise or, rarely, a local infection may develop at the site of the needle puncture. This seldom occurs. If taking any medication orally, it is being dispensed to you in packages that are not childproof. Extra precautions need to be taken to keep the oral medication away from children.

You will be carefully monitored throughout your participation to minimize the chance of any serious adverse side effects. We will provide you with any significant new findings that may develop during the course of the study, which may relate to your willingness to continue study participation. If you suspect that you might be pregnant, you must inform the study team immediately.

VI. Benefits

You may benefit directly from the treatment you receive with reduction in drug use and improvement in problems related to your drug use. The findings of the study may help doctors know more about how to treat opioid dependence and help others with this problem.

VII. Confidentiality

We will do everything we can to keep others from learning about your participation in the research. Your private information or biospecimens will only be used for the purposes of this research study, and will not be distributed to another investigator for future research studies. Any biospecimens that are collected as part of this research will not be used for commercial profit. To further help us protect your privacy, the investigators will obtain a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, the investigators cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for the purpose of audit or evaluation. A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note however, that if an insurer, employer or other outside party, learns of your participation, and obtains your consent to receive research information, then the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy. Finally, the Certificate does not prevent the researchers from reporting suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others. Such information will be reported to the appropriate authorities.

Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Your name and other personal identifying information will be stored in an electronically secure database at New York Psychiatric Institute. Signed consent forms and other forms containing identifying information will be kept in a locked file, and all interviews, assessments, etc. will be coded with initials and numbers. Electronic data are also coded and are stored on computers that are password protected. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

VIII. Study Compensation

During the study, you will receive $10 in cash to help pay for your transportation costs. You will have the chance to earn prizes for attending consecutive study visits. Each study visit will result in a draw from the prize bowl. Each draw has a chance of getting one of four outcomes: an encouraging statement (e.g. 'good job'), a small prize valued at $2.50, a large prize valued at $20, or a jumbo prize valued at $100. The chance of winning a jumbo prize us (0.2 %), the large prize (8%), the small prize (42%), and 50% of the time you will get an encouraging statement. You will accumulate an additional draw for each consecutive visit made. If you miss a visit your draws will be reset. The maximum amount over 25 weeks you may potentially earn for attending all study visits is approximately $969 in cash prizes, and $190 in cash for transportation costs.

We are required by law to report your earnings to the IRS. Therefore, your Social Security Number and amount earned will be reported, and you will receive the appropriate IRS form at the end of the year in which you were paid. Please note that payment for this study may affect your eligibility for Medicaid and other city and state support services. No information about which study you participated in will be provided to the IRS.

IX. In Case of Injury

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. Please be aware that:
1. The New York State Psychiatric Institute, Columbia University, Research Foundation for Mental Hygiene, and New York Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital.
2. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.
3. No monetary compensation for wages lost as a result of injury will be paid to you by the New York State Psychiatric Institute, Columbia University, Research Foundation for Mental Hygiene, or by New York Presbyterian Hospital.
4. By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

X. Questions

The investigators will answer to the best of their abilities any questions you may have now or in the future about the study procedures or about your response to the procedures. You should contact the Principal Investigator, Dr. Adam Bisaga, at (646)744-6155 if you have any questions. If a medical emergency occurs at night or over the weekend, you should go to the nearest hospital emergency room and have them call (914)419-8921.If you have any questions about your rights as a research participant, want feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). An IRB is a committee that protects the rights of human subjects in research studies). You may call the IRB Main Office at (646) 774-7155 during regular office hours.

XI. Documentation of Consent for Screening

I voluntarily agree to participate in the screening for the research study described above.

Print name : _____
(Participant)

Signed: _____Date: _____
I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name: _____
(Person Designated to Obtain Consent)

Signed: _____ Date: _____

Consent for Future Contact
You permit the Opioid Treatment Research Program staff to contact you in the future.

Print name : _____
(Participant)

Signed: _____Date: _____

XII. Documentation of Study Consent

I voluntarily agree to participate in the research study described above.

Print name: _____
(Participant)

Signed: _____Date: _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name: _____
(Person Designated to Obtain Consent)

Signed: _____ Date: _____

ADDENDUM 1
CONSENT FOR SIGNIFICANT OTHER CONTACT

It may be important for the staff at the clinic to discuss your problems with a close family member or friend to assess how you are doing, to help contact you if you miss a visit, or in case of an emergency. By signing this page, you consent to allow the staff to contact the following person(s) to discuss your case throughout the course of your treatment. You may refuse to grant this permission, and it will not affect your eligibility for treatment in this study.

Name:_____Relationship:_____

Address:_____

Phone Numbers:_____

Name:_____Relationship:_____

Address:_____

Phone Numbers:_____

Name:_____

Significant other contact information refused:____

Participant Signature:_____ Date_____

Investigator Signature:_____ Date_____

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 7522 **Principal Investigator:** Adam Bisaga M.D.

Name of Study: A Strategy to Improve Success of Treatment Discontinuation in Buprenorphine Responders

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**

☐ Researchers and their staff at the following organizations involved with this Research:

☑ The Sponsor of the Research,
National Institute on Drug Abuse (NIDA)
and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☑ Private laboratories and other persons and organizations that analyze your health information in connection with this study
Laboratory Corporation of America

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Adam Bisaga, MD, NYSPI, 1051 Riverside Dr. Unit 66 New York, NY 10032

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**